ORGANOCATALYTIC TRANSFORMATIONS OF CARBON DIOXIDE AND CYCLIC CARBONATES

Sergio Sopeña de Frutos

UNIVERSITAT ROVIRA i VIRGILI

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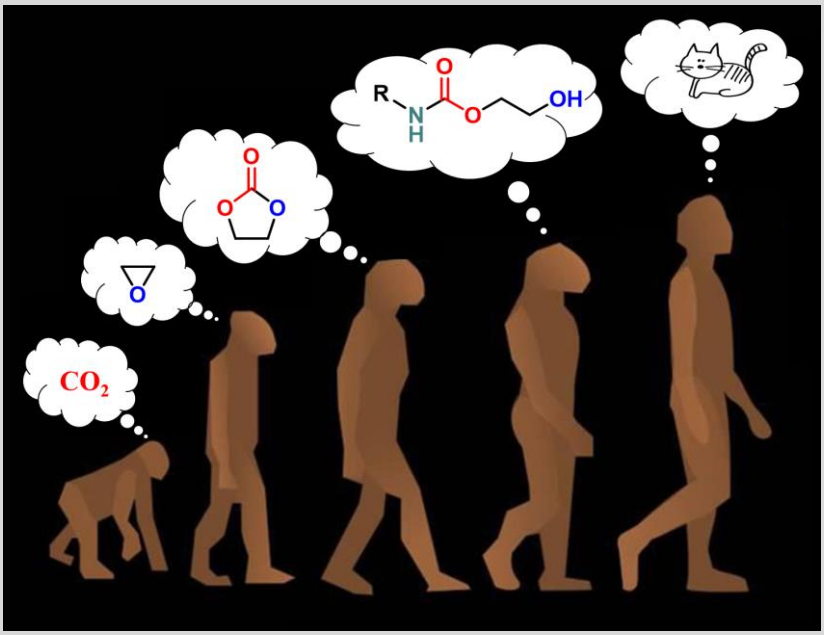
SERGIO SOPEÑA DE FRUTOS



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PhD Thesis

"Organocatalytic transformations of carbon dioxide and cyclic carbonates"

Sergio Sopeña de Frutos

Supervised by Arjan W. Kleij

Tarragona,

22th March 2018

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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, "*Organocatalytic transformations of carbon dioxide and cyclic carbonates*" presented by Sergio Sopeña de Frutos 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, 22th March 2018

Doctoral Thesis Supervisor
Prof. Dr. Arjan W. Kleij

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A mi familia, por todo.

UNIVERSITAT ROVIRA I VIRGILI
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Unos versos me sugiere este postgrado,

que Arjan ha dirigido alegremente,

cuatro años transcurridos lentamente,

de risas, lágrimas, gritos y enfados.

Aún recuerdo aquel mi primer día,

vestido con camisa y riñonera,

añorando mi ciudad que ya no era,

junto a Leti, Víctor, Luis y compañía.

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Chapter I

General Introduction

Carbon dioxide is essential to life, but currently constitutes one of the main contributors to the greenhouse effect since its concentration in the atmosphere has increased dramatically due to anthropogenic activities. Therefore, the number of technologies that have been developed using this waste material are increasing and a lot of effort is put into new processes that can potentially be scaled up. In this introducing section, a general description of the CO_2 "fixation" problem is sketched together with the current applications of this carbon feedstock in industry. Furthermore, focus is given to catalytic processes as key enabling technologies towards the valorisation of CO_2. The synthesis of value-added compounds such as cyclic carbonates and polyurethanes, and the mechanisms involved in these transformations are specifically highlighted.

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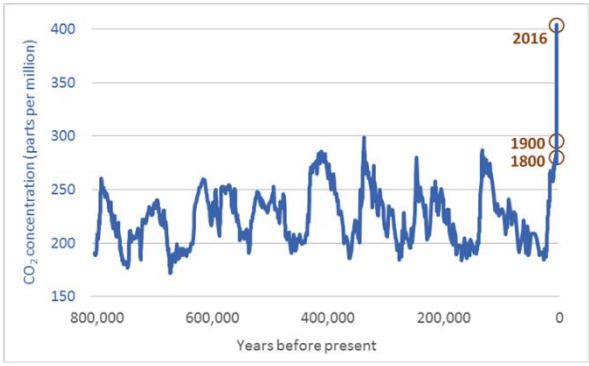
1.1 – Carbon dioxide: waste or opportunity?

Carbon dioxide (CO_2) is the waste product of several human activities including fossil fuel burning, cement manufacture, fermentation and industrial processes. Moreover, CO_2 is one of the main contributors to the greenhouse effect, apart from other known contributors such as SO_x and NO_x. Since the industrial revolution, anthropogenic emissions of CO_2 have increased and resulted to a current concentration in our atmosphere of >400 ppm (Figure **1.1**) This high concentration of CO_2 in the atmosphere has further increased global awareness of the challenges we are facing today. Despite efforts to reduce CO_2 emissions and the application of new restrictive legislations, the tendency of increasing CO_2 concentrations has not been reverted yet. In the near future, the human population will increase and consequently projected global energy requirements will cause further pressure on the need to increase the sustainability of our societies.[1] In this context, fossil fuel reserves will be sooner depleted; these reserves are essential for our current social and economic system, and alternatives have thus to be developed in order to maintain our current standard of living.

Figure 1.1: Evolution of the concentration of carbon dioxide present in the atmosphere.

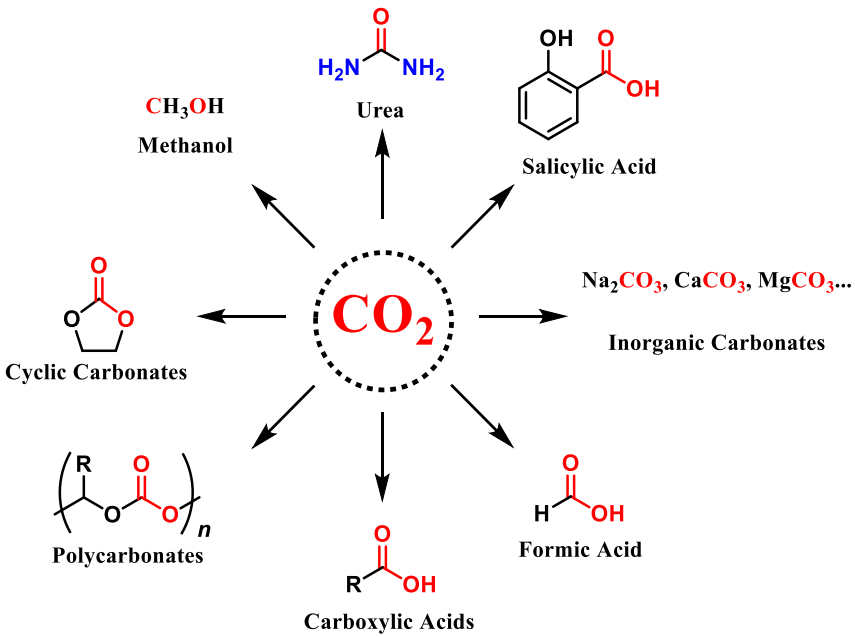


Recently, carbon dioxide, has emerged as an attractive carbon reagent that may partially substitute fossil fuels or other harmful chemicals[2] in the synthesis of organic structures.[3–7] Moreover, carbon dioxide has attractive properties for synthetic applications as it is nontoxic, non-flammable and renewable. In addition, it represents a cheap and abundant C1 building block for the production of chemicals.

1.2 – Industrial uses of carbon dioxide

Direct utilization of CO_2 as feedstock for chemical production and the synthesis of fuels constitutes a complementary strategy towards a more sustainable carbon cycle. There are many compounds that can be prepared from CO_2 such as lactones,[8] heterocyclic structures,[9,10] biobased polymers,[11–14] fuels,[15] and carboxylated structures[16–18] among others.[19–21] However, only a limited number of chemicals are produced on a larger scale (Scheme **1.1**) such as urea,[2,22] methanol, pharma ingredients, formic acid, organic carbonates, polycarbonates and polyurethanes.[4,23–25] Despite this proven potential, fact is that industrial CO_2 conversion is highly limited and involves amounts below 0.5% of the total anthropogenic CO_2 emissions.[25] The use of CO_2 as a synthetic carbon synthon also remains limited to a small selection of transformations, and in order to increase its potential new and improved (catalytic) methodologies for upgrading this waste into valuable organic compounds and materials are warranted.

Scheme 1.1: Example of products derived from carbon dioxide and manufactured on an industrial scale.

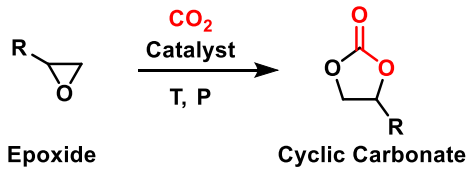


Urea,[2,22] for example, is produced on a 100 Mt scale and 70 Mt are based on the use CO_2 as feedstock,[26] and among the most well-known applications are fertilizers, explosives, nitrating agents,[27] and the synthesis of melamine and their corresponding formaldehyde-based resins.[4] Another example of an industrially relevant use of CO_2 includes the synthesis of methanol with an estimated total annual production volume of 40 Mt with 14 Mt being produced from CO_2.[26] Methanol can be used as intermediate for the synthesis of other chemicals including formaldehyde, methylethyl ether and acetic acid.[28]

1.2 – Cyclic carbonates and polyurethanes

Although there are many more chemicals whose production is based on the use of CO_2 as a raw material, in this section we will focus exclusively on cyclic carbonates and polyurethanes. Cyclic carbonates have very attractive properties such as low evaporation rates, low toxicity and biodegradability.[29] These properties make them useful for industrial or academic applications such as polar aprotic solvents with a high boiling point, as electrolytes for lithium ion batteries, and as precursors for polymeric materials[30] and fine-chemical intermediates, fuel additives, plastic materials and agricultural chemicals.[31] Furthermore, the coupling of CO_2 and epoxides (Scheme **1.2**) constitutes a greener alternative to the use of phosgene[2,31] conventionally used in combination with diols.

Scheme 1.2: Synthesis of cyclic carbonates by the coupling reaction of CO_2 and epoxides.



On the other hand, polyurethanes (PU) with a global production of 17.5 Mt (2011), are among the sixth most widely used polymers. They are important in different fields (medical care, automobile industry, insulation materials) specifically in the production of foams, seals, coatings and adhesives[32,33] because they are able to combine excellent mechanical and physical properties such as durability, elasticity and abrasive resistance.[32] Since its production involves the use of isocyanates derived from phosgene, alternative methods of

polyurethane synthesis have been developed. This new strategy in PU synthesis focuses on a different type of plastics called non-isocyanate based polyurethanes (abbreviated as NIPUs) whose production is based on the use of cyclic carbonates as raw material.[32–36] Since the latter are typically produced from CO_2 and epoxides, these NIPUs are a nice example where CO_2 recycling can have a significant impact on the overall life cycle analysis of the material avoiding the use of toxic and unsustainable reagents/monomers.

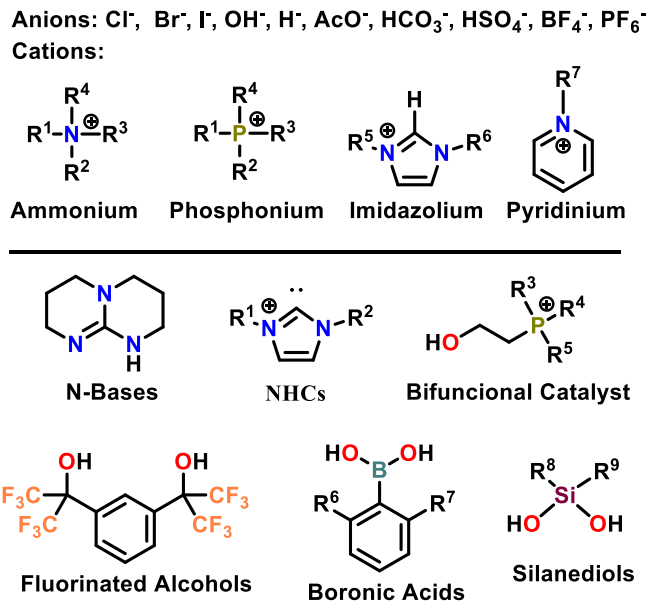
1.3 – Metal catalysis and organocatalysis

The coupling reaction of CO_2 and epoxides towards cyclic carbonates is a process characterized by a high atom economy. Moreover, this reaction aligns well with the general pursuit towards greener, safer and more efficient chemical synthesis and more sustainable processing. However, CO_2 is the most oxidized state of carbon and the activation barrier for the coupling reaction of CO_2 with epoxides is estimated between 50-70 kcal·mol^{-1}.[37–39] Catalysis thus plays an important role to enable this transformation and to valorise this attractive and renewable carbon-based building block.

Up to now, a wide range of homogeneous and heterogeneous catalysts for the formation of cyclic carbonates have been developed. Homogeneous catalysts have proven to be generally more effective compared against heterogeneous systems in terms of catalyst loading and operational conditions (i.e., temperature and pressure). On the other hand, heterogeneous catalysis (e.g. based on metal-organic frameworks, nanoparticles or supported catalysts)[40–45] present other advantages such as operational simplicity, easy recovery and recycling potential which are important features for industrial processes despite the need for harsher reaction conditions. Homogeneous metal complexes[40–44] were among the first examples of systems that enabled the conversion of CO_2 into cyclic carbonates under atmospheric pressure and ambient temperature. However, in order to become industrially viable, many aspects of such homogeneous catalysts require substantial improvement including the (long-term) sensitivity to hydrolysis and oxidation, the optimization/reduction of the cost of the ligand/metal combination and minimizing metal impurities that may stay behind after product purification and isolation. This latter aspect is particularly important when cyclic carbonates are used as intermediates in fine-chemical and pharmaceutical synthesis.

The development of new metal-free based catalytic systems (i.e., organocatalysis) has become increasingly important, and many contributions in this sub-area of CO_2 catalysis have been reported in the last years.[46] The first generation of reported organocatalytic systems applied to the synthesis of cyclic carbonates usually operate under high temperature and high pressure conditions. Hereafter examples of organocatalytic systems have been reported showing that these reactions can also be performed under more attractive and milder reaction conditions down to r.t. and low pressures of 2-10 bar.[43,44,47,48] Organocatalysts can generally be obtained from cheap starting materials and have good chemical stability towards moisture and air.[43] Therefore, effective metal-free catalytic approaches are the first choice to obtain products for which trace metal content may result in adverse health effects.

Figure 1.2: Selection of known organocatalyst(s) (components) applied in the synthesis of cyclic carbonates.



The structural diversity for reported organocatalytic systems (Figure **1.2**) applied to the synthesis of cyclic carbonates is very extensive.[43,44,47,48] Many of these binary and bifunctional organocatalyst originate from amines and organic bases,[49–52] ionic liquids or organic salts (ammonium-, phosphonium-, imidazolium- and pyrrolidinium-based ones),[53–60] N-heterocyclic carbenes (NHCs)[61–65] and various hydrogen-bond donors (HBDs).

Particularly relevant and attractive are the HBD systems due to their ability to assist in the activation of the epoxide by hydrogen-bonding, facilitating the nucleophilic attack of a co-catalytic nucleophile on the epoxide and accelerating the initial ring-opening process. Most organocatalysts require the presence of a nucleophile being either external (binary system) or internal (bifunctional system). The most widely used hydrogen-bond donors as components of organocatalysts are alcohols and diols,[66–68] fluorinated alcohols,[69,70] boronic acids,[71] silanols,[72] carboxylic acids,[73] amino alcohols,[74,75] amino acids,[73,76–78] azaphosphatranes[79,80] and ureas.[81]

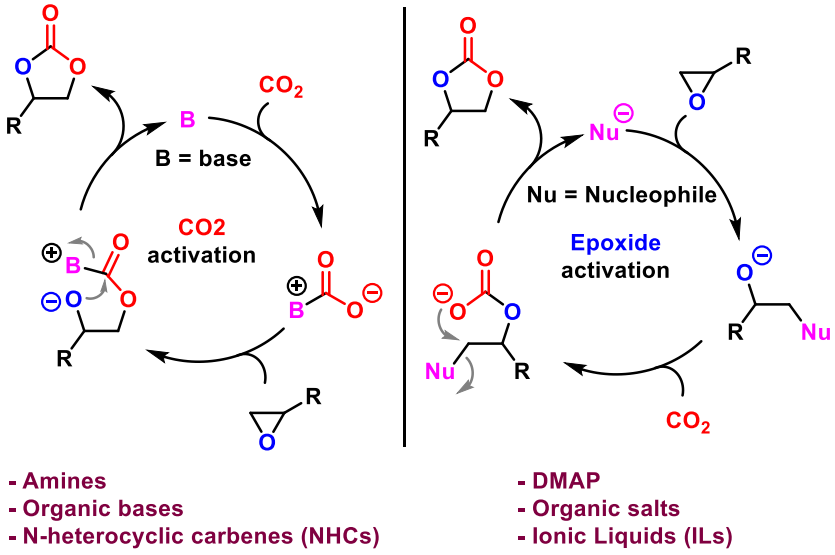
1.4 – Proposed mechanisms

The operating mechanism for an organocatalyzed coupling reaction of carbon dioxide and epoxides to afford cyclic carbonates can vary depending on the chosen catalytic system and the species involved in the activation (Scheme **1.3**), though in essence two different pathways can be clearly differentiated.

When the target molecule to activate is carbon dioxide, a "direct CO_2 activation pathway" or "halide free activation pathway" is involved (Scheme **1.3**; left). This path operates when nitrogen-based heterocycles (amines, organic bases or N-heterocyclic carbenes) act as catalyst. In this manifold, the catalyst first interacts with the CO_2 molecule resulting in a relatively stable catalyst-CO_2 adduct.[82–84] Then, the adduct (with the activated CO_2 now being nucleophilic) mediates the ring opening of the epoxide and the subsequent alkoxide species evolves towards the corresponding cyclic carbonate and regenerates the catalyst.

Alternatively, when the activated substrate is the epoxide, an "indirect CO_2 activation pathway" is involved (Scheme **1.3**; right). First, an external nucleophile facilitates ring opening of the epoxide leading to the formation of an alkoxide. The enhanced nucleophilicity of this new intermediate enables the attack of the alkoxide onto the carbon centre of the CO_2 molecule, followed by carbonate ring closure and regeneration of the nucleophile.[56]

Scheme 1.3: General proposed mechanisms for the coupling reaction of carbon dioxide and epoxides: a carbon dioxide based activation mechanism (left), and an epoxide activation based mechanism (right).



1.5 – Thesis aims and outline

The aims of the work described in this thesis were the development of new transformations based on CO_2 and the improvement of the efficiency and selectivity of previously reported synthetic protocols. More specifically, the application of natural compounds as catalysts were probed and a detailed analysis related to their activity and catalyst life time was conducted (**Chapter 2**). Furthermore, a conceptual new approach for cyclic carbonate synthesis was examined, and a new organocatalyst was designed able to perform the transformation of challenging *internal* epoxides. The mechanistic implications involved in these transformations were also studied in detail (**Chapter 3**).

Additionally, there still exists a need to develop halide-free organocatalysts providing alternative protocols for the synthesis of highly substituted cyclic carbonates distinct from the conventional use of binary catalytic systems, and efforts were thus made to develop new systems with potential to go beyond the state-of-the-art approaches (**Chapter 4**). Finally, since regioselectivity control in the aminolysis reaction of cyclic carbonates remained an

open challenge, new organocatalytic protocols may provide potential to develop urethane-based materials (cf., polyurethanes) with a controlled microstructure (**Chapter 5**).

The first experimental chapter (**Chapter 2**) describes the use of tannic acid as a cheap and versatile organocatalyst component in the coupling reaction of epoxides and CO_2. This readily available polyphenol-based natural compound showed a highly attractive catalytic performance in the transformation of terminal epoxides towards their corresponding cyclic carbonates. Furthermore, the catalytic activity and catalyst stability/life time was studied and compared against other polyphenol based catalysts. The recyclability of the tannic acid based system was examined and a new separation and recycling protocol was developed. To demostrate the synthetic potential of the new catalytic system, a wide range of epoxide substrates was investigated and converted into their cyclic organic carbonates.

In **Chapter 3**, the use of squaramides is described as a new type of hydrogen-bond donor organocatalyst in the synthesis of cyclic carbonates. The squaramide structure was systematically optimized to maximize the catalytic potential. The promising results found for the transformation of terminal epoxides combined with kinetic studies prompted us to extend the study towards internal epoxides. The substrate scope presented in Chapter 3 is among the widest in the area of organocatalytic formation of cyclic carbonates. In addition, mechanistic control studies were carried using ^{1}H NMR and UV-Vis spectroscopy showing that the squaramides are principally involved in oxoanion stabilization rather than the commonly observed “epoxide-activation” potential.

In **Chapter 4**, a new domino strategy for the organocatalytic synthesis of unprecedented, highly substituted cyclic carbonates was designed that operates via a substrate-controlled activation using epoxy alcohols as reaction partners. This protocol initially allows the generation of a less substituted cyclic carbonate intermediate that is able to equilibrate to a tri- or tetra-substituted carbonate under thermodynamic control following a similar pathway as the Payne rearrangement of epoxy alcohols. The most substituted carbonate incorporating the least substituted alcohol (most reactive) unit can be selectively trapped *in situ* displacing the equilibrium to the targeted product under mild reaction conditions. The scope of substituted cyclic carbonates developed in Chapter 4 represent the first examples of tri- and tetrasubstituted cyclic carbonates produced under organocatalytic control and in the absence of external nucleophiles.

In **Chapter 5** the use of cyclic carbonates as precursors for the formation of functional carbamates through aminolysis in the presence of various amines is reported. The productive

use of TBD (a bicyclic guanidine) as organocatalyst is illustrated via kinetic comparison with the uncatalyzed reaction. Moreover, the use of TBD allows for virtually complete regioselectivity in the C–O bond breaking process within the cyclic carbonate and C–N bond making upon formation of the carbamate. A wide range of cyclic carbonates with different substitution patterns and (functionalized) amines were tested and showed that this regioselective process is general in nature. The regioselective aminolysis of bis-cyclic carbonates demonstrates that the newly developed organocatalytic process may be of use in the formation of structurally regular oligo- and polyurethanes.

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UNIVERSITAT ROVIRA I VIRGILI
ORGANOCATALYTIC TRANSFORMATIONS OF CARBON DIOXIDE AND CYCLIC CARBONATES
Sergio Sopeña de Frutos

Chapter II

Organocatalyzed conversion of oxiranes and CO_2 into cyclic carbonates

A binary catalyst system based on tannic acid/NBu_4X (X = Br, I, Cl) represents a highly efficient organocatalyst at very low catalyst loading for the coupling between carbon dioxide and functional oxiranes affording their organic carbonates in good yields. The presence of multiple polyphenol fragments within the tannic acid structure is beneficial for synergistic effects leading to higher stabilization of the catalyst structure during catalysis. The observed (initial) TOFs exceed 200 h^{-1} which is among the highest reported for organocatalysts in this area of CO_2 conversion. The current organocatalyst system presents a useful, readily available, cheap but above all reactive alternative for most of the metal-based catalyst systems reported for the synthesis of cyclic carbonates.

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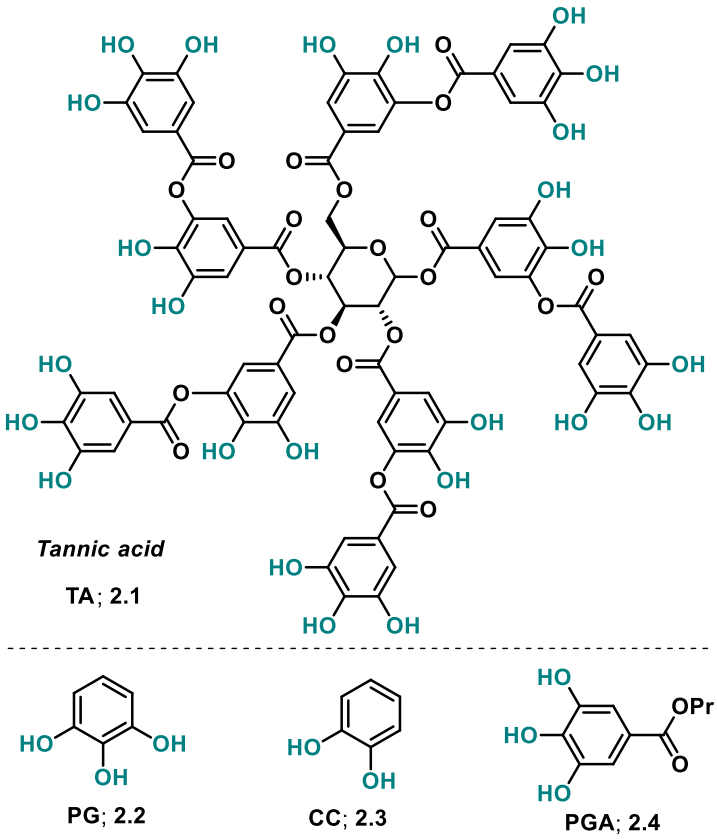
ORGANOCATALYTIC TRANSFORMATIONS OF CARBON DIOXIDE AND CYCLIC CARBONATES
Sergio Sopeña de Frutos

2.1 – Introduction

Current (catalytic) research focused on the use of carbon dioxide (CO_2) as a cheap and renewable source of carbon focuses on its incorporation into other organic scaffolds as to be able to partially replace fossil fuel based chemistries.[1–7] Considerable progress in this area has been achieved leading to a wide variety of organic structures one may obtain using CO_2 as a molecular synthon.[8–12] Among these organic products, organic carbonates[5,6,13–15] have conquered a prominent position being useful in a number of applications including their use as fuel additives, as non-protic solvents and as monomer intermediates for polymeric structures.[16] In the last decade, highly efficient catalytic methods for their preparation have emerged with those incorporating Lewis acidic metal ions probably among the most active reported to date.[13,17–20] Notwithstanding, the use of metal-based catalysts in industrial settings is not always desired and the presence of trace amounts of (toxic) metals in final products is subject of an increasingly lower limit accepted by (end-)users in commercial products.

Therefore, from this viewpoint one would ideally like to use organocatalysis[21–24] for the formation of cyclic carbonates and progress in this respect is characterized by the use of various types of catalysts based on ionic liquids,[25–27] (poly)alcohols and Brøndsted acids,[28–33] (supported) phosphonium, ammonium or imidazolium salts and derivatives,[34–41] and others.[42–47] However, organocatalysts are usually much less effective in the activation of organic substrates and their mediation requires longer reaction times, higher reaction temperatures and/or higher loadings for effective turnover.[21] Thus, the generally observed lower reactivity of organocatalysts is still posing a major challenge to be able to compete with metal-based catalysts though eventually providing more sustainable catalysis solutions.

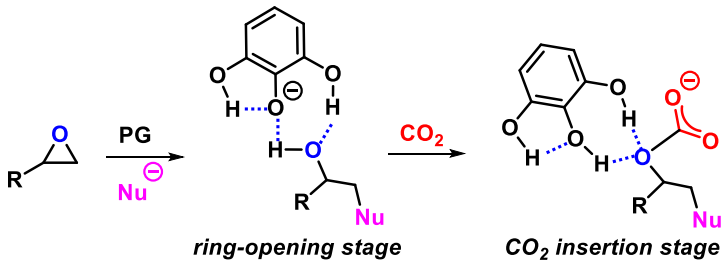
Scheme 2.1: Chemical structure of tannic acid, pyrogallol, catechol and propyl gallate.



In the course of the development of new and more efficient organocatalytic methodologies for cyclic carbonate formation, it was shown that activation of oxiranes through hydrogen-bonding using polyphenolic compounds, fluorinated alcohols and silanediols is an attractive approach.[48–51] In particular, pyrogallol (compound **2.2**, PG; Scheme **2.1**) is an example of a highly efficient organocatalyst system able to mediate the coupling between terminal epoxides and CO_2 under extremely mild reaction conditions (25 – 45 ºC, 2 – 10 bar CO_2 pressure, 2 mol% catalyst). Of particular importance is the cooperative nature of the adjacent phenol groups that allows for an extended hydrogen-bond network upon activation of the oxirane thereby lowering the activation barrier for its ring-opening by an external nucleophile (Scheme **2.2**) and beyond.[33,45] We thought that an even higher local concentration of phenolic sites would be beneficial for catalytic turnover and therefore considered tannic acid (Scheme **2.1**; TA) as catalyst additive. This additive is a

naturally occurring plant phenol that is commercially available and cheap. The presence of multiple phenol fragments in tannic acid should facilitate highly efficient activation of oxiranes through similar synergistic effects as noted previously for PG.

Scheme 2.2: Hydrogen bond based activation of epoxides by pyrogallol



In this chapter we report the use of binary catalyst systems derived from tannic acid and suitable nucleophiles for the coupling of CO_2 and various epoxides. These new catalyst systems are among the most active organocatalysts reported to date[47] with appreciable turnover frequencies able to compete with those reported for many known metal-based catalysts. The observation of synergistic effects for improved catalyst stability and lifetime creates new potential for new organocatalyst design in this area of CO_2 catalysis.

2.2 – Results and discussion

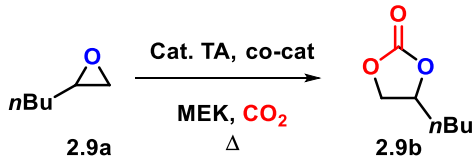
2.2.1 – Optimization of the cyclic carbonate synthesis

First, tannic acid (compound **2.1**, TA) was combined with tetrabutylammonium iodide (compound **2.5**, TBAI) to obtain a binary catalyst system capable of mediating the coupling between 1,2-epoxyhexane (compound **2.9a**, a benchmark substrate) and CO_2 in a stainless steel reactor (Figure **2.1**). The previously reported binary catalytic system formed by pyrogallol (compound **2.2**, PG) and TBAI with a catalyst and co-catalyst loading of 5 mol% each with respect to the same substrate and methyl ethyl ketone (MEK) as solvent[a] gave a NMR yield of 100% (93% isolated) of the cyclic carbonate **2.9b** at 45 ºC after 18 h. Thus, we first attempted to use similar conditions (Table **2.1**, entry 1) with a slightly lower amount of hydrogen-bond donor (*i.e.*, 0.50 mol% of TA). However, under these conditions, we observed that TA was not fully soluble, and therefore epoxide activation/turnover was more complicated. We found that increasing the reaction temperature to 80 ºC resulted in a homogeneous solution if the catalyst loading was kept low enough (0.05 mol% of TA: see Table **2.1**, entry 3), and led to quantitative formation of the cyclic carbonate **2.9b** in high selectivity (>99%). The use of the nucleophilic reagent alone (Table **2.1**, entries 4 and 5) led to a much lower yield of cyclic carbonate **2.9b**, which emphasizes the imperative role of the TA to mediate this conversion. In the presence of TA and absence of co-catalyst (TBAI) no conversion was noted (Table **2.1**, entry 6).

We then varied the co-catalyst loading (Table **2.1**, entries 7-11) and kept the TA concentration at 0.05 mol%; quantitative conversion of 1,2-epoxyhexane **2.9a** into the corresponding cyclic carbonate **2.9b** could still be achieved at a TBAI loading of 2 mol%. Interestingly, the initial TOF under these conditions was relatively high (236 h^{-1}; Table **2.1** entry 10 at t = 2 h). In the absence of TA, only an 8% yield of compound **2.9b** was noted after 2 h. The catalyst loading of TA, could be further reduced to approximately 0.03 mol% (Table **2.1**, entry 12) to yield a substantially higher conversion of epoxide **2.9a** compared to the turnover facilitated by the co-catalyst TBAI alone (Table **2.1**, entry 5).

[a] **Note 1;** the solubility of carbon dioxide is higher in polar organic solvents and in particular ketones such as MEK giving thus more effective turnover kinetics for the formation of the cyclic carbonate products.

Table 2.1: Screening of reaction conditions in the synthesis of cyclic carbonate 2.9b.



2.9a 2.9b

Entry	TA [mol%]	NBu_4X [mol%]	Solvent	T [ºC]	Yield [%][a]
1	0.50[b]	I (5.0)	MEK	45	16
2	2.0[b]	I (5.0)	MEK	80	93
3	0.05	I (5.0)	MEK	80	>99[c]
4	-	I (5.0)	MEK	80	47
5	-	I (2.0)	MEK	80	41
6	0.05	-	MEK	80	0
7	0.05	I (4.0)	MEK	80	>99
8	0.05	I (3.0)	MEK	80	>99
9	0.05	I (2.0)	MEK	80	>99
10[d]	0.05	I (2.0)	MEK	80	24
11	0.05	I (1.0)	MEK	80	82
12	0.03	I (2.0)	MEK	80	79
13	0.01	I (2.0)	MEK	80	47
14	0.05	I (5.0)	MEK	70	76
15	0.05	I (5.0)	MEK	60	53
16[e]	0.05	I (5.0)	MEK	80	>99
17	0.05	Br (2.0)	MEK	80	>99
18	0.05	Cl (2.0)	MEK	80	70
19	0.05	I (2.0)	ACE	80	>99
20[f]	0.025	I (2.0)	MEK	80	>99
21[g]	0.15	I (2.0)	MEK	80	62
22[h,i]	0.03	I (2.0)	MEK	80	35
23[g,h]	0.15	I (2.0)	MEK	80	33
24[g,h]	0.30	I (2.0)	MEK	80	55

General reaction conditions: 1,2-epoxyhexane **2.9a** (8.3 mmol), pCO_2^0 = 10 bar, co-catalyst NBu_4X (amount indicated), 18 h, 30 mL autoclave as reactor. MEK = 2-butanone and ACE = acetone (in both cases 5 mL). [a] Yield determined by ^1H NMR ($CDCl_3$) using mesitylene as an internal standard. Selectivity for the cyclic carbonate was >99%. [b] Not fully homogeneous. [c] Isolated yield 99%. [d] Using 2.5 mL of MEK, t = 2 h; TON = 472, TOF = 236 h^{-1}; the reaction in the absence of TA afforded only 8% of **2.9b**. [e] pCO_2^0 = 6 bar. [f] Using only 2.5 mL of solvent. [g] Using pyrogallol (Compound **2.2**; PG) as catalyst. [h] Reaction time was 6 h. [i] Average TOF/h/TA = 195 h^{-1}.

The reaction temperature had a significant effect on the conversion rate (Table **2.1**, entries 14 and 15 versus 3) and 80 ºC seems to be optimal for this binary catalytic system. At a lower initial pressure of 6 bar, the yield of cyclic carbonate **2.9b** remained quantitative (Table **2.1**, entry 16). Upon changing the nature of the nucleophile (Table **2.1**, entries 17 and 18), a lower yield of cyclic carbonate **2.9b** was apparent if a chloride-derived nucleophile was used. The bromide-based binary catalytic system gave a similar result, that is, quantitative conversion of epoxide **2.9a** could be attained (Table **2.1**, entry 9).[b] The use of acetone as solvent (ACE; Table **2.1**, entry 19) gave also excellent results. A further decrease of the TA loading to 0.025 mol% in only 2.5 mL of MEK still resulted in quantitative conversion (Table **2.1**, entry 20).[c]

Figure 2.1: Photograph of a stainless steel reactor system used for the coupling reactions involving epoxides and carbon dioxide.

[b] **Note 2;** compared with the reaction listed in Table **2.1**, entry 5, the background reactions in the presence of 2 mol% of tetrabutylammonium bromide (TBAB; 60%) or 2 mol% of tetrabutylammonium chloride (TBACl; 44%) show similar or improved conversion rates. However, in the presence of TA, the chloride-based binary catalytic system (Table **2.1**, entry 18) is somewhat less effective whereas the bromide- and iodide-based ones (Table **2.1**, entries 9 and 17) give quantitative conversions. As our previous studies were performed using TBAI as the nucleophilic additive, we further continued using this co-catalyst for comparative reasons.

[c] **Note 3;** possible product inhibition was also probed using a 1:1 mixture of the cyclic carbonate **2.9b** and its precursor **2.9a**, taking the reaction in the *absence* of the product as a reference. In both cases, a similar conversion was noted at the end of the reaction; therefore, one may conclude that no significant product inhibition occurs.

Finally, a comparison was made between the tannic acid based binary catalytic system TA/TBAI and the previously reported binary catalytic system of PG/TBAI (Table **2.1**, entries 21-24). Since the TA structure (Scheme **2.1**) contains in its structure five (substituted) pyrogallol units,[d] the comparison was made with the synthesis of cyclic carbonate **2.9b** mediated by 5 equiv of PG. After 18 h, a significant difference between the yields of cyclic carbonate **2.9b** promoted by TA (Table **2.1**, entry 12; 79% yield) and PG (Table **2.1**, 5 equiv, entry 21; 62% yield) was observed. At a reduced reaction time of 6 h, a much smaller difference in the yield of cyclic carbonate **2.9b** was noted (Table **2.1**, entries 22 and 23; 35% versus 32% yield). Under these conditions, the tannic acid derived binary catalytic system (TA/TBAI) still displayed an appreciably high average TOF of 195 h^{-1}.

2.2.2 – Comparison of polyphenol catalyst components

Inspired by these results, we decided to make a more elaborate comparison between TA and various polyphenol based structures (Table **2.2**) including pyrogallol (**2.2**, PG), catechol (**2.3**, CC) and propyl gallate (**2.4**, PGA).

For the comparative studies, we used a high-throughput experimentation platform (Figure **2.2**. AMTEC reactor) and estimated the reactivity of the polyphenols under similar reaction conditions (Table **2.2**, entries 1-11; reaction time 4 h). Moreover, for completion, the conversion obtained in the absence of the polyphenol additive was also examined (Table **2.2**, entry 12). In the latter case, only very low conversion was noted (8%), and thus the production of cyclic carbonate **2.9b** under these conditions (Table **2.2**) is mostly caused by the binary catalytic system comprising of the polyphenol structures.

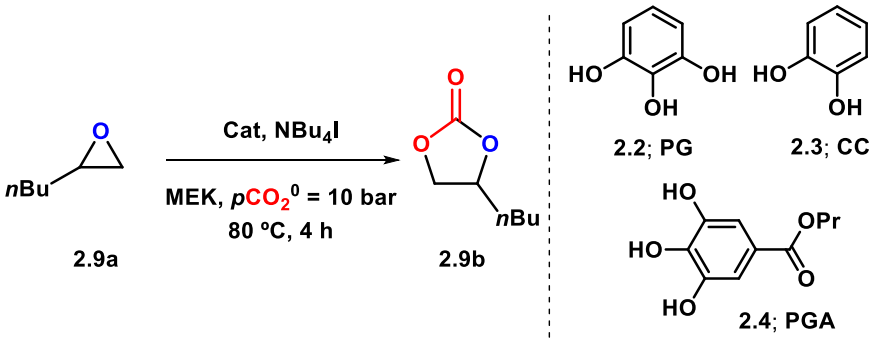
[d] **Note 4;** commercially available TA is usually a combination of polygalloyl glucoses or polygalloyl quinic acid esters, with the number of galloyl moieties per molecule depending on the plant source. Here, we have used the commercial product from Aldrich (ACS Reagent, 500 g, = 77.50 €) which loses approximately 12% of its weight upon drying. Further, as the general structure of TA contains five *pseudo*-PG units, we have compared the catalytic performance of TA (0.03 mol%; 1 equiv) with that of PG (0.15 mol%; 5 equiv).

Figure 2.2: Photograph of an AMTEC SPR-16 reactor system used for the comparative studies.

Comparisons were made between the conversion and activity of the TA based catalytic system (Table **2.2**, entry 1) and those consisting of 1, 5 or 10 equivalents of the polyphenols PG, CC or PGA (Table **2.2,** entries 3–11). According to the data in Table **2.2**, it is clear that the tannic acid based binary catalytic system shows favourable comparative reactivity behaviour with high molecular turnover numbers (TONs)[e] and turnover frequencies (TOFs).[f] It should be mentioned that is difficult to use a correct reference system for TA as PG and CC are electronically different from the *pseudo*-PG units within the TA structure, and PGA probably represents a better electronic match. Furthermore, TA contains a significant amount of water (12% weight loss upon drying) and the reported TON/TOF values in Table **2.2** are uncorrected. The reactive polyphenol units within TA structure are non-randomly distributed during catalysis, which likely reduces their relative accessibility compared to the other investigated catalytic systems. We hypothesize that intramolecular H-bonding is in fact controlling the accessibility of the polyphenol units, a phenomenon which cannot be (fully) counterbalanced by the use of a moderately polar solvent such as MEK. Since the reactions in MEK needed an increased reaction temperature (80 ºC) for the full dissolution of both binary catalytic system components, it seems plausible to assume that this solvent indeed is not able to break up intra- and intermolecular hydrogen bonding between the

[e] **Note 5;** turn over number (TON) is the number of moles of substrate that a mole of catalyst converts.
[f] **Note 6;** turn over frequency (TOF) is defined as the turnover per unit of time.

Table 2.2: Screening of various polyphenols in the synthesis of cyclic carbonate 2.9b.



Entry	Phenol	Amount [mol%]	Conv. [%]	Yield [%][a]	TON[b]	TOF[c] [h^{-1}]
1	TA	0.03	21	20	634	159
2	TA	0.15	47	44	295	74
3	PG	0.03	10	9	303	76
4	PG	0.15	32	30	200	50
5	PG	0.30	43	41	138	34
6	CC	0.03	15	14	461	115
7	CC	0.15	42	41	272	68
8	CC	0.30	51	48	158	40
9	PGA	0.03	11	10	344	86
10	PGA	0.15	46	44	290	72
11	PGA	0.30	65	64	218	54
12[d]	–	0	8	7	-	-

General reaction conditions: 1,2-epoxyhexane (Compound **2.9a**; 4.15 mmol), pCO_2^0 = 10 bar, TBAI (2.0 mol%), 4 h, 80 ºC, MEK (2.5 mL), AMTEC reactor. [a] Yield determined by ^1H NMR ($CDCl_3$) using mesitylene as an internal standard. Selectivity for the cyclic carbonate **2.9b** was >99%. [b] Total turnover number per molecule of catalyst based on reported yields [c] Average turnover frequency per molecule of catalyst based on reported yields. [d] Only 2.0 mol% TBAI used.

separate polyphenol units at lower temperatures. Despite these features, at very low loading of TA loading (0.03 mol%) the relative reactivity seems to indicate that the high local concentration of phenol groups provides some degree of synergy that leads to efficient catalysis behaviour. Thus, one should consider the overall catalytic effect rather than attempting to correlate quantitatively the findings in Table **2.2**.

Remarkably, upon comparing the reactivity of pyrogallol (**2.2**; PG), catechol (**2.3**; CC) and propyl gallate (**2.4**; PGA) as catalyst additives (Table **2.2**, entries 3-11), one can note the lower efficiency of PG among the polyphenols studied. This result contrasts a previous report found in the literature[48] where the catalytic efficiency of pyrogallol proved to be markedly better than that observed for catechol at 45 ºC. Intrigued by this discrepancy, we decided to investigate the long-term temperature effect on the catalytic performance of the polyphenol additives in more detail by measuring the conversion of 1,2-epoxyhexane **2.9a** into cyclic carbonate **2.9b** at 80 ºC at various time intervals (1, 2 and 6 h). First, we compared the kinetic profiles of TA, PG, CC and PGA during the first 6 h using equimolar amounts of polyphenol (Figure **2.3**, 0.03 mol%). Interestingly, both triphenolic derivatives PG and PGA show inferior catalytic behaviour as the conversion already seems to reach a plateau level after 4 h at this catalyst loading, whereas the tannic acid TA and catechol CC still retain good activity. These results seem to indicate some catalyst degradation for both PG and PGA based binary catalytic systems under the operating conditions.

In order to make the comparison more realistic, we also compared the catalytic performance of TA (0.03 mol%) and PG (0.15 mol%) during 18 h (Figure **2.4**). As can be noted, after approximately 5 h the reactivity of the pyrogallol based binary catalytic system decreased drastically whereas the tannic acid based system still showed appreciable activity. This further supports the view that the TA is a more stable catalyst under these conditions and has a longer lifetime compared to PG. The more effective catalytic behaviour of TA is probably the result of a higher local concentration of phenol groups present in the catalyst structure which does not induce strong intermolecular effects, though easy intramolecular H-bonding may reduce to some extent the acidity of the polyphenol favouring a longer catalyst lifetime.

Figure 2.3: Comparison of the catalytic performance of polyphenol-based binary catalytic systems in the conversion of 2.9a into 2.9b.

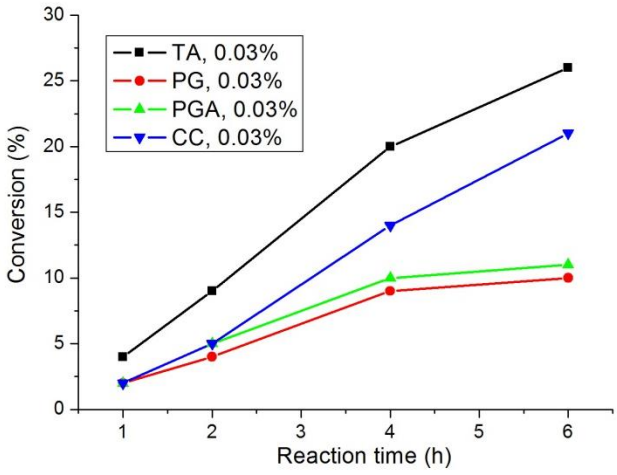
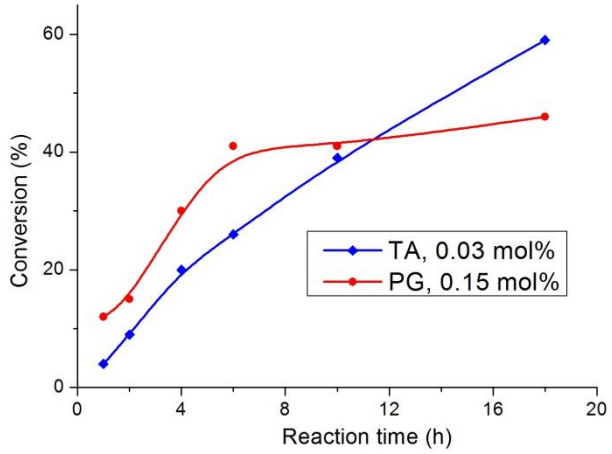
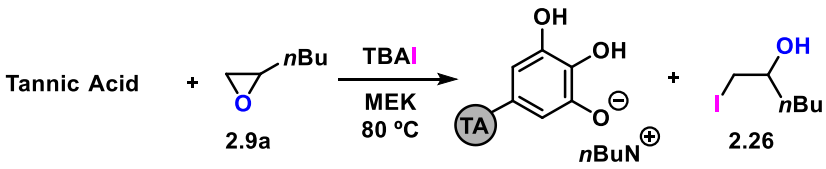


Figure 2.4: Comparison of the catalytic performance of TA and PG based binary catalytic systems in the conversion of 2.9a into 2.9b.



As previously reported in the literature in the pyrogallol case (**2.2**; Scheme **2.1**),[49] potential catalyst degradation may occur *via* irreversible proton transfer of the phenol to the substrate with the nucleophilic additive also being involved (see Scheme **2.3**).

Scheme 2.3: Irreversible proton transfer using the TA/TBAI binary catalytic system.



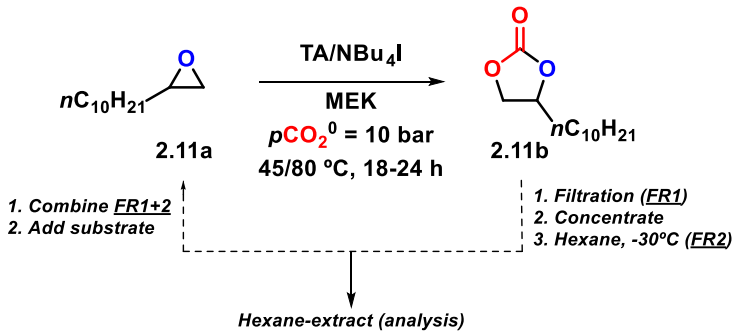
This eventually translates into lower catalytic efficiencies, and higher reaction temperatures in combination with very low catalyst loadings (0.03–0.15 mol%) may lead to unproductive catalysis behaviour and incomplete substrate conversion. Therefore, it seems that TA holds promise as a catalytic additive under dilute conditions, whereas for the other polyphenols much higher concentrations are required to maintain similar effective turnovers.

2.2.3 – Recycling studies

To probe the hypothesis that the disappearance of phenol sites may be responsible for the loss of catalytic activity, we decided to investigate the recyclability of the binary catalytic system TA/TBAI in the conversion of 1,2-epoxy-dodecane **2.11a** (Scheme **2.4**) into cyclic carbonate **2.11b** at two different reaction temperatures (45 and 80 ºC).

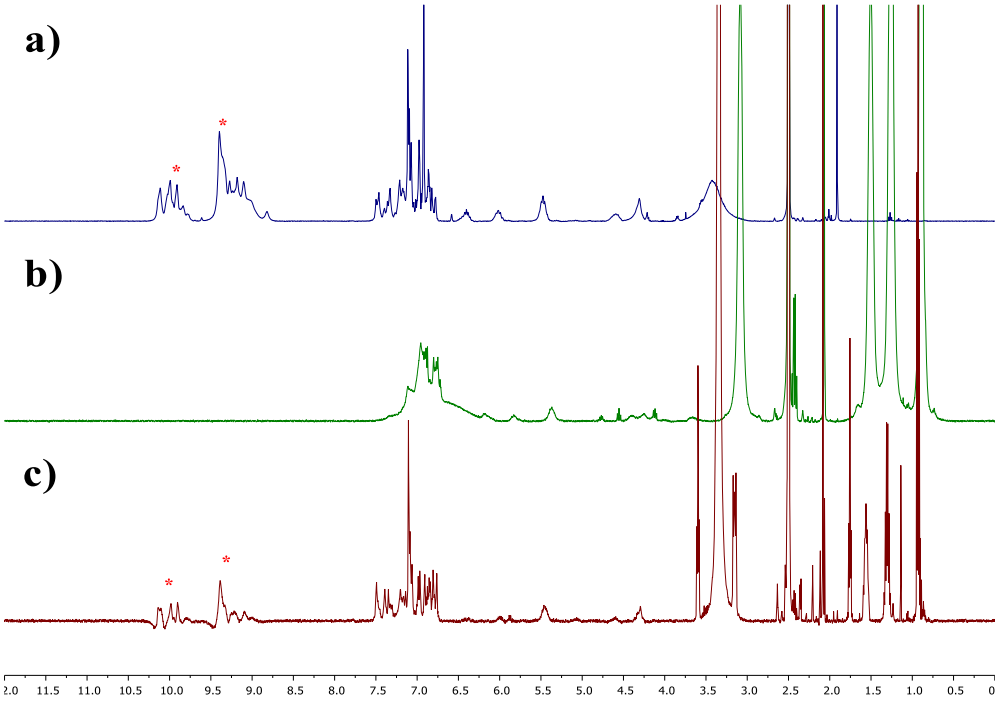
At both reaction temperatures, the catalyst was easily separated from the product-containing hexane phase. The hexane solution was then concentrated and showed virtually pure cyclic carbonate product **2.11b** indicating that no significant amounts of catalyst components were extracted. Two solid catalyst fractions (FR1 and FR2, Scheme **2.4**) could be separated and were reused in a second catalyst cycle. The catalyst recycled at 80 ºC showed a significant drop in conversion (from 89→27%) whereas at 45 ºC a similar though slightly reduced conversion drop (54→24%) was noted. After the second cycle, the catalyst was separated from the product/substrate phase and subjected to ^{1}H NMR, IR and TGA (thermo-gravimetric analysis).

Scheme 2.4: Recycling studies with epoxide 2.11a as substrate and using TA/TBAI as binary catalytic system.



The combined analytic data clearly showed a loss of reactive phenol units likely caused by competing reactions between the polyphenol and the substrate/nucleophile (see Figure **2.5**). This afforded a halo-hydrin (cf., **2.26** in Scheme **2.3**) and tetrabutylammonium-tannic acid salt based by-products, which were identified by ^{1}H NMR and were also previously reported for the degradation of PG under temperature-forcing conditions.[48] The regeneration of the TA structure was probed by treatment of the isolated solid fraction from the recycling experiments with various acids (HOAc and diluted/concentrated HCl). Treatment of the recycled material with concentrated HCl regenerated the TA species as evidenced by ^{1}H NMR (Figure **2.5**) and IR analysis showing very high similarity to the spectroscopic footprint of the commercial product.

Figure 2.5: ^{1}H NMR of tannic acid in DMSO-d_6; (a) Commercial tannic acid. (b) Tannic acid after use as catalyst. (c) Tannic acid after regeneration by treatment using diluted HCl.

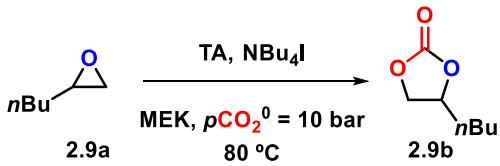


Thus, the acid treatment indicates the possibility of catalyst regeneration. When the recycled binary catalyst was reused in the synthesis of cyclic carbonate **2.11b** (Scheme **2.4**), an improved yield of 51% (versus 24% for the untreated, recovered TA) was determined at 80 ºC. The mass balance for both TA (FR1, Scheme **2.4)** and TBAI (FR2, Scheme **2.4**) was then more carefully checked. Whereas a virtually complete isolation of the original TA amount (24.6 versus 25.7 mg; 96%) was noted for FR1, a clear loss of the co-catalytic TBAI (FR2, 35.2 versus 56.8 mg; 62%) was apparent. Finally, we then checked separately the activity of a regenerated TA sample with a fresh amount of TBAI in the synthesis of cyclic carbonate **2.9b** and compared the conversion with the original data using TA (0.03 mol%) of at 80 ºC for 18 h (79% conversion; see Table **2.1**, entry 12). Fortunately, we found a comparable conversion (75%) for the regenerated TA catalyst supporting the view that it can be easily recycled upon acid treatment.

2.2.4 – TON and TOF

We then further investigated the application of the binary catalytic system TA/TBAI in the synthesis of cyclic carbonate **2.9b** using relatively low amounts of TA (Table **2.3**, 0.01–0.05 mol%) combined with 10 molar equivalents of TBAI (with respect to TA) as nucleophile.

Table 2.3: Tannic acid mediated synthesis of cyclic carbonate 2.9b under different reaction conditions.



2.9a 2.9b

Entry	TA [mol%]	NBu_4I [mol%]	t [h]	Conv. [%]	Yield [%][a]	TON [b]	TOF[c] [h^{-1}]
1	0.05	0.5	24	96	86	1721	72
2	–	0.5	24	36	32	–	–
3	0.05	0.5	66	100	100	1985	30
4	–	0.5	66	76	76	–	–
5	0.01	0.1	24	26	24	2220	92
6	–	0.1	24	18	16	–	–
7	0.01	0.1	66	53	45	4458	68
8	–	0.1	66	55	48	–	–

General reaction conditions: 1,2-epoxyhexane **2.9a** (10 mmol), pCO_2^0 = 10 bar, 80 ºC, MEK (5 mL), AMTEC reactor. [a] Yield determined by ^1H NMR ($CDCl_3$) using mesitylene as an internal standard. Selectivity for the cyclic carbonate **2.9b** was >99%. [b] Total turnover number per TA equivalent based on reported yields. [c] Average turnover frequency per TA equivalent based on reported yields.

At 0.05 mol% of TA (Table **2.3**, entry 1), cyclic carbonate **2.9b** was produced in 86% yield after 24 h with a high TON of 1721 and an average TOF of 72 h^{-1}. Notably, in the absence of TA (Table **2.3**, entry 2), cyclic carbonate **2.9b** is produced only in 32% yield. The increase in total reaction time to 66 h (Table **2.3**, entries 3 and 4) reduces this difference as expected, which may also be an effect of partial catalyst degradation. When the TA

loading was further reduced to 0.01 mol% (Table **2.3**, entries 5 and 7), the difference between the binary catalytic system and the TBAI alone becomes less significant, despite the higher and valuable TONs observed (TON = 2220 after 24 h and TON = 4458 after 66 h). Obviously the long-term stability plays a key role to attain high average activity.

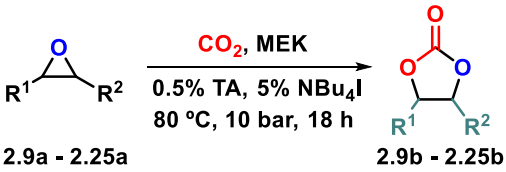
2.2.5 – Substrate scope

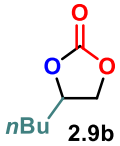
Next, the substrate scope was investigated (Scheme **2.5**) using conditions that would allow high conversion of the epoxide substrates **2.9a – 2.25a** at the reported temperature (80 ºC) and pressure (10 bar). All cyclic carbonate products **2.9b – 2.25b** were produced in a high-throughput reactor system at a 2.0 mmol substrate scale. Most of the substrates were converted in high conversion and selectivity with good to excellent isolated yields up to 94% (except for **2.15b**; 57%). Under these reaction conditions the synthesis of **2.9b** was also probed in the absence of tannic acid TA providing only a low yield of 22%.

The binary catalytic system comprised by TA/TBAI tolerates a number of functional groups including alcohol (compound **2.13b**), alkyl halide (compound **2.14b**), heterocyclic ring systems (compound **2.15b**), carbamate (compound **2.16b**), ether (compound **2.17b**, **2.20b**, **2.23b** and **2.24b**), alkene (compound **2.22b**) and alkyne (compound **2.24b**) groups. Furthermore, the sterically more hindered substrate **2.18a** could also be converted (69%) with an isolated yield of 40% for cyclic carbonate **2.18b**, whereas the internal epoxide **2.19a** gave, as expected, much poorer results in line with the more challenging nature of this conversion for organocatalytic catalyst systems.[46]

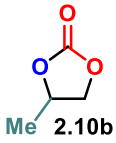
The conversion of internal epoxides was recently computed to be more energetically demanding (higher kinetic barriers) as compared to terminal epoxides.[52] Nonetheless, the formation of all carbonates was mediated by a catalyst loading of TA of only 0.5 mol%, which is an attractive feature within the context of providing a sustainable and reactive alternative for metal-based carbonate formation reactions.

Scheme 2.5: Substrate scope for the tannic acid mediated synthesis of cyclic carbonates.

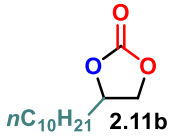




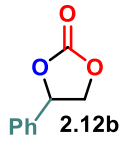
Conv: >99%
Yield: 89%
Sel: >99%



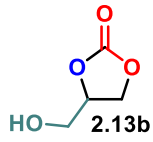
Conv: >99%
Sel: >99%
Yield: 87%



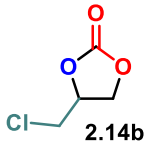
Conv: 93%
Yield: 90%
Sel: >99%



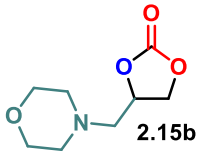
Conv: 87%
Yield: 76%
Sel: >99%



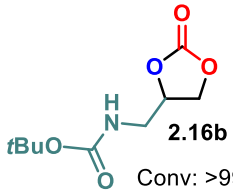
Conv: >99%
Yield: 83%
Sel: >99%



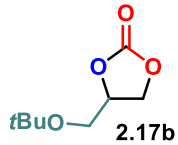
Conv: >99%
Yield: 87%
Sel: >99%



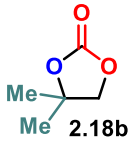
Conv.>99%
Yield: 57%
Sel: >99%



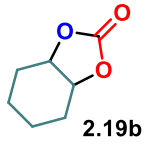
Conv: >99%
Yield: 91%
Sel: >99%



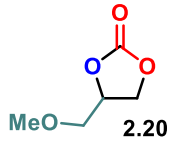
Conv: 97%
Yield: 77%
Sel: >99%



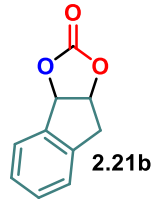
Conv: 69%
Yield: 40%
Sel: >99%



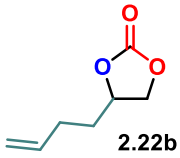
Conv: 15%
Yield: 9%
Sel: >99% (*cis*)



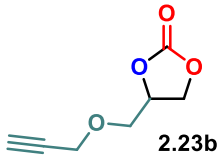
Conv: >99%
Yield: 92%
Sel: >99%



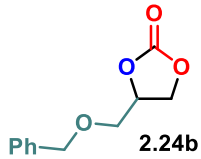
Conv: >99%
Yield: 72%
Sel: >99%



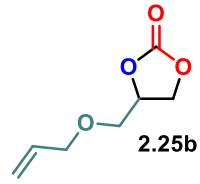
Conv: 85%
Yield: 81%
Sel: >99%



Conv: >99%
Yield: 93%
Sel: >99%



Conv: >99%
Yield: 94%
Sel: >99%



Conv: 97%
Yield: 86%
Sel: >99%

2.3 – Conclusions

In summary, we here present a novel binary catalytic system based on a naturally occurring and fairly cheap polyphenol (tannic acid), which shows excellent catalytic reactivity at exceptionally low loadings (only 0.5 mol%) being thus an attractive and sustainable organocatalytic alternative. Comparative catalysis studies have indicated that some degree of synergy between the various poly(phenol) units within the tannic acid structure that may help to increase catalyst lifetime, providing conceptually an interesting approach to further improve the potential of polyphenol-based organocatalysis in the area of CO_2 conversion. The development of a recycling process for the binary catalytic system shows great potential, especially in terms of catalyst regeneration by treatment with cheap hydrochloric acid. Terminal epoxides can be easily transformed under mild conditions and low catalyst loadings with excellent functional group diversity. The transformation of internal epoxides remains, however, challenging and other strategies are thus warranted for their effective conversion in the area of cyclic carbonate synthesis.

2.4 – Experimental section

2.4.1 – General information and instrumentation

General Information

Methyl ethyl ketone (MEK) and carbon dioxide (purchased from PRAXAIR) were used as received without further purification or drying *prior to* use. All phenolic compounds (tannic acid, pyrogallol, catechol and propyl gallate) were commercially purchased from Sigma Aldrich and used without any further purification. The tannic acid (TA) was reagent grade.[49] ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AV-300, AV-400 or AV-500 spectrometer and referenced to the residual deuterated solvent signals. FT-IR measurements were carried out on a Bruker Optics FTIR-ATR TR0 spectrometer. Thermogravimetric analyses were performed with a Mettler Toledo TGA/SDTA851 under N_2, heating between 25 and 500 ºC at a 10 ºC/min heating rate.

2.4.2 – Synthesis of epoxides

Synthesis of epoxides 2.15a, 2.16a and 2.21a

4-(Oxiran-2-ylmethyl)morpholine (compound **2.15a**),[53] *tert*-butyl-(N-propyl-2-oxirane) carbamate (compound **2.16a**)[54] and indene oxide (compound **2.21a**),[55] were prepared according to previously reported synthetic protocols.

2.4.3 – General procedure for catalytic experiments

Standard autoclave screening experiments

All reactions were performed in a 30 mL stainless steel reactor. In a typical experiment, a solution of tannic acid (0.050 mol%, 7.05 mg), tetrabutylammonium iodide (compound **2.5**; TBAI) (2 mol%, 61.3 mg), 1,2-epoxyhexane **2.9a** (8.30 mmol, 831 mg) and mesitylene

(1.00 mL, 7.18 mmol) in MEK (5 mL) were charged into a stainless steel reactor. Three cycles of pressurization and depressurization of the reactor with a pressure of CO_2 of 5 bar were carried out before finally stabilizing the pressure at 10 bar. The reactor was then heated to the required temperature and the mixture stirred for another 18 h. Then the reactor was cooled down, depressurized and an aliquot of the solution was analysed by ^{1}H NMR spectroscopy using $CDCl_3$ as the solvent. The yield was determined using mesitylene as the internal standard. In all cases, selectivity for the cyclic carbonate products was determined to be >99%.

Substrate scope experiments

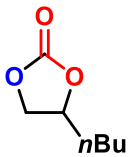
All reactions were performed in an SPR16 Slurry Phase Reactor (Amtec GmbH). First, tannic acid (0.5 mol%, 17.0 mg) and tetrabutylammonium iodide (compound **2.5**; TBAI, 5 mol%, 36.9 mg) were put into the reactors. Then, the AMTEC reaction vessels were tested for leaks charging with 15 bar of N_2 to finally reduce the pressure to 2 bar. After injection of the selected epoxide into the reactors (example: 2.00 mmol, 200 mg in the case of 1,2-epoxyhexane, compound **2.9a**) in MEK (5 mL) and using mesitylene (10.0 mol%, 24.0 mg) as internal standard (IS), the vessels were heated to the desired reaction temperature (80 ºC). Once reaching the operating temperature, the CO_2 pressure was raised to 10 bar and the reaction mixture was stirred at the appropriate temperature for 18 h. At the end of the reaction, analysis of the crude product was done as reported above in the screening phase. Isolated yields and ^{1}H and ^{13}C NMR spectra and IR spectra of all products prepared this way (cyclic carbonates **2.9b – 2.25b**) were obtained by removing the solvent and unreacted substrate under vacuum (at 0.5 mbar). The residue was then dissolved in DCM (except for the conversion of substrate **2.13a** for which the solvent was ethyl acetate) and filtered through a path of silica. After removal of the solvent, the pure cyclic carbonate products were then obtained. The identity of each of the carbonate products was confirmed by comparison to previously reported literature data.

Recycling experiments

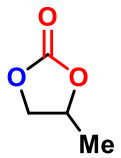
All reactions were performed in a 45 mL stainless steel reactor. In a typical experiment, a solution of tannic acid (0.250 mol%, 25.5 mg), tetrabutylammonium iodide (**2.5**; TBAI,

2.50 mol%, 55.4 mg) and 1,2-epoxy-dodecane (compound **2.11a**, 6.00 mmol, 1.25 g) in MEK (15 mL) was added to a stainless steel reactor. Three cycles of pressurization and depressurization of the reactor with a pressure of CO_2 of 5 bar were carried out before finally stabilizing the pressure at 10 bar. The reactor was then heated to the required temperature and the mixture left stirring for an additional 18 h. Then the reactor was cooled down, depressurized and the reaction mixture was separated from the precipitate (solid 1; **FR1**) and moved to a flask. The solvent was removed under vacuum and hexane (80 mL) was added. Then the hexane solution was cooled to –30 ºC. After 3 h, the flask was then warmed up to r.t. and the solution was then filtered and the collected precipitate (solid 2; **FR2**) was washed with hexane (80 mL). The combined organic phases were then concentrated under vacuum to get the pure cyclic carbonate (**2.11b**). For a new reaction cycle, first the catalyst was regenerated by treatment of **FR1** with concentrated HCl for 18 h. The mixture was filtered and washed with diethyl ether and hexane. The obtained precipitate was dried under vacuum and combined with **FR2** for a new catalytic cycle in MEK (15 mL) and transferred to a pressure reactor. Then 1,2-epoxydodecane (**2.11a**, 6.0 mmol, 1.25 g) was added and the autoclave was charged with carbon dioxide following the previously reported procedure.

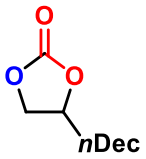
2.4.4 – Spectroscopic data for all compounds



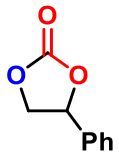
Compound 2.9b; 4-butyl-1,3-dioxolan-2-one;[56] **^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ** 4.76 – 4.64 (m, 1H), 4.52 (m, 1H), 4.07 (dd, $^2J_{HH}$ = 8.3 Hz, $^3J_{HH}$ = 7.2 Hz, 1H), 1.89 – 1.76 (m, 1H), 1.74 – 1.63 (m, 1H), 1.52 – 1.30 (m, 4H), 0.93 (t, $^3J_{HH}$ = 6.9 Hz, 3H); **^{13}C NMR (75 MHz, $CDCl_3$, 298 K) δ** 155.19, 77.36, 69.52, 33.75, 26.60, 22.42, 13.96; **IR (neat, cm^{-1})** 1785 (C=O).



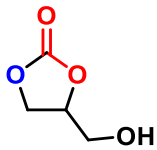
Compound 2.10b; Propylene Carbonate;[32] **^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ** 4.90 – 4.80 (m, 1H), 4.55 (dd, $^2J_{HH}$ = 8.3 Hz, $^3J_{HH}$ = 7.7 Hz. 1H), 4.02 (dd, $^2J_{HH}$ = 8.3 Hz, $^3J_{HH}$ = 7.2 Hz, 1H), 1.49 (d, $^3J_{HH}$ = 6.3 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ** 155.09, 73.60, 70.75, 19.60; **IR (neat, cm^{-1})** 1781 (C=O).



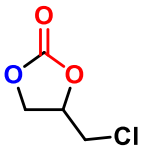
Compound 2.11b; 4-decyl-1,3-dioxolan-2-one;[57] **^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ** 4.76 – 4.63 (m, 1H), 4.56 – 4.46 (m, 1H), 4.06 (dd, $^{2}J_{HH}$ = 8.4 Hz, $^{3}J_{HH}$ = 7.3 Hz, 1H), 1.87 – 1.75 (m, 1H), 1.73 – 1.62 (m, 1H), 1.53 – 1.15 (m, 16H), 0.88 (t, $^{3}J_{HH}$ = 6.6 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ** 177.17, 77.16, 69.48, 33.95, 31.94, 29.60, 39.52, 29.41, 29.35, 24.44, 22.73, 14.16; **IR (neat, cm^{-1})** 1792 (C=O).



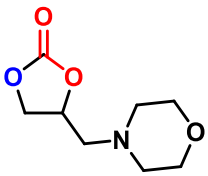
Compound 2.12b; 4-phenyl-1,3-dioxolan-2-one;[56] **^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ** 7.49 - 7.41 (m, 3H), 7.40 - 7.32 (m, 2H), 5.73 – 5.62 (m, 1H), 4.84 – 4.76 (m, 1H), 4.35 (dd, $^{2}J_{HH}$ = 8.6 Hz, $^{3}J_{HH}$ = 7.9 Hz, 1H); **^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ** 154.49, 135.94, 129.90, 129.41, 126.00, 78.12, 71.30; **IR (neat, cm^{-1})** 1778 (C=O).



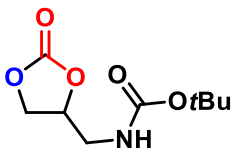
Compound 2.13b; 4-(hydroxymethyl)-1,3-dioxolan-2-one;[56] **^{1}H NMR (400 MHz, DMSO-d_6, 298 K) δ** 5.25 (bs, 1H), 4.79 (m, 1H), 4.54 – 4.45 (m, 1H), 4.28 (dd, $^{2}J_{HH}$ = 8.3 Hz, $^{3}J_{HH}$ = 5.8 Hz, 1H), 3.66 (dd, $^{2}J_{HH}$ = 12.6 Hz, $^{3}J_{HH}$ = 2.9 Hz, 1H), 3.51 (dd, $^{2}J_{HH}$ = 12.6 Hz, $^{3}J_{HH}$ = 3.3 Hz, 1H); **^{13}C NMR (101 MHz, DMSO-d_6, 298 K) δ** 155.15, 77.01, 65.86, 60.59; **IR (neat, cm^{-1})** 3426 (OH), 1773 (C=O).



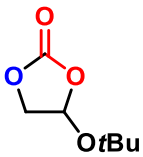
Compound 2.14b; 4-(chloromethyl)-1,3-dioxolan-2-one;[17] **^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ** 5.01 – 4.91 (m, 1H), 4.59 (dd, $^{2}J_{HH}$ = 8.8 Hz, $^{3}J_{HH}$ = 8.3 Hz, 1H), 4.41 (dd, $^{2}J_{HH}$ = 8.8 Hz, $^{3}J_{HH}$ = 5.7 Hz, 1H), 3.81 – 3.69 (m, 2H); **^{13}C NMR (75 MHz, $CDCl_3$, 298 K) δ** 154.19, 74.33, 67.11, 43.68; **IR (neat, cm^{-1})** 1780 (C=O).



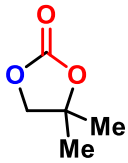
Compound 2.15b; 4-(morpholinomethyl)-1,3-dioxolan-2-one;[17] **^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ** 4.86 – 4.78 (m, 1H), 4.55 – 4.50 (m, 1H), 4.24 (dd, $^{2}J_{HH}$ = 8.3 Hz, $^{3}J_{HH}$ = 7.1 Hz, 1H), 3.69 (t, $^{3}J_{HH}$ = 4.9 Hz, 4H), 2.72 - 2.64 (m, 2H), 2.60 - 2.51 (m, 4H); **^{13}C NMR (126 MHz, $CDCl_3$, 298 K) δ** 154.91, 75.14, 67.97, 66.97, 60.51, 54.62; **IR (neat, cm^{-1})** 1781 (C=O).



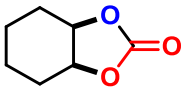
Compound 2.16b; 4-(*tert*-butylcarbamoylmethyl)-1,3-dioxolane;[58] **^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ** 5.07 (bs, 1H), 4.85 - 4.75 (m, 1H), 4.55 – 4.46 (m, 1H), 4.26 (dd, $^{2}J_{HH}$ = 8.6 Hz, $^{3}J_{HH}$ = 6.7 Hz, 1H), 3.53 - 3.41 (m, 2H), 1.43 (s, 9H); **^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ** 156.37, 154.87, 80.54, 75.96, 66.82, 42.27, 28.35; **IR (neat, cm^{-1})** 3349 (N-H), 1784 (C=O), 1688 (C=O).



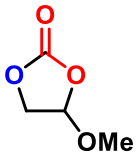
Compound 2.17b; 4-(*tert*-butoxymethyl)-1,3-dioxolan-2-one;[58] **^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ** 4.78 - 4.72 (m, 1H), 4.49 – 4.44 (m, 1H), 4.38 (dd, $^2J_{HH}$ = 8.2 Hz, $^3J_{HH}$ = 5.8 Hz, 1H), 3.60 (dd, $^2J_{HH}$ = 10.3 Hz, $^3J_{HH}$ = 4.6 Hz, 1H), 3.53 (dd, $^2J_{HH}$ = 10.3 Hz, $^3J_{HH}$ = 3.6 Hz, 1H), 1.19 (s, 9H); **^{13}C NMR (126 MHz, $CDCl_3$, 298 K) δ** 155.25, 75.27, 74.03, 66.71, 61.42, 27.43; **IR (neat, cm^{-1})** 1786 (C=O).



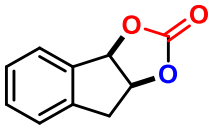
Compound 2.18b; 4,4-dimethyl-1,3-dioxolan-2-one;[59] **^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ** 4.14 (s, 2H), 1.52 (s, 6H); **^{13}C NMR (75 MHz, $CDCl_3$, 298 K) δ** 154.70, 81.79, 75.52, 26.21; **IR (neat, cm^{-1})** 1784 (C=O).



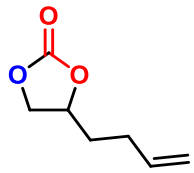
Compound 2.19b; (3aR,7aS)-hexahydrobenzo[d][1,3]dioxol-2-one;[60] **^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ** 4.71 – 4.63 (m, 2H), 1.93 – 1.82 (m, 4H), 1.69 – 1.54 (m, 2H), 1.47 – 1.34 (m, 2H); **^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ** 155.46, 75.85, 26.87, 19.26; **IR (neat, cm^{-1})** 1782 (C=O).



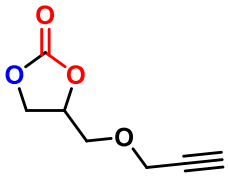
Compound 2.20b; 4-(methoxymethyl)-1,3-dioxolan-2-one;[42] **^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ** 4.84 – 4.76 (m, 1H), 4.51 – 4.46 (m, 1H), 4.37 (dd, $^2J_{HH}$ = 8.4 Hz, $^3J_{HH}$ = 6.1 Hz, 1H), 3.63 (dd, $^2J_{HH}$ = 10.9 Hz, $^3J_{HH}$ = 3.9 Hz, 1H), 3.58 (dd, $^2J_{HH}$ = 10.9 Hz, $^3J_{HH}$ = 3.8 Hz, 1H), 3.42 (s, 3H); **^{13}C NMR (126 MHz, $CDCl_3$, 298 K) δ** 155.00, 75.06, 71.61, 66.31, 59.79; **IR (neat, cm^{-1})** 1780 (C=O).



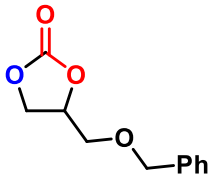
Compound 2.21b; 8,8a-dihydro-3aH-indeno[1,2-d][1,3]dioxol-2-one;[55] **^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ** 7.49 (d, $^3J_{HH}$ = 7.5 Hz, 1H), 7.40 – 7.38 (m, 1H), 7.37 – 7.28 (m, 2H), 5.99 (d, $^3J_{HH}$ = 6.7 Hz, 1H), 5.46 – 5.39 (m, 1H), 3.45 – 3.28 (m, 2H); **^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ** 154.81, 140.16, 136.52, 131.07, 128.23, 126.49, 125.67, 83.66, 79.88, 38.03; **IR (neat, cm^{-1})** 1781 (C=O).



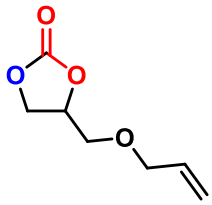
Compound 2.22b; 4-(but-3-en-1-yl)-1,3-dioxolan-2-one;[61] **^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ** 5.86 - 5.71 (m, 1H), 5.13 - 5.07 (m, 1H), 5.7 - 5.02 (m, 1H), 4.78 - 4.67 (m, 1H), 4.5- 4.50 (m, 1H), 4.08 (dd, $^3J_{HH}$ = 8.4 Hz, $^3J_{HH}$ = 7.2 Hz, 1H), 2.34 - 2.11 (m, 2H), 2.00 - 1.87 (m, 1H) 1.84 – 1.71 (m, 1H); **^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ** 155.04, 136.17, 116.61, 76.42, 69.44, 33.23, 28.80; **IR (neat, cm^{-1})** 1786 (C=O), 1642 (C=C).



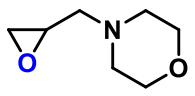
Compound 2.23b; 4-[(2-propyn-1-yloxy)methyl]-1,3-dioxolan-2-one;[58] **^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ** 4.90 – 4.80 (m, 1H), 4.54 – 4.48 (m, 1H), 4.40 (dd, $^{2}J_{HH}$ = 8.4 Hz, $^{3}J_{HH}$ = 6.1 Hz, 1H), 4.31 – 4.16 (m, 2H), 3.83 – 3.70 (m, 2H), 2.49 (t, $^{4}J_{HH}$ = 2.4 Hz, 1H); **^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ** 154.88, 78.63, 75.78, 74.74, 68.56, 66.34, 59.00; **IR (neat, cm^{-1})** 3284 (≡C–H), 2100 (C≡C), 1780 (C=O).



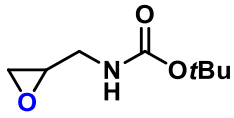
Compound 2.24b; 4-((benzyloxy)methyl)-1,3-dioxolan-2-one;[57] **^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ** 7.41 – 7.28 (m, 5H), 4.86 – 4.77 (m, 1H), 4.65 – 4.54 (m, 2H), 4.52 – 4.45 (m, 1H), 4.39 (dd, $^{2}J_{HH}$ = 8.3 Hz, $^{3}J_{HH}$ = 6.0 Hz, 1H), 3.71 (dd, $^{2}J_{HH}$ = 10.8 Hz, $^{3}J_{HH}$ = 4.1 Hz, 1H), 3.71 (dd, $^{2}J_{HH}$ = 10.8 Hz, $^{3}J_{HH}$ = 3.8 Hz, 1H); **^{13}C NMR (126 MHz, $CDCl_3$, 298 K) δ** 154.99, 137.17, 128.74, 128.26, 127.92, 75.07, 73.90, 68.97, 66.45; **IR (neat, cm^{-1})** 1792 (C=O).



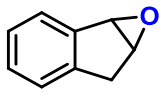
Compound 2.25b; 4-((allyloxy)methyl)-1,3-dioxolan-2-one;[61] **^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ** 5.95 – 5.79 (m, 1H), 5.28 - 5.22 (m, 2H), 4.87 – 4.76 (m, 1H), 4.53 – 4.45 (m, 1H), 4.43 – 4.35 (m, 1H), 4.13 – 3.98 (m, 2H), 3.72 – 3.65 (m, 1H), 3.64 – 3.57 (m, 1H); **^{13}C NMR (126 MHz, $CDCl_3$, 298 K) δ** 155.02, 133.77, 118.07, 75.12, 72.74, 68.97, 66.41; **IR (neat, cm^{-1})** 1783 (C=O).



Compound 2.15a; 4-(oxiran-2-ylmethyl)morpholine;[53] **^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ** 3.74 (t, $^{3}J_{HH}$ = 4.6 Hz, 4H), 3.13 – 3.07 (m, 1H), 2.80 – 2.75 (m, 1H), 2.74 – 2.71 (m, 1H), 2.64 – 2.56 (m, 2H), 2.54 – 2.46 (m, 3H), 2.30 – 2.22 (m, 1H); **^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ** 66.99, 61.52, 54.20, 50.25, 44.90; **IR (neat, cm^{-1})** 1115 (C–O–C).



Compound 2.16a; *tert*-butyl (oxiran-2-ylmethyl)carbamate;[54] **^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ** 4.82 (bs, 1H), 3.62 – 3.44 (m, 1H), 3.28 – 3.14 (m, 1H), 3.12 – 3.04 (m, 1H), 2.86 – 2.74 (m, 1H), 2.63 – 2.55 (m, 1H), 1.44 (s, 9H); **^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ** 156.04, 79.71, 50.93, 45.12, 41.78, 28.44; **IR (neat, cm^{-1})** 3300 (N–H), 1785 (C=O), 1175 (C–O–C).



Compound 2.21a; 1a,6a-dihydro-6H-indeno[1,2-b]oxirene;[55] **^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ** 7.53 – 7.49 (m, 1H), 7.30 – 7.18 (m, 3H), 4.29 – 4.27 (m, 1H), 4.16 – 4.12 (m, 1H), 3.26 – 3.19 (m, 1H), 2.99 (dd, $^2J_{HH}$ = 17.9 Hz, $^3J_{HH}$ = 2.9 Hz, 1H); **^{13}C NMR (75 MHz, $CDCl_3$, 298 K) δ** 143.60, 140.91, 128.61, 126.28, 126.13, 125.24, 59.19, 57.75, 34.67; **IR (neat, cm^{-1})** 1736 (C–O–C).

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Chapter III

Squaramide based organocatalysts in cyclic carbonate synthesis

Squaramides are presented as highly modular, easy to optimize and highly efficient catalysts for the conversion of epoxides and carbon dioxide into cyclic carbonates. The catalytic potential of these squaramides, in combination with a suitable halide nucleophile, is particularly noted when internal epoxides are examined as substrates and their transformation into disubstituted cyclic carbonates marks a rare case of an effective organocatalyst for these challenging conversions. Control experiments support the mechanistic view that the squaramides are predominantly involved in the stabilization of intermediate oxo- and carbonato-type anions which, after their formation, are able to displace a bromide nucleophile from an initially formed 1:1 assembly comprising the squaramide host.

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UNIVERSITAT ROVIRA I VIRGILI
ORGANOCATALYTIC TRANSFORMATIONS OF CARBON DIOXIDE AND CYCLIC CARBONATES
Sergio Sopeña de Frutos

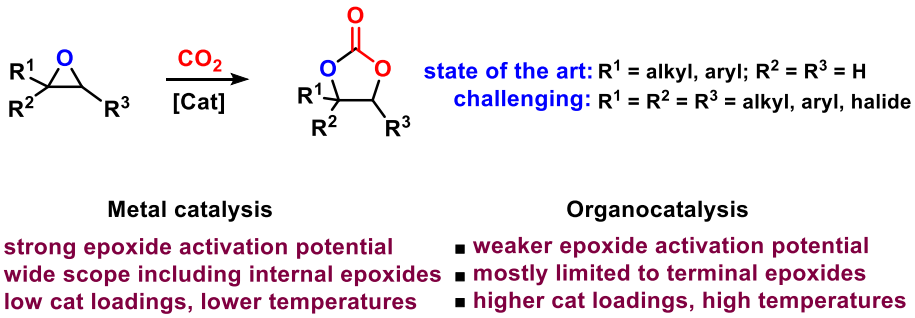
3.1 – Introduction

Small molecule activation, and particularly carbon dioxide (CO_2) conversion, continues to challenge the synthetic communities to devise more efficient and sustainable catalysis protocols. CO_2 is a renewable carbon feed stock that has shown potential to provide an alternative for some fossil fuel based chemical synthesis,[1–4] though generally there still exists a requirement for new catalyst development to expand on the portfolio of organic compounds that can be derived from this waste molecule.[5–11] Despite the high kinetic stability, catalysis has manifested itself as the primary technology for the conversion and fixation of CO_2. Among the most widely studied reactions that utilize CO_2 as a substrate are those that lead to either cyclic[12–18] or poly-carbonates,[19–21] using cyclic ethers as reaction partners. Both categories of organic carbonates have attracted interest from academic and industrial communities, and various commercial processes have now been developed.

The synthesis of cyclic carbonates has witnessed a spectacular progress over the last decade with the field being clearly dominated by metal-catalyzed approaches.[22–28] Indeed, homogeneous metal catalysis has demonstrated to solve a series of important challenges in the area including the use more challenging cyclic ether substrates such as internal di-[29–36] and trisubstituted epoxides,[37–41] and oxetanes.[42–45] Recently, metal-free approaches have been presented as sustainable alternatives for metal-catalyzed formation of cyclic carbonates.[46–50] Intrinsically, organocatalytic activation of the cyclic ether substrates is less powerful compared to metal-based conversions (see Scheme **3.1**). As a result, poorer overall kinetics and substrate scope are typically observed requiring thus significantly higher catalyst loading and/or reaction temperatures.

Among the substrate activation strategies, hydrogen-bonding (HB) has been prevalent and has delivered a simple though effective means towards organocatalytic formation of cyclic carbonates from CO_2 and mostly terminal epoxides.[51–60] However, in order to uplift the potential of organocatalysis, new strategies are warranted in order to be more competitive to metal catalyzed cyclic carbonate synthesis. Principally, the coupling of internal epoxides and CO_2 remains a challenging task with limited evolution in cyclic carbonate product scope observed over the years.[58,59,61–63]

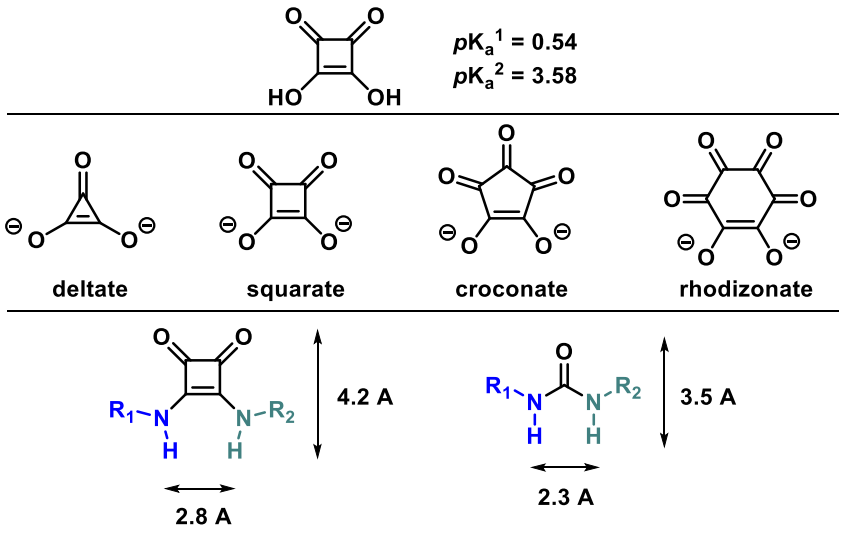
Scheme 3.1: Comparison of organocatalytic and metal-based approaches in cyclic carbonate formation.



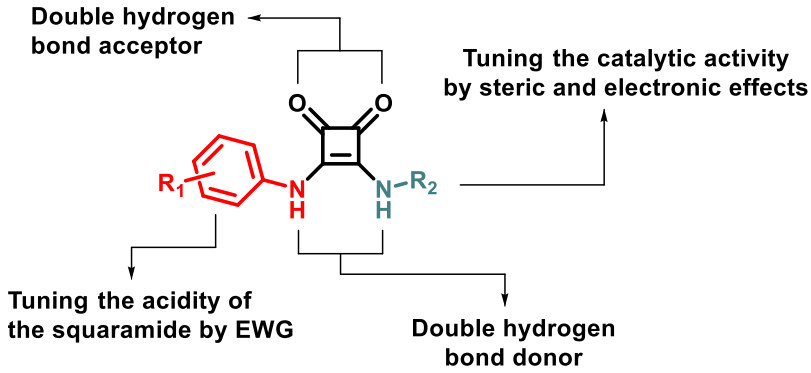
Recent developments in the area of hydrogen-bonding catalysis of cyclic carbonate formation have demonstrated that catalyst design plays an imperative role to boost activity. For instance, Dufaud reported on cavitand-based hosts for ammonium guests thereby increasing the reactivity of the counter-anion (nucleophile) towards ring opening of the epoxide and subsequent cyclic carbonate formation.[64] Jerome, Tassaing, Detrembleur and coworkers developed binary catalysts based on fluorinated alcohols that are highly active catalysts for terminal epoxide/CO_2 couplings,[65] whereas Werner communicated the use of various attractive, modular bifunctional phosphonium and ammonium based organocatalysts.[56,59,66] However, organocatalysts that are able to mediate the coupling reaction between internal epoxides and CO_2 under comparatively mild conditions remain scarce.[63,67,68] In this context, in 2016 Kleij and coworkers reported a cavitand-based polyphenols as binary catalytic systems that show interesting potential towards internal epoxide/CO_2 couplings, and these systems also showed very high turnover numbers (TONs) and initial turnover frequencies (TOFs) of up to 500 h^{-1} for terminal epoxide conversion into mono-substituted cyclic carbonates.[67]

During the search towards more powerful catalysts for cyclic carbonate formation, we considered the use of squaramides (Scheme **3.2**) as these structures have been shown to have excellent substrate activation potential in the area of organocatalysis.[69] Importantly, these squaramides have highly modular properties and can be built up stepwise[70–73] providing either sterically and electronically tunable symmetrical or nonsymmetrical structures (Scheme **3.3**). Squaramides have previously been shown to strongly bind halide anions[74–77] which are useful nucleophilic components of binary catalysts for cyclic carbonate formation.

Scheme 3.2: General information related to squaramides and comparison with ureas.



Scheme 3.3: Modular synthesis and tunable properties of the squaramide structure.



We anticipated that oxoanions, which are *in situ* produced by epoxide ring-opening, could easily displace halide nucleophile thereby forming a conceptually new catalytic approach in cyclic carbonate synthesis. Oxoanions have typically a stronger interaction with squaramides compared to halides, and the stabilization of oxoanionic species thus offers new unexplored potential to pre-organize both nucleophile and substrate favoring the preparation of cyclic carbonates.

Chapter III

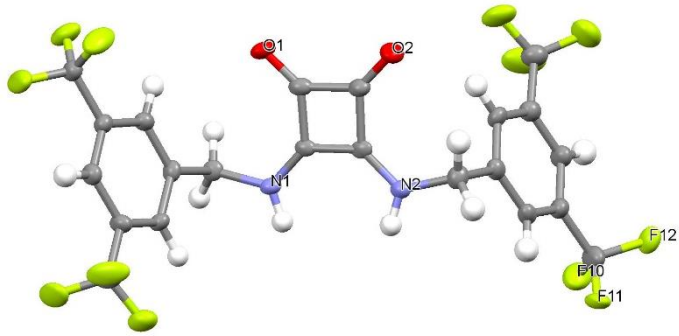
In this chapter, we demonstrate that squaramide based binary catalytic systems have exceptional potential for cyclic carbonate preparation, and moreover show unique behavior to facilitate the conversion of both terminal as well as internal epoxide substrates with high efficiency. The results illustrate that organocatalysis can offer a competitive and sustainable alternative to metal catalysis in this area of CO_2 conversion.

3.2 – Results and discussion

3.2.1 – Optimization of the catalyst structure

A series of symmetrically and non-symmetrically disubstituted squaramides **3.1 – 3.21** (Scheme **3.4**) were prepared to investigate the influence of their substitution on the catalytic performance of the squaramide in combination with tetrabutylammonium iodide (**3.24**, TBAI) as nucleophilic additive. Both symmetrical squaramides (**3.1 – 3.9,** Scheme **3.4**) as well as nonsymmetrically substituted squaramides (**3.10 – 3.21,** Scheme **3.4**) were considered. In order to facilitate a fair comparison among all binary catalytic systems, the use of 2-butanone (MEK) as solvent was required to maintain homogeneous solutions during the catalytic reactions.[a]

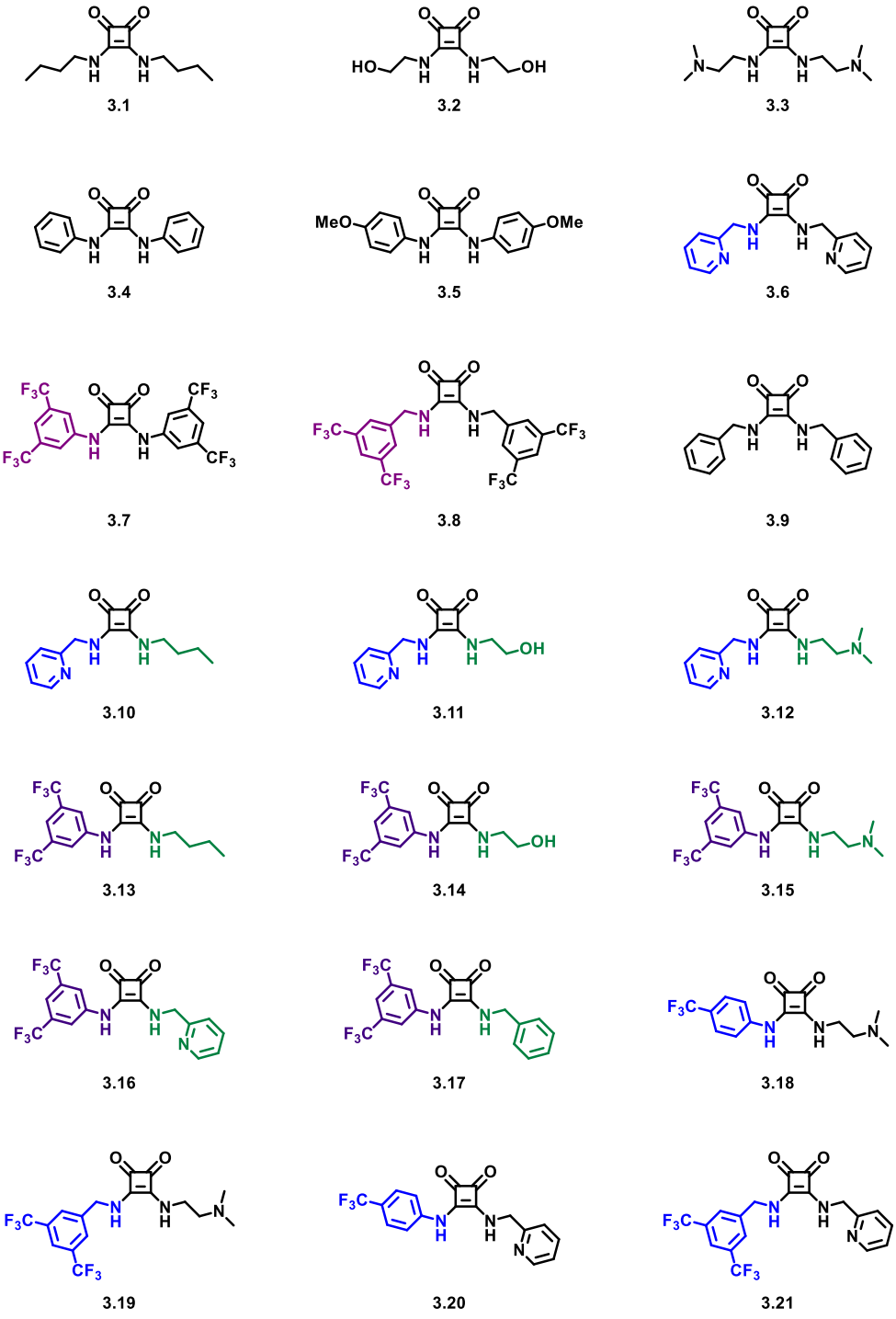
Figure 3.1: X-ray molecular structure of squaramide 3.8.



Under comparatively mild conditions (45 ºC, 10 bar) formerly used for polyphenol based binary catalysts,[55] the use of squaramide/TBAI combinations based on **3.1 – 3.9** (Table **3.1**, entries 1–9) resulted in various yields for cyclic carbonate **3.31b** (4–58 %). Both binary catalytic systems **3.6**/TBAI and **3.7**/TBAI gave the best results and comprise of secondary amide groups substituted by (2-pyridyl)methylene and bis-3,5-di-trifluoromethyl-aryl groups (cf., crystallographic analysis of squaramide **3.8**, Figure **3.1**).

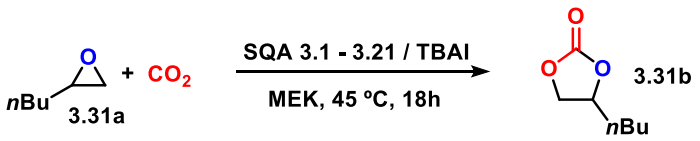
[a] **Note 1;** note that several symmetrical squaramides proved to be partially insoluble in neat 1,2-epoxyhexane and therefore MEK had to be added to solubilize these compounds.

Scheme 3.4: List of squaramide structures tested in this study.



Therefore, we prepared nonsymmetrical squaramides in a subsequent screening stage using at least one of these aforementioned substitutions, and the catalytic efficiency of compounds **3.10 – 3.21** was investigated in the formation of cyclic carbonate **3.31b** (Table **3.1**, entries 10–21). The most satisfactorily results (yield of **3.31b** up to 75%) were obtained with squaramides **3.15** and **3.16**, which both have one amide unit substituted by a bis-3,5-di-trifluoromethyl-aryl group flanked by a second amide unit having dimethylaminoethylene or a (2-pyridyl)methylene substitution, respectively (Table **3.1**, entries 15 and 16). Thus, for the best catalytic efficiency the presence of both electron-withdrawing and electron-donating NR-groups in the squaramide scaffold seems a requisite.

Table 3.1: Screening of binary catalytic systems based on squaramides 3.1 – 3.21 and TBAI in the conversion of 1,2-epoxyhexane and CO_2 into cyclic carbonate 3.31b.



Entry	SQA	Yield 3.31b [%][a]	Entry	SQA	Yield 3.31b [%][a]
1	3.1	36	**12**	3.12	30
2	3.2	4	**13**	3.13	53
3	3.3	46	**14**	3.14	56
4	3.4	16	**15**	3.15	75
5	3.5	54	**16**	3.16	74
6	3.6	58	**17**	3.17	59
7	3.7	52	**18**	3.18	58
8	3.8	28	**19**	3.19	42
9	3.9	10	**20**	3.20	65
10	3.10	44	**21**	3.21	36
11	3.11	16	**22**	–	0

General reaction conditions: 1,2-epoxyhexane **3.31a** (2.0 mmol), squaramide (5.0 mol%), TBAI (5.0 mol%), MEK (5.0 mL), pCO_2^0 = 10 bar, 45 ºC, 18 h, mesitylene (15 mol%); MEK = methyl ethyl ketone, SQA = squaramide. [a] Determined by ^{1}H NMR ($CDCl_3$) using mesitylene as internal standard. The selectivity towards **3.31b** was >99%.

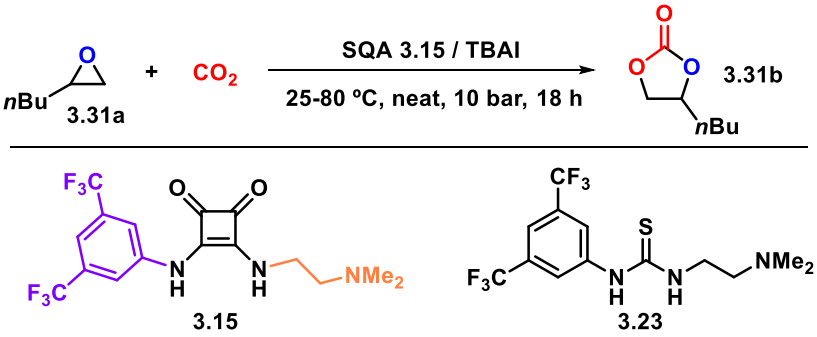
3.2.2 – Screening of terminal epoxides

Next, the catalytic protocol towards the formation of cyclic carbonate **3.31b** was optimized using **3.15**/TBAI as a binary catalytic system under *neat* conditions (Table **3.2**). The coupling of 1,2-epoxyhexane and CO_2 at 25 ºC showed an encouraging 64% yield of cyclic carbonate **3.31b** (Table **3.2**, entry 1). Increasing the initial pressure to 30 bar did not improve this yield (Table **3.2**, entry 2), but further variation of the **3.15**/TBAI ratio and reaction temperature proved to be beneficial (Table **3.2**, entries 3–14). A TBAI loading of 6.0 mol% increased the yield to 79% (Table **3.2**, entry 5) whereas higher reaction temperatures (45 and 80 ºC) gave as expected faster kinetics, thereby shortening the required time towards full conversion of the epoxide substrate. For instance, the reaction performed at 80 ºC with **3.15**/TBAI (both 2.0 mol%) was finished within 1 h with an appreciably high turnover frequency (Table **3.2**, entry 11; TOF = 85 h^{-1}).[b] Comparatively, the use of TBAI alone (in the absence of the squaramide) only gave 11% yield of cyclic carbonate **3.31b** (Table **3.2**, entry 12), thus clearly showing the beneficial presence of the squaramide. Interestingly, a thiourea-based hydrogen-bond epoxide activator (Compound **3.23**; Table **3.2**; entry 15) displayed much lower reactivity towards cyclic carbonate formation compared to the structurally related squaramide **3.15** (Table **3.2**, entry 11), emphasizing the crucial nature of the squaramide component towards the overall reactivity of the binary systems.

The kinetic profiles for the preparation of cyclic carbonate **3.31b** from 1,2-epoxyhexane **3.31a** and CO_2 were also determined at 25, 45 and 80 ºC (Figure **3.2**). Importantly, the halide additive gave much poorer catalysis compared to the binary catalytic system **3.15**/TBAI (Table **3.2**; entries 8, 9, 12 and 14) in the temperature range 25–80 ºC with, for instance, only 11% yield of **3.31b** at 80 ºC after 1 h. Therefore, the coupling of 1,2-epoxyhexane and CO_2 seems to be quite efficient at 80 ºC using equimolar amounts (2.0 mol%) of squaramide **3.15** and TBAI.

[b] **Note 2;** we also prepared a bifunctional version of squaramide **3.15** with a triethylammonium iodide end group. This catalyst (compound **3.22**) provided at a 0.05 mol% of catalyst loading and 80 ºC/10 bar a turnover number of 1100 in 66 h (average TOF = 17 h^{-1}). This result indicates that supported version of squaramide **3.15** (using for instance a benzyl bromide functionalized polystyrene commercially available from Sigma Aldrich) may hold promise to recycle these types of catalysts.

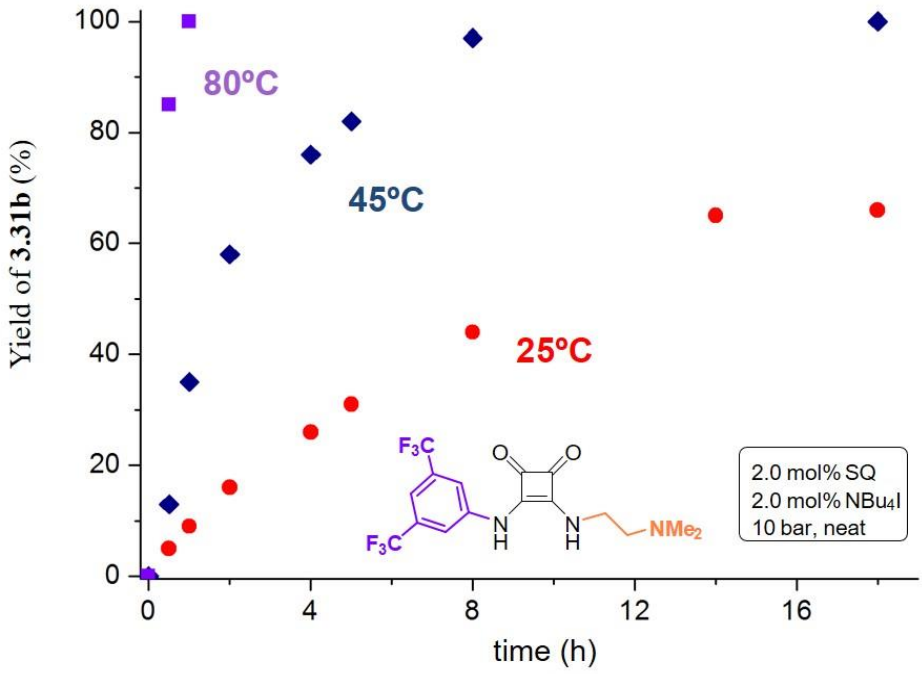
Table 3.2: Optimization of the catalytic formation of cyclic carbonate 3.31b using squaramide 3.15 and TBAI as binary catalytic system.



Entry	Catalyst [mol%]	TBAI [mol%]	T [ºC]	t [h]	Yield 3.31[b] [%]a
1	2.0	2.0	25	18	64
2[b]	2.0	2.0	25	18	53
3	4.0	2.0	25	18	67
4	1.0	2.0	25	18	47
5	2.0	6.0	25	18	79
6	2.0	4.0	25	18	72
7	2.0	1.0	25	18	38
8	–	4.0	25	18	0
9	–	2.0	25	18	0
10	2.0	2.0	45	18	100
11	2.0	2.0	80	1	100[c]
12	–	2.0	80	1	11
13	3.0	6.0	25	18	86
14	–	6.0	25	18	0
15[d]	2.0	2.0	25	18	36

General reaction conditions: 1,2-epoxyhexane **3.31a** (8.0 mmol), catalyst (2.0 mol%), TBAI (2.0 mol%), neat, pCO_2^0 = 10 bar, 18 h, mesitylene (15 mol%). [a] Determined by ^1H NMR ($CDCl_3$) using mesitylene as internal standard. The selectivity towards **3.31b** was >99%. [b] Initial pressure was 30 bar. [c] Yield was 85% after 0.5 h, calculated TOF = 85 h^{-1}. [d] Using thiourea **3.23** (2.0 mol%) as hydrogen-bond activator.

Figure 3.2: Kinetic profiles for the formation of cyclic carbonate 3.31b at different reaction temperatures using squaramide 3.15 and TBAI as binary catalytic system.



3.2.3 – Screening of internal epoxides

The high activity profile for the squaramide-based binary catalytic system **3.15**/TBAI prompted us to investigate the potential of this system in the conversion of more challenging internal epoxides, and cyclohexene oxide (**3.32a**, CHO) was chosen as a benchmark substrate (Table **3.3**). Various co-catalytic nucleophiles including tetrabutylammonium bromide (**3.25**, TBAB) tetraethylammonium bromide (**3.26**, TEAB), potassium bromide (**3.27**, KBr) and bis[triphenylphosphine]iminium chloride (**3.28**, PPNCl) were examined.[c]

First TBAB was considered (Table **3.3**, entries 1–6) and the combination of 2.0 mol% of squaramide **3.15** with 4.0 mol% TBAB provided a 73% yield of cyclic carbonate **3.32b** (Table **3.3**, entry 1). Lowering the TBAB loading was not favorable towards product

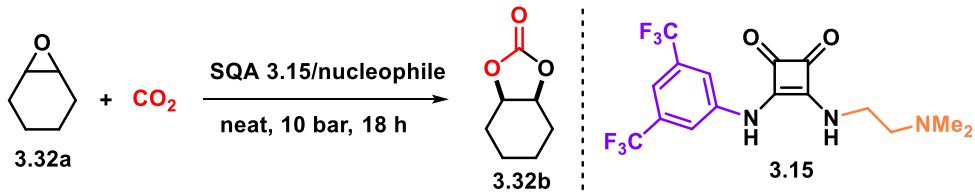
[c] **Note 3;** the preferential use of bromide and chloride nucleophiles for internal epoxides is based on previous results reported in the literature. Check references [51 - 63]

formation, not even in the presence of a higher amount of squaramide **3.15** (Table **3.3**, entries 2 and 4). The use of TBAB alone also gave an appreciable yield of cyclic carbonate **3.32b** (Table **3.3**, entries 5 and 6). Therefore, too competitive interactions of the squaramide with the halide anion reduce the ability to convert internal epoxides as the HB-assisted ring opening of the latter is significantly slower compared with terminal epoxides.

This hypothesis was further supported by the use of a chloride-based nucleophile, PPNCl (Table **3.3**, entries 7 and 8); the binary catalytic system **3.15**/PPNCl proved to be significantly less active than the nucleophilic additive itself and strong binding of the chloride by the squaramide is apparent.[76,77] Therefore, other bromide-based nucleophiles were then screened (Table **3.3**, entries 9–16) to improve the dynamic exchange of the bromide anion by *in situ* generated oxoanions. Whereas the use of KBr (**3.27**; Table **3.3**, entries 9 and 10) was not productive, the presence of TEAB (**3.26**; Table **3.3**, entries 11-16) showed promise in terms of yield of cyclic carbonate **3.32b**, and a clear positive influence of the squaramide **3.15** on the catalytic activity was noted. However, in several reactions, we noted that the nucleophilic additive alone was not (fully) soluble under neat conditions, which makes it difficult to assess the actual influence of the squaramide on the conversion kinetics. Fortunately, in the presence of propylene carbonate as a solvent we were able to assess this aspect properly (Table **3.3**, entries 15 and 16), and about a five-fold increase in the yield of cyclic carbonate **3.32b** was noted when the binary catalyst system was used (87 vs. 18%).

This clearly demonstrates the beneficial character of using a binary catalytic system that comprises of a squaramide scaffold combined with this bromide-containing nucleophile (TEAB), with the latter exhibiting a stronger ion pairing effect compared to TBAB and thus a weaker interaction with the squaramide. The conditions reported in entries 13 and 15 of Table **3.3** thus seem to be optimal for the conversion of other internal epoxides as coupling partners for CO_2 using this organocatalytic binary system.

Table 3.3: Screening of conditions for the catalytic formation of cyclic carbonate 3.32b using squaramide 3.15 and various nucleophiles as binary catalytic systems.



Entry	SQA 3.15 [mol%]	Nu [mol%]	T [ºC]	P [bar]	Yield 3.32b [%][a]
1	2.0	TBAB, 4.0	80	10	73
2	2.0	TBAB, 2.0	80	10	37
3	2.0	TBAB, 2.0	80	30	55
4	4.0	TBAB, 2.0	80	10	51
5	–	TBAB, 2.0	80	10	36
6	–	TBAB, 4.0	80	10	50
7	2.0	PPNCl, 2.0	80	10	14
8	–	PPNCl, 2.0	80	10	57
9	2.0	KBr, 4.0	80	10	1[b]
10	–	KBr, 4.0	80	10	0[b]
11	2.0	TEAB, 4.0	80	10	59
12	–	TEAB, 4.0	80	10	1[b]
13	3.0	TEAB, 6.0	80	30	88
14	–	TEAB, 6.0	80	30	1[b]
15[c]	3.0	TEAB, 6.0	80	30	87
16[c]	–	TEAB, 6.0	80	30	18

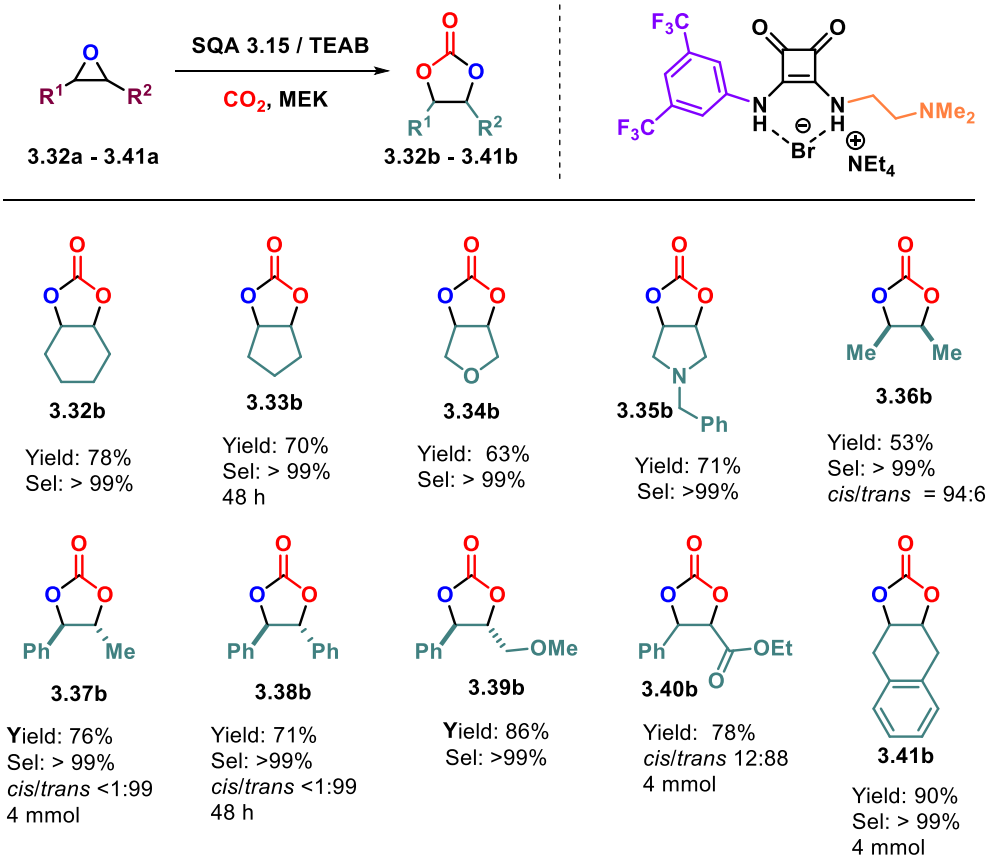
General reaction conditions: cyclohexene oxide **3.32a** (8.0 mmol), squaramide **3.15** (2.0 – 4.0 mol%), nucleophile (2.0 – 6.0 mol%), neat, pCO_2^0 = 10 bar, 18 h, mesitylene (15 mol%). Nu stands for the nucleophilic additive. [a] Determined by ^{1}H NMR ($CDCl_3$) using mesitylene as internal standard. The selectivity towards **3.32b** was >99%, and only the *cis*-isomer was formed. [b] Not fully soluble. [c] Propylene carbonate (1.5 mL) was used as a solvent.

3.2.4 – Substrate scope

Next, the scope in internal epoxide substrates was investigated (Scheme **3.5**; synthesis of cyclic carbonates **3.32b – 3.41b**) to further evaluate the efficiency of the binary catalytic system **3.15**/TEAB (3.0 and 6.0 mol%, respectively) at 80 ºC and 30 bar. Various substitution patterns in the epoxide partner were examined and fortunately, the developed protocol proved to be beneficial towards the preparation of a wide variety of cyclic carbonate products in appreciable isolated yields (53–90%).

Whereas the benchmark product (cyclohexene carbonate **3.32b**) was isolated in 78% yield (*cis* isomer), also five-membered bicyclic epoxides could be converted into their corresponding cyclic carbonates (**3.33b** and **3.35b**) in good yields despite the fact in the synthesis of **3.33b** we observed slower conversion kinetics. Cyclic carbonates **3.34b** and **3.35b** that incorporate additional heteroatoms were also isolated in similar yields as obtained for cyclic carbonate **3.32b**. Next, a series of disubstituted acyclic epoxides with different size features were tested and these could all be converted into their cyclic carbonates **3.36b – 3.40b** in good yields and chemoselectivities. Notably, epoxides with an increasing degree of steric impediment were tolerated including those that can combine a phenyl and methyl fragment (**3.37b**), a phenyl and ethyl ester substituent (**3.40b**; original *cis*/*trans* ratio retained), two phenyl groups (**3.38b**) or having a phenyl/methoxymethyl combination (**3.39b**). The scope in cyclic carbonate products displayed in Scheme **3.5** is among the widest reported for organocatalyst systems in this area, and more specifically for the conversion of internal epoxides.

Scheme 3.5: Substrate scope using squaramide 3.15 / TEAB (3.0/6.0 mol%) as binary catalytic system at 80 ºC, 30 bar initial pressure for 18 h, and on a 8.0 mmol scale. Deviations from this standard protocol are indicated in the scheme.

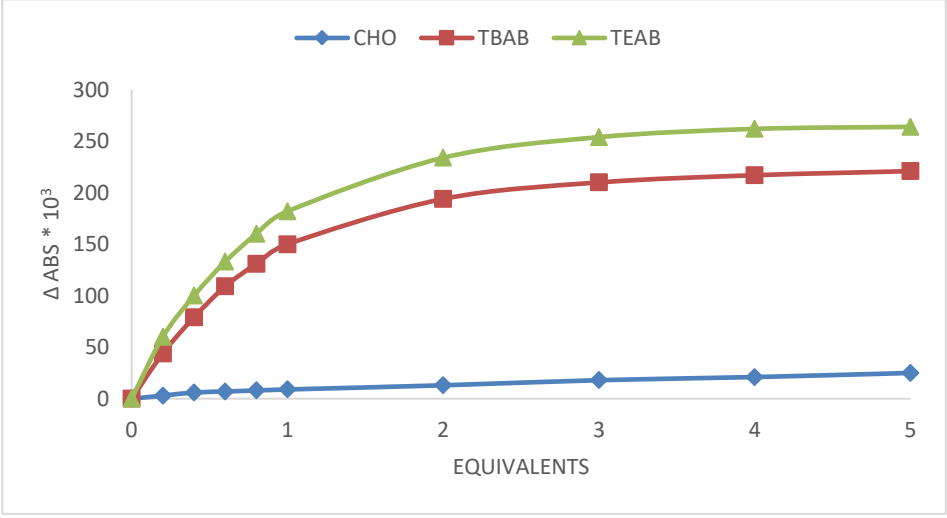


3.2.5 – UV and $^{1}H/^{19}F$ NMR titration studies

In order to gain more insight into the operating mechanism, various titration studies were carried out using symmetrical and nonsymmetrical squaramides **3.7** and **3.15**, and different anionic guests (Table **3.4**). As may be expected from previous literature[74–77] describing the interaction between halides and symmetrical squaramide hosts, bromide anions interact strongly with **3.7** and high association constants (K_{ass}) were determined when using either TBAB or TEAB (Table **3.4**, entries 1 and 2). Addition of a large excess (100 equiv) of cyclohexene oxide (**3.32a**; CHO) to host **3.7** did not provoke significant changes in the UV-Vis spectrum (Figure **3.3**) and apparently the interaction between squaramide **3.7** and CHO

is mostly weak. This also becomes apparent from ^{1}H NMR titration experiments (CD_3CN) using higher concentrations of squaramide **3.7** showing virtually no displacement of the signals corresponding to the host molecule when adding up to 100 equiv of CHO. More importantly, in the presence of 4 equiv of TBAB, squaramide **3.7** displays a significant downshift ($\Delta\delta$ = + 0.49 ppm) for the NH resonance (δ = 7.91 ppm) while the ArH signal (δ = 7.69 ppm) undergoes a modest upfield shift of –0.06 ppm. These characteristics do not change upon addition of 100 equiv of CHO to this 1:4 mixture of squaramide **3.7** and TBAB. This suggests that the epoxide is unable to compete with the bromide anion forming a hydrogen-bonded host-guest assembly. Consequently, this implies that the catalytic activity of squaramides in the formation of cyclic carbonates does not relate to initial activation of the epoxide through hydrogen bonding but, instead, it is primarily associated to their stabilization potential of oxoanionic species which evolve after ring opening of the epoxide substrate.

Figure 3.3: Variation in the absorbance of squaramide 3.7 at a chosen wavelength (λ = 330 nm) when different amounts of guest substrates were added.

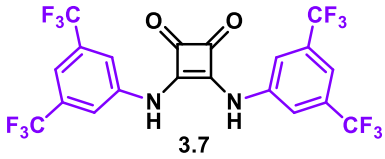


To further substantiate this hypothesis, oxoanions were used as titrants and added to a solution of nonsymmetrical squaramide **3.15** (the squaramide used in the optimization and substrate scope phases) and the determined association constants compared to the ones derived from addition of either TBAB or TEAB (Table **3.4**, entries 4–7) to squaramide **3.15**. Interestingly, clearly weaker association of bromide anions with nonsymmetrical host **3.15**

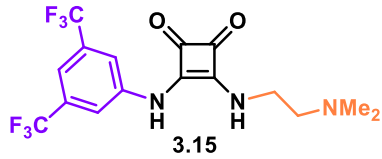
were revealed (Table **3.4**, entries 4 and 5) with K_{ass} about two orders of magnitude lower when compared with the titrations that involved symmetrical host **3.15** (Table **3.4**, entries 1 and 2).

In the presence of model oxoanionic species tetrabutylammonium *para*-nitrophenolate **3.29** [TBA(PNP)] and tetrabutylammonium acetate **3.30**, [TBA(AcO)], significantly higher K_{ass} values are determined for 1:1 host-guest binding of PNP and AcO to squaramide **3.15** (Table **3.4**, entries 6 and 7). Despite some disparity between the nature of the oxoanions that evolve after epoxide ring opening (cf., alkoxide stage) and CO_2 insertion into the alkoxide species (linear carbonate stage), these results provide a rational explanation for the more preferred binding of oxoanions with host **3.15**, a result that closely follows literature precedent for substantially stronger binding of oxoanions compared to halides by symmetrical squaramides.[76,77]

Table 3.4: Titration studies carried out with squaramides 3.7 and 3.15 and various salts.



3.7



3.15

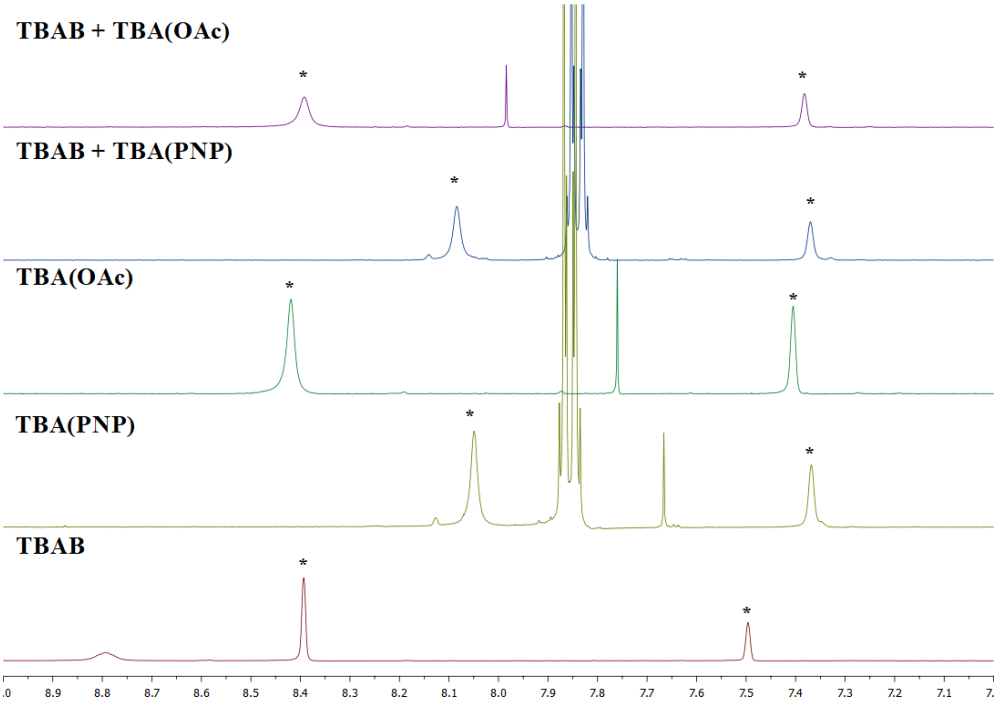
Entry	Guest	Host/Guest	Log (K_{ass})	K_{ass} ($\times 10^5$ M^{-1})
1	TBA**B**	**3.7**·TBA**B**	5.57	3.72
2	TEA**B**	**3.7**·TEA**B**	5.55	3.55
3	CHO	**3.15**·CHO	–[a]	–[a]
4	TBA**B**	**3.15**·TBA**B**	3.48	0.030
5	TEA**B**	**3.15**·TEA**B**	3.58	0.038
6	TBA(**PNP**)	**3.15**·TBA(**PNP**)	4.43	0.269
7	TBA(**OAc**)	**3.15**·TBA(**AcO**)	6.38	23.9

General conditions: [**3.7**] = 2.0 × 10^{-5} M or [**3.15**] = 2.5 × 10^{-5} M, CH_3CN, rt. Stock solutions of the guests had a concentration 100 – 1000 times higher than the host concentration. SQA = squaramide, CHO = cyclohexene oxide, TBA(PNP) = tetrabutylammonium *p*-nitro-phenolate, TBA(AcO) = tetrabutylammonium acetate. [a]Interaction was too weak to determine a reliable association constant.

This preferred binding is also noted when analyzing NMR solutions (CD_3CN) of **3.15**/TBA(OAc) and **3.15**/TBA(OAc)/TBAB (1:5 mixtures of **3.15** and OAc or Br),

respectively, and comparing these data with the spectroscopic features of **3.15**/TBAB. This comparison revealed that the chemical shifts noted in the ^{19}F and ^{1}H NMR spectra (Figure **3.4**) of the mixture of anions are closely related to those measured for **3.15**/TBA(OAc), and therefore this qualitative data is in line with the view that oxoanions indeed are able to compete for binding to the squaramide host in the presence of bromide.

Figure 3.4: Selected region of the ^{1}H NMR (400 MHz, CD_3CN, 298 K; 7.0-9.0 ppm) comparison of squaramide 3.15 (1 equiv) in the presence of different TBA salts (5 equiv) as indicated.



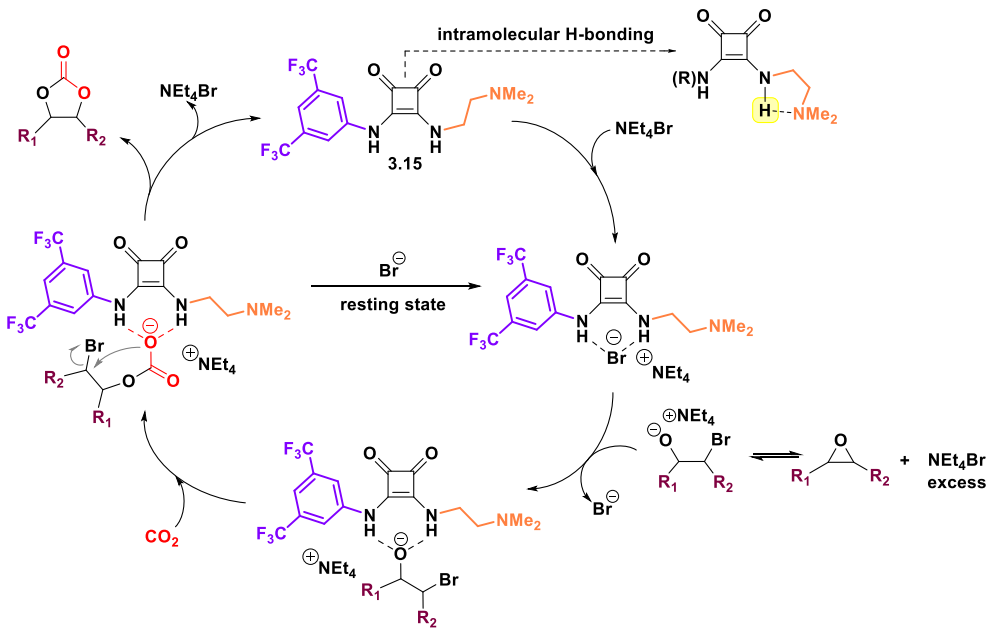
3.2.6 – Mechanism

From these titration studies and NMR control experiments a mechanistic profile for the binary catalytic **3.15**/TEAB is proposed (Scheme **3.6**). First, the squaramide **3.15** binds a bromide anion that originates from the TEAB additive that is present in excess to the host. Whereas epoxides are not likely to compete for binding to **3.15** in the presence of bromide, the excess of bromide can induce ring-opening of the epoxide substrate to give rise to an

alkoxide species that can displace the bromide anion in the intermediate **3.15**-Br and evolves towards the formation of an oxoanion-stabilized species.

Subsequently, reaction of this species with CO_2 gives rise to a linear carbonate (a second, strongly binding oxoanionic intermediate) that undergoes cyclization to produce the cyclic carbonate product and regenerates the squaramide **3.15**. Since bromide binding to **3.15** is strong, it is reasonable to suggest that the host-guest assembly **3.15**-Br can be considered as the resting state of this catalytic system, with the bromide anion that is released in the ring-closing step affording the carbonate product being captured by the squaramide host **3.15**. Notably, the squaramide is thus primarily involved in the stabilization of oxanionic intermediates and not, as reported for the vast majority of organocatalysts in this area, in the initial activation step of the epoxide through hydrogen bonding.

Scheme 3.6: Proposed mechanistic manifold for the formation of cyclic carbonates by the binary squaramide based catalytic system 3.15/TEAB.

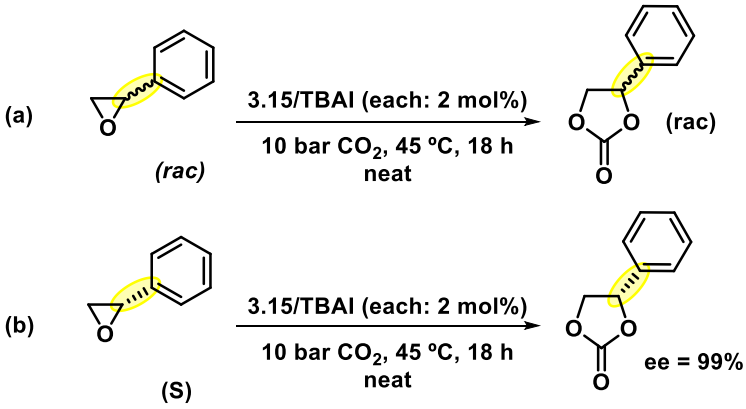


Squaramides **3.15** and **3.16** (the latter with a pending 2-pyridyl group) were shown to be the best systems for cyclic carbonate formation and this is likely a result of intramolecular hydrogen-bonding (Scheme **3.6**) of the alkyldimethylamino or pyridyl N-atom increasing to some extent the acidity of the involved NH fragment, therefore adding some further

stabilization of the oxoanionic intermediates and reducing the aggregation grade among the squaramides units.[78]

As observed for internal epoxide conversions (Scheme **3.5**), all reactions occur with retention of configuration pointing at a double-inversion pathway in line with the proposal of Scheme **3.6**. Further experimental evidence is provided by the coupling of CO_2 with (*S*)-styrene oxide using **3.15**/TBAB at 45 ºC and 10 bar: the product, styrene carbonate, was obtained stereospecifically with an *ee* of 99% (Scheme **3.7**).

Scheme 3.7: Control experiments related to the confirmation of a double inversion pathway.



3.3 – Conclusions

In summary, squaramides are presented in this chapter as modular and useful components of binary catalytic systems when combined with halides, and provide interesting new potential for the coupling of terminal and internal epoxides with CO_2 to prepare cyclic carbonates. As opposed to many organocatalysts that activate the epoxide by hydrogen bonding, the squaramides are primarily involved in the stabilization of oxoanionic species during catalysis and thus offer a new conceptual approach in this area.

This potential is illustrated by the conversion of 10 internal epoxides which are generally difficult substrates to activate especially by organocatalytic systems. Therefore, new catalyst designs may help to bridge the gap between metal- and organo-catalysis aiming towards improving the sustainability in cyclic carbonate synthesis and other related CO_2 conversion processes.

3.4 – Experimental section

3.4.1 – General information and instrumentation

General information

Methylethyl ketone (MEK) and carbon dioxide (purchased from PRAXAIR) were used as received without further purification or drying prior to use. ^{1}H NMR spectra were recorded on Bruker AV-300, AV-400 or AV-500 spectrometers and referenced to the residual deuterated solvent signals FT-IR measurements were carried out on a Bruker Optics FTIR-ATR TR0 spectrometer. UV-Vis titrations were performed with a UV-1800PC spectrophotometer at 25 ºC. Exact mass analyses and X-ray diffraction studies were performed by the Research Support Area (RSA) at ICIQ.

3.4.2 – Synthesis of squaramides and epoxides

Synthesis of diethyl squarate[70]

Squaric acid (44 mmol) was suspended in ethanol (50 mL) and stirred under reflux for 20 h. The reaction mixture was cooled and the solvent was removed *in vacuo*. The white solid residue was dissolved again in ethanol and brought to reflux for 30 min. This step was repeated three times to obtain full conversion of squaric acid into diethyl squarate.

Synthesis of squaramides 3.1 – 3.3, 3.6, and 3.8 – 3.9[71]

The corresponding amine (2.1 equiv) was added to a solution of diethyl squarate and triethyl amine (4 equiv) in ethanol. The mixture was stirred at rt for 18 h. Then the reaction mixture was filtered and the precipitate was washed with diethyl ether and hexane, giving the desired squaramide.

Synthesis of squaramides 3.4, 3.5 and 3.7[72]

To a stirred solution of diethyl squarate and zinc trifluoromethanesulfonate (20 mol%) in toluene/*N*-methylpyrrolidine (19:1, v/v) was added the corresponding aryl amine (2.1 equiv). The solution was heated to 100 ºC and stirred for 12 h. Then the reaction mixture was cooled down to rt and crystals were obtained, which were isolated by filtration and washed with toluene to give the desired squaramide.

Synthesis of squaramides 3.10 – 3.21[73]

In a screw-capped vial, diethyl squarate (2 mmol) was dissolved in methanol (2 mL). Then, the first amine (1 equiv) was added at rt. After the corresponding reaction time (1 – 7 days), a precipitate was formed and additional methanol (2 mL) was added. Then, a second amine (1 equiv) was added and after 24 h, the reaction mixture was purified by filtration and the precipitate was washed with diethyl ether and hexane giving the pure squaramide products.

Synthesis of bifunctional squaramide 3.22

Squaramide **3.15** (229 mg, 0.58 mmol) was dissolved in acetone (4.0 mL) and iodomethane (0.11 mL, 1.74 mmol, 3 equiv) was added. The mixture was stirred for 24 h and the precipitate was collected by filtration and subsequently washed with methanol, diethylether and hexane. Yield of **3.22**: 77%.

Synthesis of thiourea 3.23[79]

At rt, *N*,*N*-dimethylethylenediamine (557 mg, 0.69 mL, 6 mmol) was added dropwise to a stirred solution of 3,5-bis(trifluoromethyl)phenylisocyanate (2.5g, 1.68 mL, 9 mmol, 1.5 equiv) in DCM (10 mL). The reaction mixture was stirred for 18 h and concentrated under reduced pressure. Then, the reaction crude was purified by flash column chromatography affording the desired product as a white solid.

Synthesis of epoxides 3.35a, 3.39a and 3.41a[29,80,81]

Epoxides 3-benzyl-6-oxa-3-azabicyclo[3.1.0]hexane (**3.35a**) and 1a,2,7,7a-tetrahydro naphtho [2,3-b]oxirane (**3.41a**) were prepared from the corresponding alkenes according to previously reported epoxidation protocols.[29,80] 3-Phenyloxiran-2-yl)methanol (**3.39a**) was prepared from commercially available phenyl glycidol following a previously reported protection protocol.[81]

3.4.3 – General procedure for the catalytic experiments

Typical catalytic experiment

All reactions were performed in a 30 ml stainless steel reactor. In a typical experiment, a solution of the squaramide (3.0 mol%), ammonium salt (6.0 mol%), epoxide (8.0 mmol) and mesitylene (15 mol%) was added to a stainless steel reactor. Three cycles of pressurization and depressurization of the reactor with 5 bar of CO_2 pressure were carried out before finally stabilizing the pressure at 10 – 30 bar. The reactor was then heated to the required temperature and left stirring for another 18 h. The reactor was cooled down, depressurized and an aliquot of the solution was analyzed by means of ^{1}H NMR spectroscopy using $CDCl_3$ as the solvent. The yield was determined using mesitylene as the internal standard. In all cases, selectivity for the cyclic carbonate products was found to be >99%. For the reactions carried out in the substrate scope phase, the pure products were obtained by flash chromatographic purification.

3.4.4 – Titration studies

General procedure for ^{1}H and ^{19}F NMR titration studies

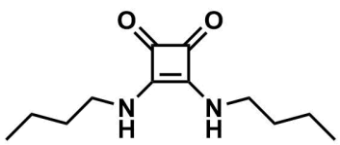
Squaramide **3.15** (9.0 mg) and 5 equiv of the corresponding ammonium salt [TBA**B**, TBA(**PNP**) or TBA(**OAc**)] were added in a screw-capped vial. Then 1.0 mL of deuterated acetonitrile was added. After dissolving all the components, the solution was put in a NMR

tube and measured by NMR. ^{1}H and ^{19}F-NMR competition experiments were carried out by comparison with spectra obtained in the presence of only one type of guest (*i.e.*, TBA salt).

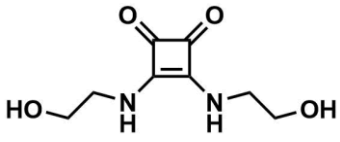
General procedure for UV-Vis spectroscopy titration studies

The UV lamp was warmed for 1 h before carrying out the titration experiments. The baseline was set after filling both cuvettes with acetonitrile (3.0 mL). The concentration of squaramides was fixed in such a way that the value for the absorbance was never higher than 1.0. The cuvette (3.0 mL volume) was filled with 2.0 mL of squaramide solution. The concentration of "ligand" or "guest" (TEA**B**, TBA**B**, TBA(**PNP**), TBA(**OAc**) or cyclohexene oxide) was fixed at a concentration 100 to 1000 times higher than the concentration of the squaramides. Different aliquots of the "ligand" solution were then added and the UV spectrum was recorded after each addition. Note that SpecFit/32 software[d] was used to correct for the increase in the total volume.

3.4.5 – Spectroscopic data for all compounds

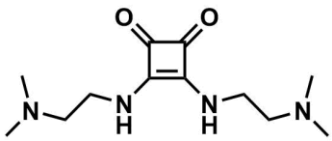


Compound 3.1; 3,4-bis(butylamino)cyclobut-3-ene-1,2-dione;[82] **^{1}H NMR (400 MHz, DMSO, 298 K) δ** 7.29 (bs, 2H), 3.60 - 3.40 (m, 4H), 1.54 - 1.43 (m, 4H), 1.37 - 1.24 (m, 4H), 0.89 (t, $^{3}J_{HH}$ = 7.3 Hz, 6H); **^{13}C NMR (101 MHz, DMSO, 298 K) δ** 182.28, 167.73, 42.91, 32.83, 18.99, 13.51; **IR (neat, cm^{-1})** 3159 (N-H), 2956 - 2871 (C-H), 1802 (C=O), 1632 (C=C).

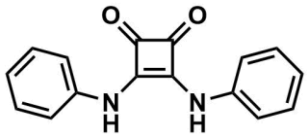


Compound 3.2; 3,4-bis((2-hydroxyethyl)amino)cyclobut-3-ene-1,2-dione; ^{1}H NMR (400 MHz, DMSO, 298 K) δ 7.57 (bs, 2H), 4.94 – 4.87 (m, 2H), 3.69 - 3.54 (m, 4H), 3.52 (t, $^{3}J_{HH}$ = 4.3 Hz, 4H); **^{13}C NMR (101 MHz, DMSO, 298 K) δ** 182.51, 167.93, 60.83, 45.77; **IR (neat, cm^{-1})** 3452 (O-H), 3179 (N-H), 2984 - 2931 (C-H), 1797 (C=O), 1618 (C=C); **HRMS (ESI–; MeOH):** *m/z* calcd. ($C_8H_{11}N_2O_4$) 199.0724; $(M–H)^-$ found: 199.0726.

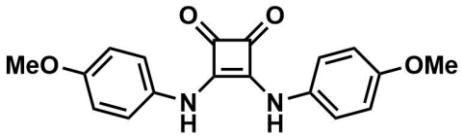
[d] **Note 4;** Specfit/32, version 3.0; Spectra Software Associates: Bradford-on-Avon, U.K., 2005. Specfit/32 is a multivariate data analysis program for modeling and fitting multiwavelength titration data sets giving more reliable parameters than single-wavelength fits. For software details and the related nonlinear algorithms see: (a) Gampp, H.; Maeder, M.; Meyer, C. J.; Zuberbühler, D. A. *Talanta* **1985**, *32*, 95. (b) Gampp, H.; Maeder, M.; Meyer, C. J.; Zuberbühler, D. A. *Talanta* **1986**, *33*, 943.



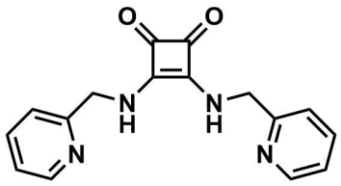
Compound 3.3; 3,4-bis((2-(dimethylamino)ethyl)amino) cyclobut-3-ene-1,2-dione; ^{1}H NMR (400 MHz, DMSO, 298 K) δ 7.51 (bs, 2H), 3.67 - 3.57 (m, 4H), 2.39 (t, $^{3}J_{HH}$ = 6.0 Hz, 4H), 2.17 (s, 6H); **^{13}C NMR (101 MHz, DMSO, 298 K) δ** 182.42, 167.52, 59.25, 45.01, 40.93; **IR (neat, cm^{-1})** 3161 (N-H), 2974 - 2765 (C-H), 1797 (C=O), 1634 (C=C); **HRMS (ESI–; MeOH):** *m/z* calcd. ($C_{12}H_{21}N_4O_2$) 253.1670; $(M-H)^-$ found: 253.1672.



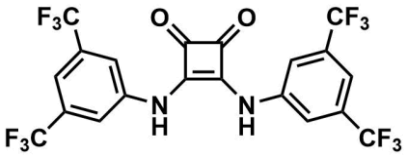
Compound 3.4; 3,4-bis(phenylamino)cyclobut-3-ene-1,2-dione; ^{1}H NMR (400 MHz, DMSO, 298 K) δ 9.88 (bs, 2H), 7.52 - 7.48 (m, 4H), 7.42 - 7.36 (m, 4H), 7.12 - 7.06 (m, 2H); **^{13}C NMR (101 MHz, DMSO, 298 K) δ** 181.59, 165.64, 138.52, 129.36, 123.27, 118.47; **IR (neat, cm^{-1})** 3141 (N-H), 3007 - 2800 (C-H), 1797 (C=O), 1667 (C=C), 1600 (C=C); **HRMS (ESI–; $CHCl_3$):** *m/z* calcd. ($C_{16}H_{11}N_2O_2$) 263.0826; $(M-H)^-$ found: 263.0828.



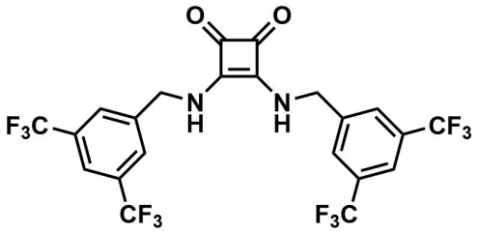
Compound 3.5; 3,4-bis((4-methoxy phenyl) amino)cyclobut-3-ene-1,2-dione; ^{1}H NMR (400 MHz, DMSO, 298 K) δ 9.68 (bs, 2H), 7.40 (d, $^{3}J_{HH}$ = 8.9 Hz, 4H), 6.95 (d, $^{3}J_{HH}$ = 8.9 Hz, 4H), 3.74 (s, 6H); **^{13}C NMR (101 MHz, DMSO, 298 K) δ** 181.25, 165.05, 155.59, 131.79, 120.05, 114.54, 55.30; **IR (neat, cm^{-1})** 3100 (N-H), 3000 – 2800 (C.H), 1798 (C=O), 1660 (C=C), 1613 (C=C); **HRMS (ESI–; MeOH):** *m/z* calcd. ($C_{18}H_{15}N_2O_4$) 323.1037; $(M-H)^-$ found: 323.1043.



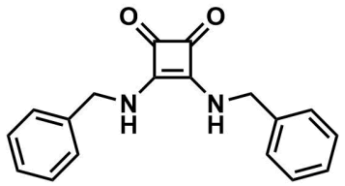
Compound 3.6; 3,4-bis((pyridin-2-ylmethyl)amino) cyclobut-3-ene-1,2-dione; ^{1}H NMR (500 MHz, DMSO, 298 K) δ 8.56 (d, $^{3}J_{HH}$ = 4.3 Hz, 2H), 8.07 (bs, 2H), 7.81 (td, $^{3}J_{HH}$ = 7.6 Hz, $^{4}J_{HH}$ = 1.7 Hz, 2H), 7.38 (d, $^{3}J_{HH}$ = 7.8 Hz, 2H), 7.32 (dd, $^{3}J_{HH}$ = 7.2 Hz, $^{3}J_{HH}$ = 5.3 Hz, 2H) 4.95 – 4.75 (m, 4H); **^{13}C NMR (126 MHz, DMSO, 298 K) δ** 182.86, 167.84, 157.52, 149.16, 137.11, 122.62, 121.57, 48.28; **IR (neat, cm^{-1})** 3153 (N-H), 3046 - 2933 (C-H), 1797 (C=O), 1645 (C=C); **HRMS (ESI+; MeOH):** *m/z* calcd. ($C_{16}H_{15}N_4O_2$) 295.1190; $(M+H)^+$ found: 295.1190.



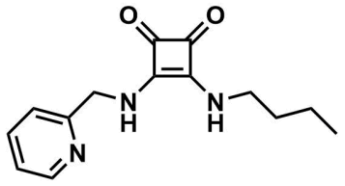
Compound 3.7; 3,4-bis((3,5-bis(trifluoro methyl) phenyl)amino)cyclobut-3-ene-1,2-dione;[72] **^{1}H NMR (500 MHz, DMSO, 298 K) δ** 7.88 (s, 4H), 7.68 (s, 2H); **^{13}C NMR (126 MHz, DMSO, 298 K) δ** 184.71, 166.29, 141.06 (q, $^{2}J_{CF}$ = 33.0 Hz), 131.58 (q, $^{1}J_{CF}$ = 272.9 Hz), 123.47, 119.68, 116.35; **^{19}F NMR (376 MHz, DMSO, 298 K) δ** –61.88; **IR (neat, cm^{-1})** 2923 (N-H), 1800 (C=O), 1676 (C=C).



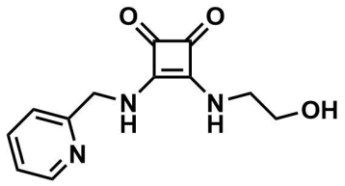
Compound 3.8; 3,4-bis((3,5-bis(trifluoro methyl)benzyl) amino) cyclo but-3-ene-1,2-dione; ^{1}H NMR (500 MHz, DMSO, 298 K) δ 8.02 (m, 6H), 4.89 (m, 4H); **^{13}C NMR (126 MHz, DMSO, 298 K) δ** 182.92, 167.76, 142.51, 130.54 (q, $^{2}J_{CF}$ = 32.80 Hz), 128.30, 122.86 (q, $^{1}J_{CF}$ = 272.7 Hz), 121.12, 45.76; **^{19}F NMR (376 MHz, DMSO, 298 K) δ** -61.54; **IR (neat, cm^{-1})** 3162 (N-H), 2942 (C-H), 1804 (C=O), 1655 (C=C); **HRMS (ESI–; CHCl$_3$):** *m/z* calcd. ($C_{22}H_{11}F_{12}N_2O_2$) 563.0634; $(M–H)^-$ found: 563.0637.



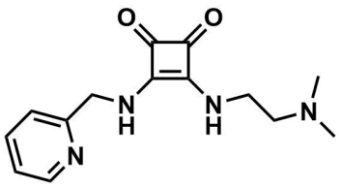
Compound 3.9; 3,4-bis(benzylamino)cyclobut-3-ene-1,2-dione; ^{1}H NMR (500 MHz, DMSO, 298 K) δ 7.71 (bs, 2H), 7.46 - 7.21 (m, 10H), 4.87 - 4.57 (m, 4H); **^{13}C NMR (126 MHz, DMSO, 298 K) δ** 182.64, 167.56, 138.91, 128.66, 127.50, 127.43, 46.83; **IR (neat, cm^{-1})** 3153 (N-H), 2937 (C-H), 1796 (C=O), 1640 (C=C); **HRMS (ESI–; CHCl$_3$):** *m/z* calcd. ($C_{18}H_{15}N_2O_2$) 291.1139; $(M–H)^-$ found: 291.1137.



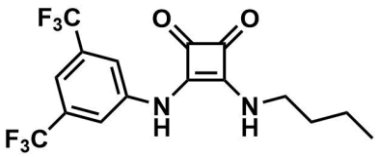
Compound 3.10; 3-(butylamino)-4-((pyridin-2-yl methyl)amino)cyclobut-3-ene-1,2-dione; ^{1}H NMR (400 MHz, DMSO, 298 K) δ 8.58 (d, $^{3}J_{HH}$ = 4.2 Hz, 1H), 7.82 (td, $^{3}J_{HH}$ = 7.7 Hz, $^{4}J_{HH}$ = 1.7 Hz, 1H), 7.51 (bs, 1H), 7.38 (d, $^{3}J_{HH}$ = 7.8 Hz, 1H), 7.34 (dd, $^{3}J_{HH}$ = 7.1 Hz, $^{3}J_{HH}$ = 5.2 Hz, 1H), 4.99 - 4.71 (m, 2H), 3.61 - 3.44 (m, 2H), 1.55 - 1.46 (m, 2H), 1.38 - 1.27 (m, 2H), 0.89 (t, $^{3}J_{HH}$ = 7.3 Hz, 3H); **^{13}C NMR (126 MHz, DMSO, 298 K) δ** 182.79, 182.36, 167.99, 167.52, 157.54, 149.13, 137.09, 122.59, 121.56, 48.24, 42.95, 32.76, 18.98, 13.48; **IR (neat, cm^{-1})** 3161 (N-H), 3053 - 2870 (C-H), 1799 (C=O), 1642 (C=C); **HRMS (ESI–; CHCl$_3$):** *m/z* calcd. ($C_{14}H_{16}N_3O_2$) 258.1248; $(M–H)^-$ found: 258.1244.



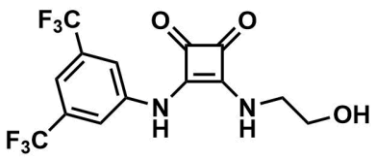
Compound 3.11; 3-((2-hydroxyethyl)amino)-4-((pyridin-2-ylmethyl) amino)cyclobut-3-ene-1,2-dione; ^{1}H NMR (400 MHz, DMSO, 298 K) δ 8.57 (d, $^{3}J_{HH}$ = 4.3 Hz, 1H), 7.98 (bs, 1H), 7.81 (td, $^{3}J_{HH}$ = 7.7 Hz, $^{4}J_{HH}$ = 1.7 Hz, 1H), 7.67 (bs, 1H), 7.37 (d, $^{3}J_{HH}$ = 7.8 Hz, 1H), 7.33 (dd, $^{3}J_{HH}$ = 7.2 Hz, $^{3}J_{HH}$ = 5.1 Hz, 1H), 4.93 - 4.88 (m, 1H), 4.87 - 4.76 (m, 2H), 3.63 - 3.55 (m, 1H), 3.52 (t, $^{3}J_{HH}$ = 4.1 Hz, 3H); **^{13}C NMR (126 MHz, DMSO, 298 K) δ** 182.89, 182.50, 168.15, 167.64, 157.57, 149.18, 137.12, 122.62, 121.57, 60.82, 48.28, 45.87; **IR (neat, cm^{-1})** 3153 (N-H), 2928 (C-H), 1802 (C=O), 1639 (C=C); **HRMS (ESI–; CHCl$_3$):** *m/z* calcd. ($C_{12}H_{12}N_3O_3$) 246.0884; $(M–H)^-$ found: 246.0891.



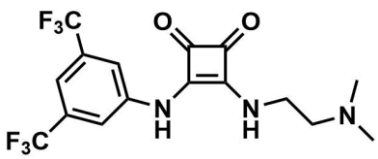
Compound 3.12; 3-((2-(dimethylamino)ethyl) amino)-4-((pyridin-2-ylmethyl) amino) cyclobut-3-ene-1,2-dione; ^{1}H NMR (500 MHz, DMSO, 298 K) δ 8.57 (d, $^{3}J_{HH}$ = 4.1 Hz, 1H), 8.04 (bs, 1H), 7.81 (td, $^{3}J_{HH}$ = 7.7 Hz, $^{4}J_{HH}$ = 1.8 Hz, 1H), 7.52 (bs, 1H), 7.37 (d, $^{3}J_{HH}$ = 7.8 Hz, 1H), 7.34 - 7.30 (m, 1H), 4.83 (m, 2H), 3.62 (m, 2H), 2.42 - 2.36 (m, 2H), 2.17 (s, 3H), 2.16 (s, 3H); **^{13}C NMR (126 MHz, DMSO, 298 K) δ** 182.85, 182.42, 167.77, 167.52, 157.52, 149.16, 137.12, 122.62, 121.61, 59.20, 48.25, 45.02, 41.03; **IR (neat, cm^{-1})** 3159 (N-H), 2940 - 2758 (C-H), 1800 (C=O), 1638 (C=C); **HRMS (ESI–; $CHCl_3$):** *m/z* calcd. ($C_{14}H_{17}N_4O_2$) 273.1357; $(M–H)^-$ found: 273.1354.



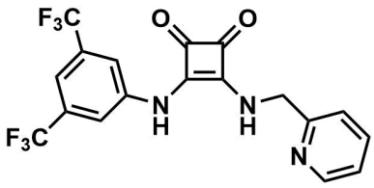
Compound 3.13; 3-((3,5-bis(trifluoromethyl) phenyl)amino)-4-(butylamino) cyclobut-3-ene-1,2-dione; ^{1}H NMR (500 MHz, DMSO, 298 K) δ 10.11 (bs, 1H), 8.01 (s, 2H), 7.69 (bs, 1H), 7.61 (s, 1H), 3.71 - 3.55 (m, 2H), 1.62 - 1.50 (m, 2H), 1.40 - 1.28 (m, 2H), 0.91 (t, $^{3}J_{HH}$ = 7.3 Hz, 3H); **^{13}C NMR (126 MHz, DMSO, 298 K) δ** 184.78, 180.31, 169.79, 162.23, 141.13, 131.18 (m), 123.17 (q, $^{1}J_{CF}$ = 272.6 Hz), 117.92, 114.55, 32.52, 18.97, 13.43; **^{19}F NMR (376 MHz, DMSO, 298 K) δ** –61.87; **IR (neat, cm^{-1})** 3179 (N-H), 3087 - 2878 (C-H), 1794 (C=O), 1657 (C=C); **HRMS (ESI–; $CHCl_3$):** *m/z* calcd. ($C_{16}H_{13}F_6N_2O_2$) 379.0887; $(M-H)^-$ found: 379.0885.



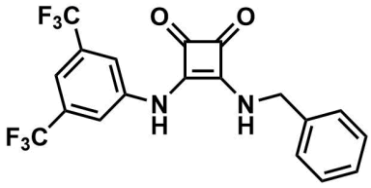
Compound 3.14; 3-((3,5-bis(trifluoromethyl) phenyl)amino)-4-((2-hydroxyethyl) amino) cyclo but-3-ene-1,2-dione; ^{1}H NMR (500 MHz, DMSO, 298 K) δ 10.25 (bs, 1H), 8.04 (s, 2H), 7.89 (bs, 1H), 7.63 (s, 1H), 5.04 (bs, 1H), 3.74 - 3.64 (m, 2H), 3.62 - 3.55 (m, 2H); **^{13}C NMR (126 MHz, DMSO, 298 K) δ** 184.76, 180.32, 169.87, 162.29, 141.25, 131.49 (m), 123.22 (q, $^{1}J_{CF}$ = 271.70 Hz), 117.80, 114.51, 60.43, 46.33; **^{19}F NMR (376 MHz, DMSO, 298 K) δ** –61.84; **IR (neat, cm^{-1})** 3270 (N-H), 3050 - 2990 (C-H), 1797 (C=O), 1673 (C=C); **HRMS (ESI–; $CHCl_3$):** *m/z* calcd. ($C_{14}H_9F_6N_2O_3$) 367.0523; $(M–H)^-$ found: 367.0516.



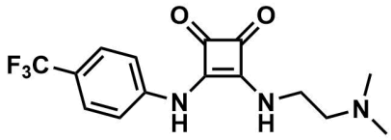
Compound 3.15; 3-((3,5-bis(trifluoromethyl) phenyl)amino)-4-((2-(dimethylamino)ethyl) amino) cyclobut-3-ene-1,2-dione; ^{1}H NMR (500 MHz, DMSO, 298 K) δ 8.03 (s, 2H), 7.75 (bs, 1H), 7.58 (s, 1H), 3.74 - 3.66 (m, 2H), 2.46 (t, $^{3}J_{HH}$ = 5.8 Hz, 2H), 2.20 (s, 6H); **^{13}C NMR (126 MHz, DMSO, 298 K) δ** 184.78, 180.24, 169.54, 162.19, 141.27, 131.35 (q, $^{2}J_{CF}$ = 33.0 Hz), 122.99 (q, $^{1}J_{CF}$ = 272.9 Hz), 117.79, 114.44, 58.73, 44.96, 41.48; **^{19}F NMR (376 MHz, DMSO, 298 K) δ** –61.95; **IR (neat, cm^{-1})** 3203 (N-H), 3051 - 2782 (C-H), 1800 (C=O), 1663 (C=C); **HRMS (ESI–; $CHCl_3$):** *m/z* calcd. ($C_{16}H_{14}F_6N_3O_2$) 394.0996; $(M–H)^-$ found: 394.0989.



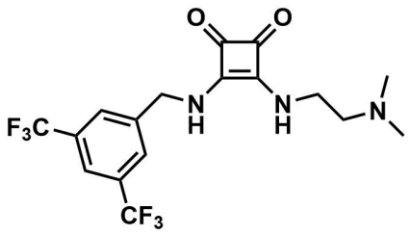
Compound 3.16; 3-((3,5-bis(trifluoromethyl) phenyl)amino)-4-((pyridin-2-ylmethyl)amino) cyclobut-3-ene-1,2-dione; ^{1}H NMR (400 MHz, DMSO, 298 K) δ 10.38 (bs, 1H), 8.60 (d, $^{3}J_{HH}$ = 4.2 Hz, 1H), 8.29 (bs, 1H), 8.08 - 8.01 (m, 2H), 7.84 (td, $^{3}J_{HH}$ = 7.7 Hz, $^{4}J_{HH}$ = 1.7 Hz, 1H), 7.69 - 7.60 (m, 1H), 7.44 (d, $^{3}J_{HH}$ = 7.8 Hz, 1H), 7.36 (dd, $^{3}J_{HH}$ = 7.2 Hz, $^{3}J_{HH}$ = 5.4 Hz, 1H), 5.00 – 4.91 (m, 2H); **^{13}C NMR (126 MHz, DMSO, 298 K) δ** 184.82, 180.75, 169.72, 162.64, 156.62, 149.20, 141.15, 137.27, 131.49 (m), 123.28 (q, $^{1}J_{CF}$ = 272.8 Hz), 122.88, 121.79, 118.10, 114.77, 48.53; **^{19}F NMR (376 MHz, DMSO, 298 K) δ** -61.84; **IR (neat, cm^{-1})** 3338 - 3270 (N-H), 3097 (C-H), 1796 (C=O), 1680 (C=C); **HRMS (ESI–; MeOH):** *m/z* calcd. ($C_{18}H_{10}F_6N_3O_2$) 414.0683; $(M–H)^-$ found: 414.0675.



Compound 3.17; 3-(benzylamino)-4-((3,5-bis (trifluoromethyl)phenyl) amino) cyclobut-3-ene-1,2-dione; ^{1}H NMR (400 MHz, DMSO, 298 K) δ 10.15 (bs, 1H), 8.10 (bs, 1H), 8.04 – 7.98 (m, 2H), 7.67 – 7.63 (m, 1H), 7.44 – 7.37 (m, 4H), 7.36 – 7.30 (m, 1H), 4.87 – 4.78 (m, 2H); **^{13}C NMR (101 MHz, DMSO, 298 K) δ** 185.31, 181.06, 169.91, 163.11, 141.49, 138.67, 131.71 (m), 129.19, 128.13, 123.91 (q, $^{1}J_{CF}$ = 272.9 Hz), 118.60, 115.26, 47.79; **^{19}F NMR (376 MHz, DMSO, 298 K) δ** -61.85; **IR (neat, cm^{-1})** 3153 (N-H), 3072 - 2955 (C-H), 1796 (C=O), 1656 (C=C); **HRMS (ESI–; $CHCl_3$):** *m/z* calcd. ($C_{19}H_{11}F_6N_2O_2$) 413.0730; $(M–H)^-$ found: 413.0724.

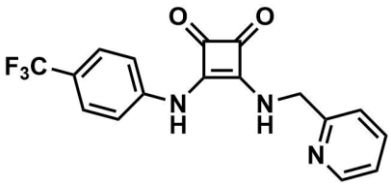


Compound 3.18; 3-((2-(dimethylamino)ethyl) amino)-4-((4-(trifluoromethyl)phenyl) amino) cyclobut-3-ene-1,2-dione; ^{1}H NMR (400 MHz, DMSO, 298 K) δ 10.10 (bs, 1H), 7.79 (bs, 1H), 7.73 - 7.57 (m, 4H), 3.75 - 3.67 (m, 2H), 2.46 (t, $^{3}J_{HH}$ = 5.9 Hz, 2H), 2.21 (s, 6H); **^{13}C NMR (126 MHz, DMSO, 298 K) δ** 184.88, 180.08, 169.55, 162.84, 142.74, 126.71, 124.54 (q, $^{1}J_{CF}$ = 271 Hz), 122.30 (q, $^{2}J_{CF}$ = 31.90 Hz), 117.96, 58.92, 45.06, 41.51; **^{19}F NMR (376 MHz, DMSO, 298 K) δ** –60.24; **IR (neat, cm^{-1})** 3180 (N-H), 2985 - 2786 (C-H), 1794 (C=O), 1660 (C=C); **HRMS (ESI–; $CHCl_3$):** *m/z* calcd. ($C_{15}H_{15}F_3N_3O_2$) 326.1122; $(M–H)^-$ found: 326.1118.

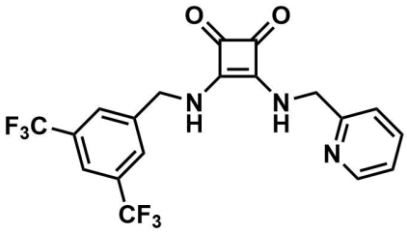


Compound 3.19; 3-((3,5-bis(trifluoromethyl) benzyl)amino)-4-((2-(dimethylamino) ethyl) amino)cyclobut-3-ene-1,2-dione; ^{1}H NMR (500 MHz, DMSO, 298 K) δ 8.06 (s, 2H), 7.99 (s, 1H), 7.50 (bs, 1H), 4.95 - 4.87 (m, 2H), 3.67 - 3.53 (m, 2H), 2.38 (t, $^{3}J_{HH}$ = 5.6 Hz, 2H), 2.13 (s, 6H); **^{13}C NMR (126 MHz, DMSO, 298 K) δ** 183.04, 182.44, 168.18, 167.14, 142.73, 130.67 (q, $^{2}J_{CF}$ = 32.9 Hz), 128.49, 123.32 (q, $^{1}J_{CF}$ = 272.8

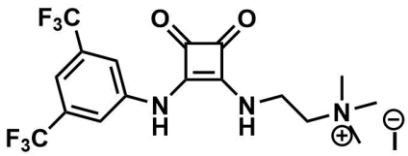
Hz), 121.01, 59.21, 45.76, 44.96, 41.16; **^{19}F NMR (376 MHz, $CDCl_3$, 298 K) δ** –61.41; **IR (neat, cm^{-1})** 3169 (NH), 2947 - 2771 (CH), 1801 (C=O), 1643 (C=C); **HRMS (ESI–; $CHCl_3$):** *m/z* calcd. ($C_{13}H_{19}N_5O_3$) 408.1152; $(M–H)^-$ found: 408.1147.



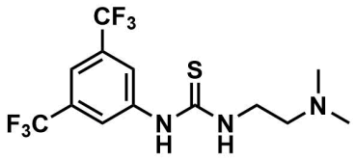
Compound 3.20; 3-((pyridin-2-ylmethyl) amino)-4-((4-(trifluoromethyl) phenyl amino) cyclobut-3-ene-1,2-dione; ^{1}H NMR (400 MHz, DMSO, 298 K) δ 10.12 (bs, 1H), 8.64 – 8.57 (m, 1H), 8.30 (bs, 1H), 7.84 (td, $^3J_{HH}$ = 7.7 Hz, $^4J_{HH}$ = 1.6 Hz, 1H), 7.69 (d. $^3J_{HH}$ = 8.7 Hz, 2H), 7.62 (d, $^3J_{HH}$ = 8.4 Hz, 2H), 7.44 (d, $^3J_{HH}$ = 7.8 Hz, 1H), 7.36 (dd, $^3J_{HH}$ = 7.2 Hz, $^3J_{HH}$ = 5.4 Hz, 1H), 5.01 - 4.91 (m, 2H); **^{13}C NMR (126 MHz, DMSO, 298 K) δ** 184.81, 180.53, 169.68, 163.25, 156.78, 149.25, 142.66, 137.39, 126.74, 124.47 (q, $^1J_{CF}$ = 271.1 Hz), 122.95, 122.49 (q, $^2J_{CF}$ = 32.1 Hz), 121.85, 118.11, 48.57; **^{19}F NMR (376 MHz, DMSO, 298 K) δ** –59.87; **IR (neat, cm^{-1})** 3181 (N-H), 3012 (C-H), 1795 (C=O), 1666 (C=C); **HRMS (ESI–; $CHCl_3$):** *m/z* calcd. ($C_{17}H_{11}F_3N_3O_2$) 346.0809; $(M–H)^-$ found: 346.0816.



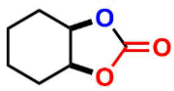
Compound 3.21; 3-((3,5-bis(trifluoromethyl) benzyl) amino)-4-((pyridin-2-ylmethyl) amino) cyclobut-3-ene-1,2-dione; ^{1}H NMR (400 MHz, DMSO, 298 K) δ 8.57 - 8.50 (m, 1H), 8.09 - 8.04 (m, 3H), 7.79 (td, $^3J_{HH}$ = 7.7 Hz, $^4J_{HH}$ = 1.5 Hz, 1H), 7.40 - 7.29 (m, 2H), 4.96 -4.88 (m, 2H), 4.86 - 4.75 (m, 2H); **^{13}C NMR (126 MHz, DMS, 298 K) δ** 183.41, 183.23, 168.71, 167.86, 157.86, 149.56, 143.07, 137.59, 130.91 (q, $^2J_{CF}$ = 32.8 Hz), 128.88, 123.64 (q, $^1J_{CF}$ = 272.8 Hz), 123.12, 122.03, 121.63, 48.70, 46.22; **^{19}F NMR (376 MHz, DMSO, 298 K) δ** –60.99; **IR (neat, cm^{-1})** 3156 (N-H), 3063 - 2952 (C-H), 1799 (C=O), 1643 (C=C); **HRMS (ESI–; $CHCl_3$):** *m/z* calcd. ($C_{19}H_{12}F_6N_3O_2$) 428.0839; $(M–H)^-$ found: 428.0832.



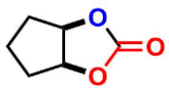
Compound 3.22; 2-((2-((3,5-bis (trifluoro methyl) phenyl)amino)-3,4-dioxo cyclobut-1-en-1-yl) amino)-N,N,N-trimethyl ethan aminium iodide; ^{1}H NMR (400 MHz, DMSO, 298 K) δ 10.35 (bs, 1H), 8.01 (s, 2H), 7.75 (bs, 1H), 7.71 (s, 1H), 4.16 - 4.02 (m, 2H), 3.57 (t, $^3J_{HH}$ = 6.6 Hz, 2H), 3.14 (s, 9H); **^{19}F NMR (376 MHz, DMSO, 298 K) δ** –61.80; **IR (neat, cm^{-1})** 3161 (N-H), 3045 - 2987 (C-H), 1794 (C=O), 1696 (C=C).



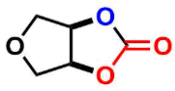
Compound 3.23; 1-(3,5-bis(trifluoromethyl) phenyl)-3-(2-(dimethyl amino)ethyl) thiourea;[83] **^{1}H NMR (500 MHz, DMSO, 298 K) δ** 10.25 (bs, 1H), 8.30 – 8.24 (m, 2H), 8.08 (bs, 1H), 7.73 – 7.69 (m, 1H), 3.63 - 3.52 (m, 2H), 2.45 (t, $^3J_{HH}$ = 5.7 Hz, 2H), 2.19 (s, 6H); **^{13}C NMR (126 MHz, DMSO, 298 K) δ** 180.14, 142.04, 130.27 (q, $^2J_{CF}$ = 32.7 Hz), 123.12 (q, $^1J_{CF}$ = 272.6 Hz), 121.38, 115.80, 56.91, 44.94, 41.76; **^{19}F NMR (376 MHz, DMSO, 298 K) δ** –61.71; **IR (neat, cm^{-1})** 3288 - 3040 (N-H), 2827 - 2780 (C-H), 1272 (C=S), 1128 (C-F).



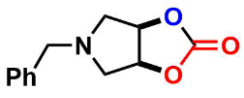
Compound 3.32b; *Cis*-hexahydrobenzo[d][1,3]dioxol-2-one;[23] **^{1}H NMR (300 MHz, $CDCl_3$, 298 K) δ** 4.73 - 4.62 (m, 2H), 1.96 - 1.81 (m, 4H), 1.72 - 1.56 (m, 2H), 1.51 - 1.33 (m, 2H); **^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ** 155.47, 75.86, 26.93, 19.32; **IR (neat, cm^{-1})** 2943 - 2868 (C-H), 1781 (C=O).



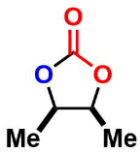
Compound 3.33b; *Cis*-tetrahydro-3aH-cyclopenta[d][1,3]dioxol-2-one; [30] **^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ** 5.13 - 5.07 (m, 2H), 2.20 - 2.13 (m, 2H), 1.86 - 1.61 (m, 4H); **^{13}C NMR (126 MHz, $CDCl_3$, 298 K) δ** 155.54, 81.94, 33.22, 21.63; **IR (neat, cm^{-1})** 2987 – 2885 (C-H), 1778 (C=O).



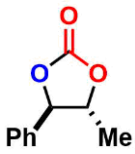
Compound 3.34b; *Cis*-(tetrahydrofuro[3,4-d][1,3]dioxol-2-one;[29] **^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ** 5.21 - 5.19 (m, 2H), 4.29 - 4.24 (m, 2H), 3.59 - 3.53 (m, 2H); **^{13}C NMR (126 MHz, $CDCl_3$, 298 K) δ** 154.44, 80.10, 73.16; **IR (neat, cm^{-1})** 2872 (C-H), 1777 (C=O).



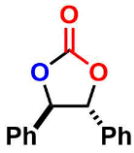
Compound 3.35b; *Cis*-5-benzyltetrahydro-3aH-[1,3] dioxolo [4,5-c]pyrrol-2-one; ^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ 7.38 - 7.21 (m, 5H), 5.07 - 5.03 (m, 2H), 3.66 (s, 2H), 3.327 - 3.21 (m, 2H), 2.27 - 2.18 (m, 2H); **^{13}C NMR (126 MHz, $CDCl_3$, 298 K) δ** 155.30, 137.37, 128.60, 127.55, 79.31, 58.75, 58.11; **IR (neat, cm^{-1})** 3030 – 2745 (C-H), 1778 (C=O); **HRMS (ESI+; MeOH):** *m/z* calcd. ($C_{12}H_{14}NO_3$) 220.0968; $(M–H)^+$ found: 220.0962.



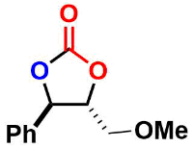
Compound 3.36b; *Cis*-4,5-dimethyl-1,3-dioxolan-2-one;[84] Ratio cis/trans 94:6. **^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ** 4.89 - 4.81 (m, cis-, 2H), 4.37 - 4.33 (m, trans-, 2H), 1.48 (d, *trans*, $^3J_{HH}$ = 5.7 Hz, 6H), 1.39 (d, *cis*, $^3J_{HH}$ = 5.9 Hz, 6H); **^{13}C NMR (126 MHz, $CDCl_3$, 298 K) δ** 154.70, 80.01, 76.11, 18.55, 14.53; **IR (neat, cm^{-1})** 2990 (C-H), 1784 (C=O).



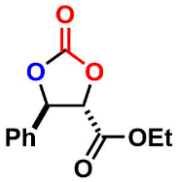
Compound 3.37b; *Trans*-4-methyl-5-phenyl-1,3-dioxolan-2-one;[32] **^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ** 7.47 - 7.40 (m, 3H), 7.38 - 7.33 (m, 2H), 5.13 (d, $^3J_{HH}$ = 8.0 Hz, 1H), 4.60 (dq, $^3J_{HH}$ = 8.0 Hz, $^3J_{HH}$ = 6.2 Hz, 1H), 1.55 (d, $^3J_{HH}$ = 6.2 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ** 154.37, 135.13, 129.83, 129.28, 126.08, 84.97, 80.85, 18.40; **IR (neat, cm^{-1})** 2988 - 2939 (C-H), 1799 (C=O).



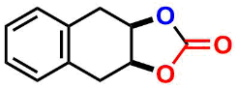
Compound 3.38b; *Trans*-4,5-diphenyl-1,3-dioxolan-2-one;[29] Ratio *cis/trans* <1:99. **^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ** 7.50 - 7.39 (m, 6H), 7.36 - 7.29 (m, 4H), 5.44 (s, 2H); **^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ** 154.21, 134.93, 129.93, 129.36, 126.21, 85.50; **IR (neat, cm^{-1})** 3063 - 2945 (C-H), 1813 (C=O).



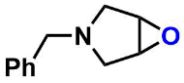
Compound 3.39b; *Trans*-4-(methoxymethyl)-5-phenyl-1,3-dioxolan-2-one; ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 7.46 - 7.40 (m, 3H), 7.38 - 7.32 (m, 2H), 5.53 (d, $^3J_{HH}$ = 6.5 Hz, 1H), 4.59 (dt, $^3J_{HH}$ = 6.5 Hz, $^3J_{HH}$ = 3.7 Hz, 1H) 3.74 (dd, $^2J_{HH}$ = 11.2 Hz, $^3J_{HH}$ = 3.8 Hz, 1H), 3.66 (dd, $^2J_{HH}$ = 11.2 Hz, $^3J_{HH}$ = 3.8 Hz, 1H), 3.47 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ** 154.38, 136.35, 129.71, 129.35, 125.92, 82.41, 79.49, 70.79, 59.91; **IR (neat, cm^{-1})** 2934 (C-H), 1791 (C=O); **HRMS (ESI+; MeOH):** *m/z* calcd. ($C_{11}H_{12}NaO_4$) 231.0628; $(M–Na)^+$ found: 231.0624.



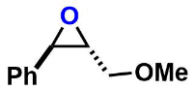
Compound 3.40b; *Trans*-ethyl 2-oxo-5-phenyl-1,3-dioxolane-4-carboxylate;[85] Ratio *cis/trans* = 12:88; the same diastereoisomeric ratio as present in the epoxide substrate. **^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ** 7.50 - 7.44 (m, 3H), 7.42 - 7.37 (m, 2H), 5.65 (d, $^3J_{HH}$ = 5.6 Hz, 1H), 4.90 (d, $^3J_{HH}$ = 5.6 Hz, 1H), 4.41 - 4.34 (m, 2H), 1.37 (t, $^3J_{HH}$ = 7.2 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ** 167.04, 153.27, 135.73, 130.06, 129.50, 125.59, 80.12, 79.37, 63.15, 14.22; **IR (neat, cm^{-1})** 2985 (C-H), 1812 (C=O), 1740 (C=O).



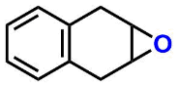
Compound 3.41b; *Cis*-3a,4,9,9a-tetrahydronaphtho[2,3-d][1,3]dioxol-2-one;[29] **^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ** 7.29 - 7.24 (m, 2H), 7.23 - 7.18 (m, 2H), 5.21 – 5.15 (m, 2H), 3.18 – 3.10 (m, 2H), 2.92 – 2.85 (m, 2H); **^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ** 154.48, 132.23, 129.05, 128.07, 75.07, 32.94; **IR (neat, cm^{-1})** 2973 (C-H), 1772 (C=O).



Compound 3.35a; 3-Benzyl-6-oxa-3-azabicyclo[3.1.0]hexane;[80] **^{1}H NMR (300 MHz, $CDCl_3$, 298 K) δ** 7.35 - 7.20 (m, 5H), 3.78 - 3.56 (m, 4H), 3.20 (d, $^3J_{HH}$ = 11.8 Hz, 2H), 2.56 (d, $^3J_{HH}$ = 11.7 Hz, 2H); **^{13}C NMR (126 MHz, $CDCl_3$, 298 K) δ** 138.83, 128.92, 128.40, 127.19, 60.31, 56.14, 53.63; **IR (neat, cm^{-1})** 3028 - 2798 (C-H), 1453 (C-O-C).



Compound 3.39a; (2*R*,3*R*)-2-(methoxymethyl)-3-phenyloxirane;[81] **^{1}H NMR (300 MHz, $CDCl_3$, 298 K) δ** 7.40 - 7.22 (m, 5H), 3.83 - 3.74 (m, 2H), 3.54 (dd, $^{2}J_{HH}$ = 11.5 Hz, $^{3}J_{HH}$ = 5.2 Hz, 1H) 3.45 (s, 3H), 3.24 - 3.18 (m, 1H); **^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ** 137.01, 128.65, 128.43, 125.86, 72.36, 61.13, 59.46, 55.91; **IR (neat, cm^{-1})** 2985 -2826 (C-H), 1462 (C-O-C).



Compound 3.41a; 1a,2,7,7a-tetrahydronaphtho[2,3-b]oxirane;[86] **^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ** 7.18 - 7.01 (m, 4H), 3.52 - 3.46 (m, 2H), 3.37 - 3.15 (m, 4H); **^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ** 131.49, 129.26, 126.54, 51.73, 29.75; **IR (neat, cm^{-1})** 3004 (C-H), 1456 cm^{-1} (C-O-C).

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UNIVERSITAT ROVIRA I VIRGILI
ORGANOCATALYTIC TRANSFORMATIONS OF CARBON DIOXIDE AND CYCLIC CARBONATES
Sergio Sopeña de Frutos

Chapter IV

Organocatalyzed domino [3+2] cycloaddition/Payne-type rearrangement using carbon dioxide

An unprecedented organocatalytic approach towards highly substituted cyclic carbonates from tri- and tetra-substituted oxiranes and carbon dioxide is reported. The protocol involves the use of a simple and cheap superbase under mild and additive-free conditions towards the initial formation of a less substituted carbonate product. The latter equilibrates to a tri- or even tetra-substituted cyclic carbonate under thermodynamic control and can be easily trapped *in situ* providing overall a new domino process for synthetically elusive heterocyclic scaffolds. Control experiments provide a rationale for the observed cascade reactions, which demonstrate high similarity with the well-known Payne rearrangement of epoxy alcohols.

This work was communicated as:

Sergio Sopeña, Mariachiara Cozzolino, Eduardo C. Escudero-Adán, Marta Martínez Belmonte and Arjan W. Kleij, *Angew. Chem. Int. Ed*. **2018**, *submitted*.

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ORGANOCATALYTIC TRANSFORMATIONS OF CARBON DIOXIDE AND CYCLIC CARBONATES
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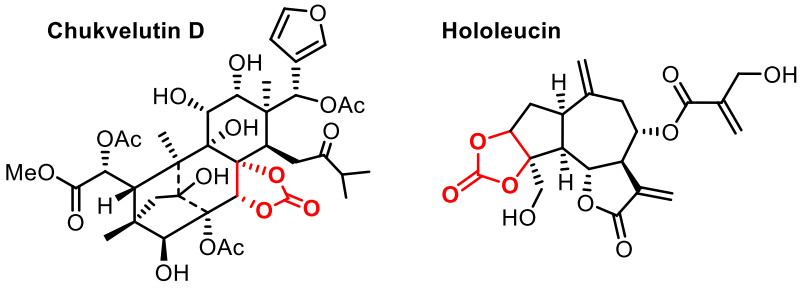
4.1 – Introduction

The chemistry of cyclic organic carbonates has developed to a high level of sophistication over the years.[1–6] In particular, these heterocyclic structures were initially targeted for potential use as electrolytes of lithium ion batteries and useful precursors towards polycarbonate polymers.[7–9] More recently, focus has shifted to the use of cyclic carbonates as synthetic precursors for a range of fine-chemical and pharma-relevant scaffolds.[10–14] In this respect, both the functionalization and degree of substitution of the cyclic carbonate ring has proven to be crucial to develop catalytic procedures that allow for enantio- or diastereoselective transformations including the formation of allylic compounds,[15–18] heterocyclic scaffolds,[19,20] macrocyclic compounds[21,22] among others.[23–28]

Figure 4.1: Natural products with cyclic carbonate functionalities within their structure.

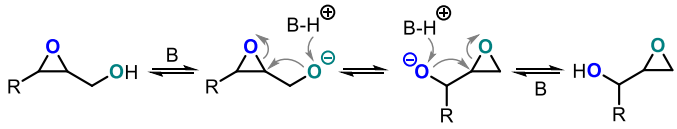


Therefore, synthetic methodologies that give easy access to highly substituted and functionalized cyclic carbonates have gained much importance over the last years and are crucial towards advanced synthetic developments. The most popular and straightforward approach towards cyclic carbonate synthesis is the [3+2] cycloaddition of CO_2 to epoxides under Lewis acid catalysis.[29–31] Despite the considerable progress noted over the years in this field, the use of tri- and even tetrasubstituted epoxides as coupling partners has been extremely challenging due to the steric requirements of these reactions.[32–36]

The relevance of highly substituted carbonates is illustrated by the occurrence of several natural compounds such as the triterpenoid carbonate Chukvelutin D and the sesquiterpenoid carbonate Hololeucin (Figure **4.1**).[37] While biosynthetic pathways exist

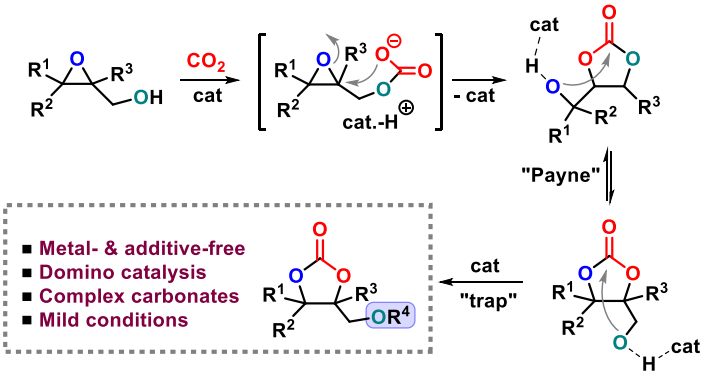
towards these complex structures, no synthetic methodologies towards tetra-substituted cyclic carbonates from epoxides and CO_2 have been reported to date. Therefore, the discovery of new concepts that can alleviate the problems associated with the formation of these highly substituted cyclic carbonates can revive new potential in synthetic organic chemistry.

Scheme 4.1: Payne rearrangement of 1,2-epoxy alcohols.



In the course of our research program towards the creation of more complex cyclic carbonate structures,[25,32,35,38,39] we reasoned that the base-assisted isomerization of 2,3-epoxyalcohols known as the Payne rearrangement (Scheme **4.1**)[40] could offer a potential metal-free blueprint towards the synthesis of highly substituted cyclic carbonates. Recently Kleij reported a substrate-controlled divergent synthesis of cyclic carbonates and carbonates from epoxyalcohols and amines, respectively, under Al(III) catalysis.[41] This work showed the potential of the Al-catalyst to act as a bifunctional entity with proton-relay capabilities and a crucial role for the alcohol unit of the substrate.

Scheme 4.2: New strategy for the synthesis of highly substituted cyclic carbonates.



We envisioned that a proper organocatalyst could combine both (1) the requisite proton-shuttling process thereby mediating the synthesis of the cyclic carbonate from an epoxy

alcohol and CO_2, and (2) induce subsequently a base-assisted Payne type rearrangement of the hydroxymethyl-substituted cyclic carbonate. By selectively trapping of the more reactive hydroxy-methyl substituted carbonate (Scheme **4.2**), a simple and conceptually novel route towards structurally elusive tri- and tetrasubstituted cyclic carbonates would become available. Herein we present a new domino strategy being metal- and nucleophile-free, and being generally applicable towards [3+2] cycloadditions involving highly substituted epoxy alcohols and CO_2 as substrates. As far as we know, this catalytic process is unprecedented in product scope and (in this respect) outcompetes all metal-based catalytic approaches reported to date.

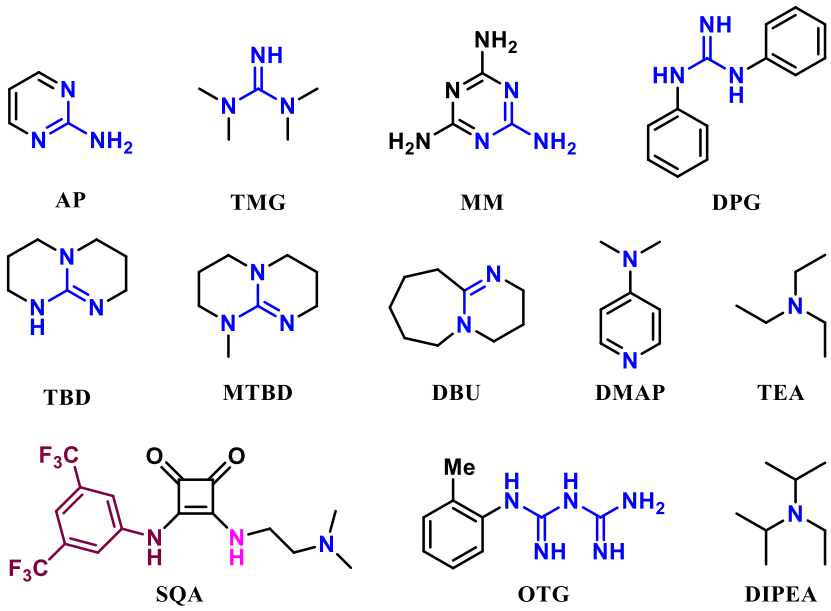
4.2 – Results and discussion

4.2.1 – Monosubstituted epoxides

4.2.1.1 – Screening of organocatalysts

First, we decided to test our hypothesis with a range of *N*-containing bases (Figure **4.2**) using glycidol **4.1a** as a benchmark substrate (Table **4.1**). Under relatively mild conditions (45 ºC, 10 bar) and importantly, in the absence of an external nucleophile, the cyclic carbonate **4.1b** could be easily prepared in up to 95% yield (85% isolated) using DBU as catalyst (Table **4.1**; entry 7).

Figure 4.2: N-heterocyclic bases used in this study.

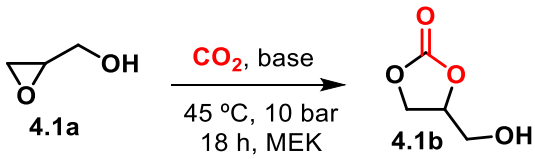


Several other *N*-bases[a] were also productive in the synthesis of glycidol carbonate **4.1b** including TBD (Table **4.1**; entry 1, 91%), MTBD (Table **4.1**; entry 8, 90%) and DMAP

[a] **Note 1;** 1,5,7-triazabicyclo[4.4.0]dec-5-ene (**TBD**); 1,1,3,3-tetramethylguanidine (**TMG**), melamine monomer (**MM**); 1,3-diphenylguanidine (**DPG**); 1-(*o*-tolyl)biguanide (**OTG**); 2-aminopyridine (**AP**); 1,8-

(Table **4.1**, entry 10, 90%). Despite the excellent NMR yield obtained with TMG as catalyst (95%), the presence of some polyether was also detected by NMR analysis of the reaction crude (Table **4.1**; entry 2). Other organocatalysts such us OTG and TEA (Table **4.1**; entries 5 and 9) achieved the synthesis of **4.1b** with moderate to good yields. All other investigated N-containing bases including guanidine derivatives MM, DPG and AP (Table **4.1**; entries 3, 4 and 6), tertiary amines (DIPEA, entry 11) and a bifunctional squaramide with a tertiary amine pending group (Table **4.1**; entry 12) resulted in very low yields.

Table 4.1: Results of the screening of organocatalysts with glycidol as benchmark substrate.



Entry	Catalyst	Yield / [%]
1	TBD	91
2	TMG	95[a]
3	MM	0
4	DPG	11
5	OTG	60
6	AP	3
7	DBU	95
8	MTBD	90
9	TEA	78
10	DMAP	90
11	DIPEA	-
12	SQ	26
13	No catalyst	1

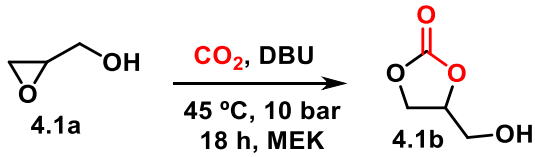
General reaction conditions: Autoclave: glycidol (8.0 mmol), catalyst loading (5.0 mol%), mesitylene (10 mol%), MEK (5.0 mL), 45 ºC, 18 h, pCO_2^0 = 10 bar; [a] Polyether also formed (3%).

diazabicyclo(5.4.0)undec-7-ene (**DBU**); 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (**MTBD**); triethyl amine (**TEA**); 4-(dimethylamino)pyridine (**DMAP**); *N*,*N*-diisopropylethyl amine (**DIPEA**); squaramide (**SQA**).

4.2.1.2 – Screening of reaction conditions using DBU

To further study this reaction using DBU as catalyst, also other reaction conditions were screened. An increase in the catalyst loading to 10 mol% (Table **4.2**; entry 1) did not improve the yield, but reducing to 1 mol% caused a decrease to 69% (Table **4.2**; entry 3). Then, we focused on the effect of the concentration of glycidol (Table **4.2**; entries 5-7). Excellent results were observed when using concentrated systems (>1 M), although it seems that a minimum amount of solvent is required probably due to an increase in viscosity of the system (Table **4.2**; entries 8 and 10). As expected, a decrease of the operating temperature reduces the yield (Table **4.2**; entries 8 and 9) but an increase of the pressure did not improve the yield of glycidol carbonate (Table **4.2**; entries 4 and 9). Finally, only low yields were noted when methyl glycidol was used as substrate pointing towards a key role of the hydroxyl group in the epoxide substrate (entry 11).

Table 4.2: Screening of reaction conditions in the DBU-mediated synthesis of carbonate 4.1b.



Entry	Glycidol [mmol]	DBU [mol%]	[M]	T [ºC]	P [bar]	t [h]	MEK [mL]	Yield [%]
1	8	10	1.6	45	10	18	5	92
2	8	5	1.6	45	10	18	5	95[a]
4	8	1	1.6	45	10	18	5	69
5	2	5	0.4	45	10	18	5	69
6	2	5	1	45	10	18	2	>99
7	2	5	2	45	10	18	1	>99
8	8	5	1.6	rt	10	18	5	43
9	8	1	1.6	45	30	18	5	70
10	8	1	neat	rt	10	18	neat	34
11	8[b]	5	1.6	45	10	18	5	9

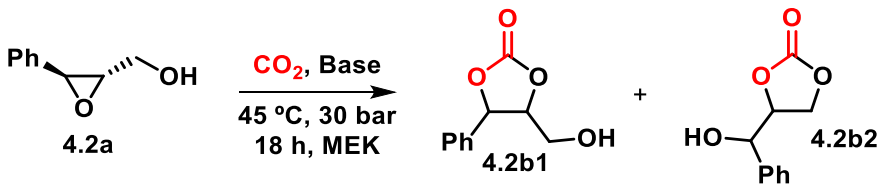
General reaction conditions: Autoclave, glycidol (amount indicated), DBU (amount indicated), MEK, 45 ºC, pCO_2^0 = 10 bar, 18 h; [a] Isolated yield 85%; [b] Methyl glycidol used as substrate.

4.2.2 – Disubstituted epoxides

4.2.2.1 – Screening of catalysts

Inspired by the excellent results found for glycidol, more challenging substrates (disubstituted epoxy alcohols) were probed and (*R*,*R*)-phenyl glycidol **4.2a** was selected as benchmark substrate. Only the *N*-containing bases which gave the best results in the previous screening reactions that involved glycidol were examined (Table **4.1**). The conversion of epoxy alcohol **4.2a** was tested under suitable reaction conditions (45 ºC, 30 bar and a catalyst loading of 10 mol%). Interestingly, for this internal epoxide both TBD and DBU (Table **4.3**; entries 1 and 2) clearly showed the highest yield of targeted carbonates **4.2b1** and **4.2b2** accompanied by the formation of a triol product as detected by NMR. The use of DMAP showed moderate results in terms of overall yield but a higher degree of selectivity towards the formation of the mono-substituted cyclic carbonate **4.2b2** (Table **4.3**; entry 3). DIPEA and TEA showed no observable catalytic activity in this reaction (Table **4.3**; entries 4 and 5) and the bromide-based nucleophile TBAB showed only a yield of 7% for the cyclic carbonate mixture (ratio **4.2b1**/**4.2b2** = 55:45). This shows that the *in situ* formation of a nucleophilic species derived from the epoxy alcohol substrate is far more effective than the use of an external nucleophile.

Table 4.3: Screening of organocatalysts for the conversion of disubstituted epoxides.



Entry	Catalyst	Conv / [%]	4.2b1 / [%]	4.2b2 / [%]	Triol / [%]
1	TBD	>99	8	72	20
2	DBU	>99	25	62	13
3	DMAP	45	7	93	0
4	DIPEA	<1	0	0	0
5	TEA	<1	0	0	0
6	TBAB	7	55	45	0

General reaction conditions: HEL multi-reactor, phenyl glycidol (0.30 mmol), catalyst loading (10 mol%), 45 ºC, pCO_2^0 = 30 bar, MEK (1.0 mL).

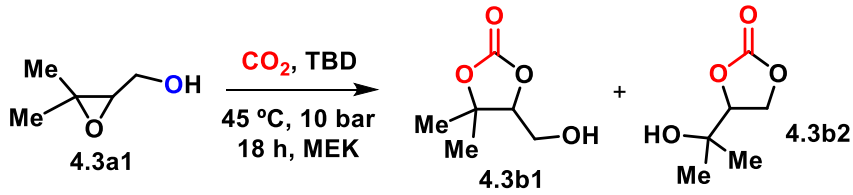
4.2.3 – Trisubstituted epoxides

4.2.3.1 – Screening of reaction conditions

Since TBD and DBU gave similar results in terms of yield (>99%) but TBD was more selective towards the formation of one cyclic carbonate compared to DBU for the conversion of **4.2a** (product ratios **4.2b1**:**4.2b2** were 1:9 versus 1:2.5, respectively), we finally selected TBD as the preferred catalyst to investigate the reaction conditions in the conversion of trisubstituted epoxide **4.3a1** (Table **4.4**).

Interestingly, when similar conditions were applied as for the mono- and di-substituted epoxide conversions (45 ºC, 10 bar, 10 mol% TBD), quantitative conversion of trisubstituted epoxide **4.3a1** into carbonates **4.3b1** and **4.3b2** was achieved (**4.3b1**:**4.3b2** ratio = 7:3, Table **4.4**, entry 2). As expected, the reduction of the catalyst loading led to the formation of the cyclic carbonate products in lower yield (Table **4.4**; entry 3). When the reaction was carried out at room temperature, a dramatic decrease in the yield was observed (Table **4.4**; entry 4). Harsher reaction conditions (80 ºC, 30 bar) generated virtually the same carbonate mixture together with trace amounts of triol product (Table **4.4**; entry 5).

Table 4.4: Screening of reaction conditions for the conversion of trisubstituted epoxy alcohol 4.3a1.



Entry	TBD / mol%	Solvent	Conv / %	4.3b1 / %	4.3b2 / %
1	20	MEK	>99	70	30
2	10[a]	MEK	>99	69	31
3	5	MEK	80	60	40
4	20	MEK	13[b]	60	40
5	10	MEK	>99[c, d, e]	63	29
6	10	MEK	>99[f]	69	31
7	10	MEK	>99[g]	68	32
8	10	EtAcO	25	80	20
9	10	$HCCl_3$	47	64	36
10	10	DCM	92	63	32
11	10	THF	39	52	48
12	10	ACN	>99	70	30
13	10	MeOH	58	70	30

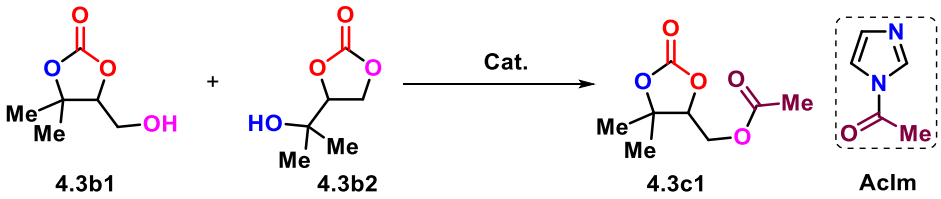
General reaction conditions: Autoclave, substrate (1.0 mmol), 45 ºC, pCO_2^0 = 10 bar, 18 h, solvent (5.0 mL). [a] The use of DBU gave the same results compared to TBD under similar conditions. [b] Room temperature. [c] T = 80 ºC. [d] pCO_2^0 = 30 bar. [e] Also triol (8 %) was formed; [f] 72 h. [g] MEK (1.0 mL).

Also, variations in the reaction time and concentration showed no remarkable changes in the cyclic carbonate product ratio (Table **4.4**; entries 6 and 7). Different solvents were also tested with the best results found for those reactions employing MEK or ACN (Table **4.4**; entries 8-13). Finally, when TBD was replaced by DBU under the best reaction conditions (Table **4.4**; entry 2) the same experimental result was obtained. The combined results of Table **4.4** strongly suggest that a thermodynamic mixture of carbonates is typically formed with carbonate **4.3b1** being the major component.

4.2.3.2 – Selective protection of the primary alcohol

Since the trisubstituted cyclic carbonate **4.3b1** cannot be obtained through classical nucleophilic ring opening of the epoxide, its formation is therefore ascribed to an equilibration between **4.3b1** and **4.3b2** (both carbonates being thermodynamically linked) under the experimental conditions with a key role for the base (TBD or DBU).

Table 4.5: Study of the activity for different catalytic acetyl transfer reactions.



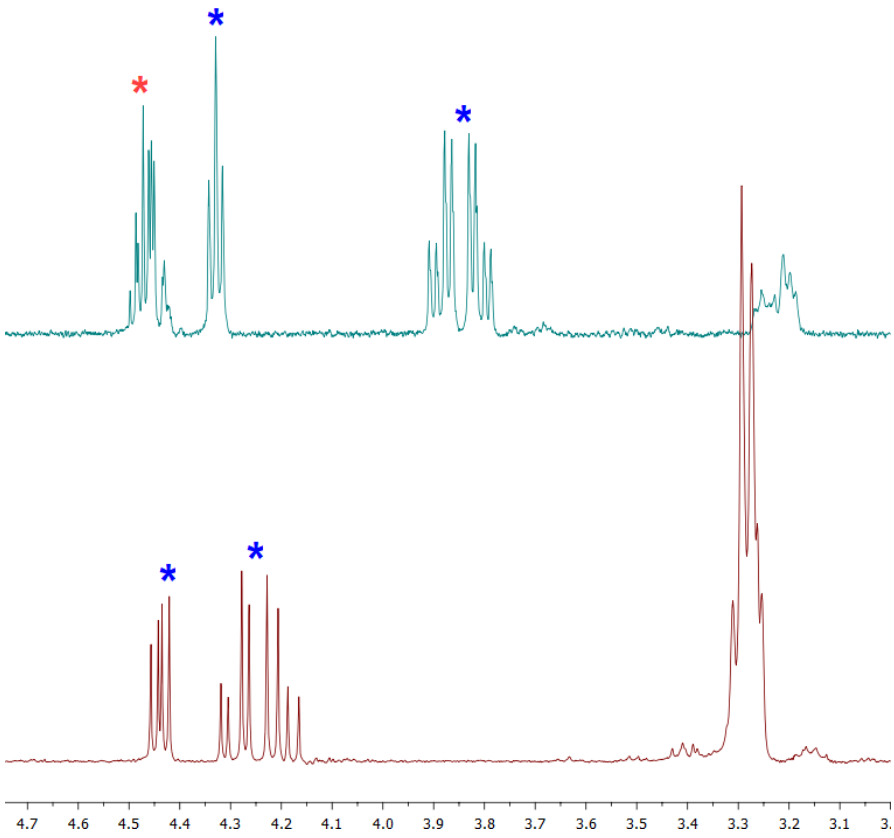
4.3b1 + 4.3b2 → 4.3c1 (AcIm)

Entry	Catalyst	Time / [h]	Conversion / [%]
1	TBD	1	>99
2	DBU	4	>99
3	–	72	<1

General reaction conditions: Cyclic carbonate mixture (0.34 mmol; ratio **4.3b1**:**4.3b2** = 7:3), catalyst loading (20 mol%), MEK (1.7 mL), 1-acetylimidazole (1.5 equiv.), rt.

This hypothesis could be confirmed as the isolated mixture of cyclic carbonates **4.3b1** and **4.3b2** (ratio 7:3) was selectively and quantitatively converted (see Figure **4.3**) into the acetyl-protected, trisubstituted carbonate **4.3c1** in the presence of either TBD or DBU (Table **4.5**; entries 1 and 2), while no conversion was noted in the absence of any catalyst.

Figure 4.3: Selected ^{1}H NMR region (3.0–4.7 ppm) of the carbonate product mixture (top; red (4.3b2) and blue (4.3b1) stars) and selective formation of product 4.3c1 (blue stars) after *in situ* acetylation (bottom).

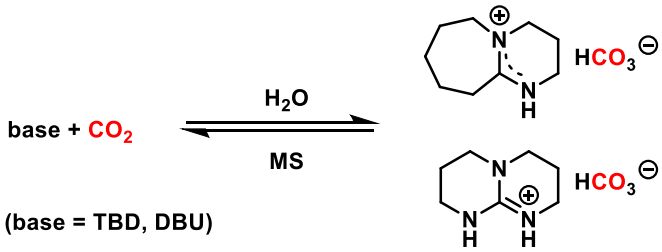


4.2.3.3 – One pot synthetic protocol

Further efforts focused on the development of an *in situ* protecting protocol avoiding the isolation of the previously formed cyclic carbonate mixture. TBD and DBU behave in the same way in the transformation of trisubstituted epoxides towards their corresponding cyclic carbonates in terms of cyclic carbonate formation and selective primary alcohol protection. Therefore, we chose DBU as a cheaper catalytic solution. Since DBU acts as catalyst for both the coupling reaction of carbon dioxide and oxiranes and the primary alcohol protection reaction, first 1-acetylimidazole was directly added to the reaction mixture. This

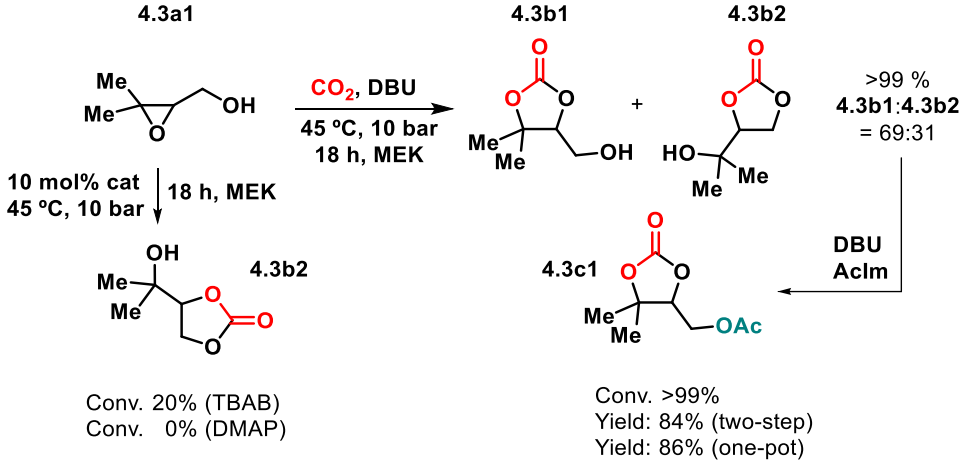
first attempt showed no conversion due to a known catalyst deactivation mechanism[42–44] that operates when DBU reacts with CO_2 in the presence of water (Scheme **4.3**).

Scheme 4.3: Catalyst deactivation by reaction with CO_2 in the presence of water.



The addition of molecular sieves to the reaction slightly improved the yield, but the addition of a new batch of DBU (1 equiv) resulted in quantitative and selective conversion of the cyclic carbonate mixture into the most substituted cyclic carbonate product. Finally, the formation of **4.3c1** from **4.3a1** through a one-pot domino sequence (Scheme **4.4**) was successfully probed and provided the trisubstituted cyclic carbonate **4.3c1** in 86% yield compared to 84% yield obtained in the two-step synthetic route in the presence of DBU/AcIm.[45,46] These results imply that the more substituted carbonate product is favored and can be conveniently and selectively trapped *in situ* to provide elusive CO_2 derived heterocycles.

Scheme 4.4: One-pot protection protocol and comparison with the two-step synthesis.



4.2.4 – Substrate scope

The successful synthesis of carbonate **4.3c1** inspired us to examine the generality of this domino process using primarily tri- and tetra-substituted epoxides (Scheme **4.5**). Thus, we probed more functional epoxide precursors in the preparation of **4.4c1 - 4.7c1** and found that in all these cases the trisubstituted acetyl-protected carbonates could be selectively formed and in high isolated yields (75-90%). Importantly, the presence of additional double bonds or epoxide groups did not interfere with the chemo-selectivity of these conversions, and only the conversion of the glycidol fragments was observed. For **4.4c1** (*cf.*, synthesis of cyclic carbonate **4.3c1**) the one-pot procedure was feasible and provided a higher yield (90%) of the carbonate compared to the two-step procedure (83%). For all subsequent syntheses (*cf.*, **4.5c1** – **4.11c1**) we therefore used the one-pot, three step sequence.

Delightfully, the tetra-substituted carbonates **4.8b1 – 4.10c1** could also be prepared conveniently in appreciable isolated yields (40-75%) and the structure of compound **4.8b1** could be confirmed by X-ray analysis (see Figure **4.4**). However, for the coupling of carbon dioxide and tetrasubstituted epoxides the selectivity towards the formation of the corresponding *tetra*-substituted cyclic carbonate using a similar domino process has some restriction. Upon formation of the carbonate mixture, the bulkiness around the alcohol unit may reduce the kinetics of the requisite carbonate interconversion prior to the protection step using 1-acetylimidazole. Generally, the ratio between the tetra- and di-substituted products remained unaffected upon protection. Only full selectivity towards the formation of the tetrasubstituted carbonate was observed for compound **4.9c1** and consequently a higher yield (75%) could be attained. Nonetheless, the five examples of tetrasubstituted cyclic carbonates constitute the first [3+2] cycloadditions between tetra-substituted epoxides and CO_2.[16]

Scheme 4.5: Substrate scope when using tri- and tetra-substituted epoxides using a domino [3+2] cycloaddition/Payne-type rearrangement process in the presence of DBU and AcIm.

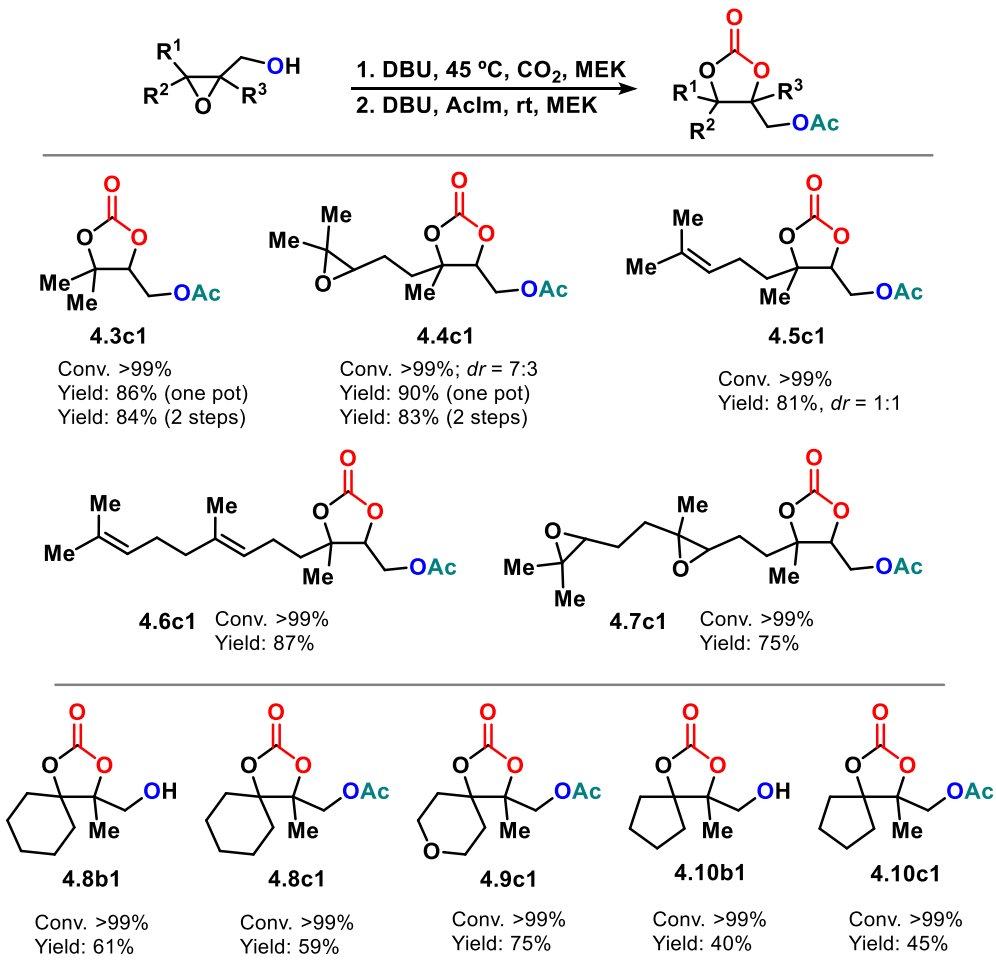
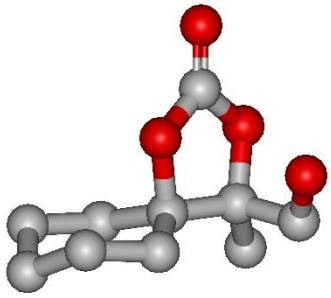


Figure 4.4: X-ray molecular structure of the tetrasubstituted cyclic carbonate 4.8b1.

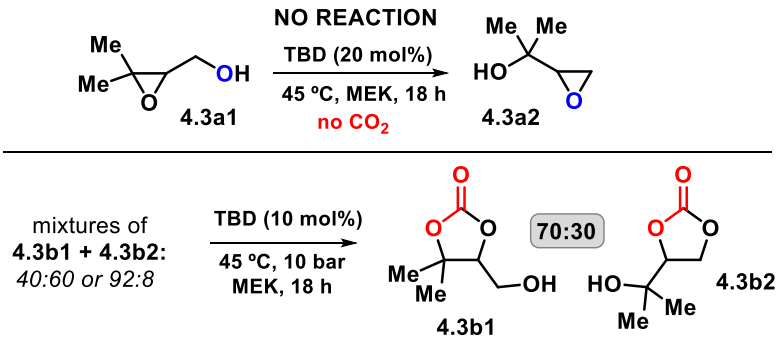


4.2.5 – Control experiments

In order to further support the mechanistic proposal that a Payne-like rearrangement takes place between carbonate products and that the desired tri/tetra-substituted products can be trapped by selective protection, we carried out a number of control experiments (Scheme **4.6**).

First, the conversion of trisubstituted epoxide **4.3a1** was probed in the *absence* of CO_2 to see whether Payne rearrangement occurs *prior to* carbonate formation, but no conversion of **4.3a1** into the mono-substituted epoxide **4.3a2** (Scheme **4.6**; top) was noted. This implies that the presence of (electrophilic) CO_2 is required for the domino conversion leading to the trisubstituted carbonate product. Different mixtures of cyclic carbonates **4.3b1** and **4.3b2** (**4.3b1**/**4.3b2** = 40:60 and 92:8) were then subjected to the general catalytic conditions (Scheme **4.6**; bottom), and both equilibrated to a 70:30 mixture of **4.3b1** and **4.3b2**. These observations support the view that the formation of the mixture of carbonates is base-mediated and follows initial formation of **4.3b2** from **4.3a1**.

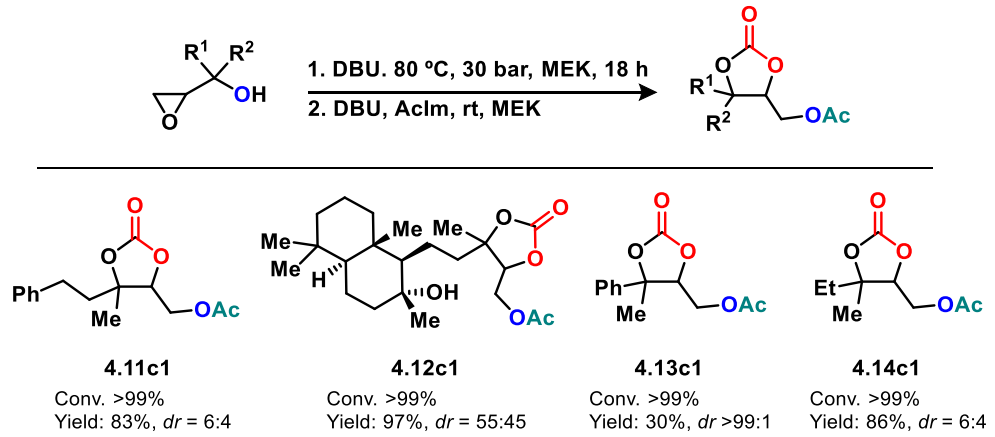
Scheme 4.6: Control experiments to support the rearrangement at the carbonate level.



Similar types of acetyl-protected *tri*-substituted carbonates **4.11** – **4.15c1** (Scheme **4.7**) were also conveniently and selectively derived from *mono*-substituted epoxides having a tertiary alcohol unit. The synthesis of these latter compounds further illustrates the value of this domino approach and its potential application as a general synthetic protocol for the formation of highly substituted cyclic carbonates from CO_2. More importantly, it also shows as in the case of trisubstituted epoxides that the more substituted product can be trapped as demonstrated in Table **4.5**. While the conversion of these mono-substituted epoxides is more

sluggish due to steric effects upon activating CO_2 through the alcohol unit and higher reaction temperatures (80 ºC) are thus warranted, similar 7:3 mixtures of carbonates were observed *prior to* alcohol protection by 1-acetylimidazole.

Scheme 4.7: Substrate scope for the conversion of mono-substituted epoxides.



4.11c1
Conv. >99%
Yield: 83%, *dr* = 6:4

4.12c1
Conv. >99%
Yield: 97%, *dr* = 55:45

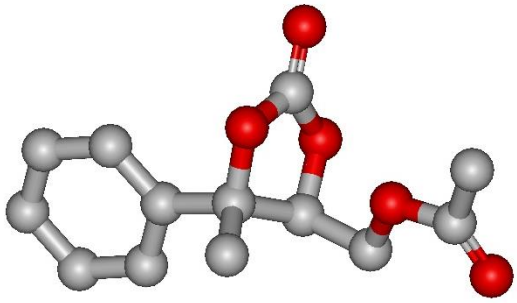
4.13c1
Conv. >99%
Yield: 30%, *dr* >99:1

4.14c1
Conv. >99%
Yield: 86%, *dr* = 6:4

The connectivity pattern of one of the prepared trisubstituted cyclic carbonate structures could be confirmed by X-ray analysis (compound **4.13c1**, see Figure **4.5**). The selective formation of this carbonate **4.13c1**, however, was compromised by the presence of an electron-withdrawing Ph group that enables a faster protection than equilibration of the intermediate mixture of carbonates. Consequently, a lower ratio (83:17) between the protected tri- and mono-substituted carbonate was formed.[b]

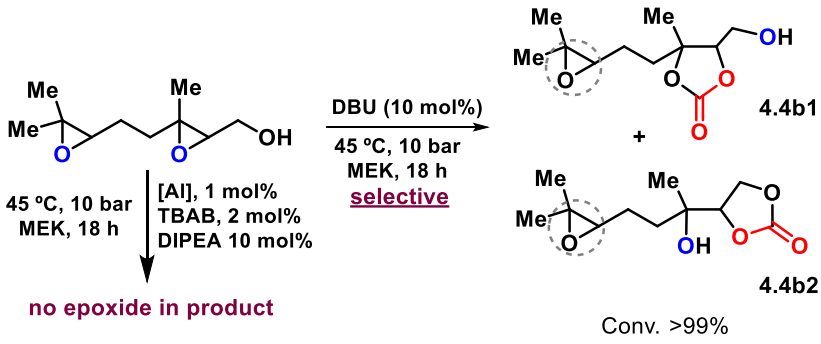
[b] **Note 2;** trisubstituted carbonate **4.13c1** was isolated as a single diastereoisomer (*dr* >99:1) by chromatographic separation in a relatively low yield (30%). Note that initially quantitative formation of a mixture of both tri- and mono-substituted cyclic carbonate product (ratio tri/mono; 83:17, *dr* = 57:43 in favour of the trisubstituted product)

Figure 4.5: X-ray molecular structure determined for compound 4.13c1.



Finally, the selective conversion of an epoxy alcohol within a diepoxide substrate by using a DBU-promoted [3+2] cycloaddition in the presence of CO_2 could be highlighted. The catalytic conversion of epoxides in general requires the use of an external nucleophile for the initial ring opening step of the epoxide, with harsher experimental conditions required for the more substituted epoxides. Epoxy alcohols, however, undergo conversion under organocatalytic control without the need for a nucleophilic additive (this chapter) giving access to a thermodynamic mixture of cyclic carbonate products. This emphasizes the key difference in reactivity observed between standard epoxides and epoxy alcohols having similar substitution patterns.

Scheme 4.8: Difference in reactivity for epoxide and epoxy alcohol units within the same substrate.



Scheme **4.8** shows the difference in reactivity of geraniol diepoxide in the coupling reaction with CO_2 towards the formation of cyclic carbonates using either **metal** or **organo** catalysis. When geraniol diepoxide **4.4a1** is converted with an aluminum-based binary

catalytic system[41] *both* epoxides present in the substrate structure are transformed. However, when the same substrate is converted in the presence of DBU as catalyst, *selective* transformation of the epoxy alcohol unit takes place and the corresponding thermodynamic mixture of cyclic carbonates is produced. This regioselective transformation of similar epoxide groups within a single substrate may be of value in synthetic chemistry.

4.3 – Conclusions

Sterically hindered epoxides are highly challenging substrates in the [3+2] cycloaddition of epoxides and CO_2 towards cyclic carbonates. In this chapter we propose a conceptual new strategy for the synthesis of highly substituted (tri/tetra) carbonates by employing a substrate-controlled activation of CO_2 through an epoxy alcohol unit to first give rise to a thermodynamic mixture of cyclic carbonates. This latter mixture is then conveniently converted into the most substituted *O*-protected carbonate product by selective trapping of the most reactive alcohol using 1-acetylimidazole. Both steps are catalyzed by an organic superbase (DBU or TBD) and the protocol is characterized by its unusual scope in reaction partners, the mild reaction conditions and site-selectivity compared against a known Al-based methodology. While organocatalysis typically suffers from a lower degree of substrate activation potential, the presented results in this chapter demonstrate a unique case where organocatalysis outcompetes metal-based approaches in the transformation of CO_2 into cyclic carbonates.

As far as we know, the first examples of organocatalytic mediated synthesis of tri- and tetra-substituted cyclic carbonates using [3+2] cycloadditions are here reported, and the work further illustrates that cascade approaches may be of great use to expand on the use of multifunctional cyclic carbonates in synthetic chemistry.

4.4 – Experimental section

4.4.1 – General information and instrumentation

General information

Methylethyl ketone (MEK) and carbon dioxide (purchased from PRAXAIR) were used as received without further purification or drying prior to use. Glycidol, methyl glycidyl ether and phenyl glycidol were purchased at Aldrich, Acros or TCI and used without further purification. ^{1}H NMR spectra were recorded on Bruker AV-300, AV-400 or AV-500 spectrometers and referenced to the residual deuterated solvent signals. FT-IR measurements were carried out on a Bruker Optics FTIR-ATR TR0 spectrometer. Exact mass analyses and X-ray diffraction studies were performed by the Research Support Area (RSA) at ICIQ.

4.4.2 – Synthesis of epoxides

Synthesis of tri-substituted epoxides

Epoxides (3,3-dimethyloxiran-2-yl)methanol (**4.3a1**), (3-(2-(3,3-dimethyloxiran-2-yl)ethyl)-3-methyloxiran-2-yl)methanol (**4.4a1**), and (3-(2-(3-(2-(3,3-dimethyloxiran-2-yl)ethyl)-3-methyloxiran-2-yl)ethyl)-3-methyloxiran-2-yl)methanol (**4.7a1)** were prepared from the corresponding alkenes according to previously reported epoxidation protocols by addition of 2 equivalents of *m*CPBA per alkene unit present in the substrate.[25] Epoxides (3-methyl-3-(4-methylpent-3-en-1-yl)oxiran-2-yl)methanol (**4.5a1**) and (*Z*)-(3-(4,8-dimethylnona-3,7-dien-1-yl)-3-methyloxiran-2-yl)methanol (**4.6a1**) were synthesized following a vanadium-based epoxidation method.[47]

Synthesis of tetra-substituted epoxides

Epoxides (2-methyl-1-oxaspiro[2.5]octan-2-yl)methanol (**4.8a1**), (2-methyl-1,6-dioxaspiro[2.5]octan-2-yl)methanol (**4.9a1**) and (2-methyl-1-oxaspiro[2.4]heptan-2-yl)methanol (**4.10a1**) were prepared from the corresponding ketone according to a previously reported 3-step synthetic route.[48]

Synthesis of mono-substituted epoxides

Epoxides 2-(oxiran-2-yl)propan-2-ol (**4.3a2**), 2-(oxiran-2-yl)-4-phenylbutan-2-ol (**4.11a2**), sclareol epoxide (**4.12a2**), 1-(oxiran-2-yl)-1-phenylethan-1-ol (**4.13a2**) and 2-(oxiran-2-yl)butan-2-ol (**4.14a2**) were prepared from the corresponding ketones according to previously reported epoxidation protocols.[41]

4.4.3 – General procedure for the catalytic experiments

Formation of the cyclic carbonate product mixtures

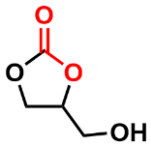
All reactions were performed in a 30 mL stainless steel reactor. In a typical experiment, a solution of the TBD (10.0 – 20.0 mol%) and epoxide (2.0 mmol) in MEK (5.0 mL) was added to a stainless steel reactor. Three cycles of pressurization and depressurization of the reactor with 5 bar of CO_2 pressure were carried out before finally stabilizing the pressure at 10 – 30 bar. The reactor was then heated to the required temperature and left stirring for another 18 h. The reactor was cooled down, depressurized and an aliquot of the solution was analyzed by means of ^{1}H NMR spectroscopy using $CDCl_3$ as the solvent. For the reactions carried out in the substrate scope phase related the free OH-containing cyclic carbonate products, the products were purified by flash chromatographic purification.

One-pot protection protocol

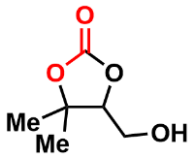
Upon targeting the protected cyclic carbonate product, the autoclave reactor was opened, and the reaction mixture was stirred for 15 min open to air. Then DBU (1 equiv) was

directly added at room temperature to the reaction mixture, followed by the addition of 1-acetylimidazole (1.5 equiv). After 1.5 h, the reaction was transferred to a round-bottom flask, concentrated and purified by flash column chromatography using a mixture of acetate/hexane as eluent.

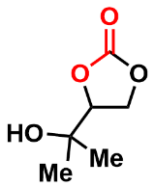
4.4.4 – Spectroscopic data for all compounds



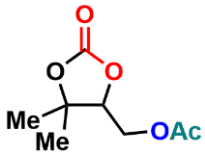
Compound 4.1b; 4-(hydroxymethyl)-1,3-dioxolan-2-one;[49] **^{1}H NMR (400 MHz, DMSO, 298 K) δ** 5.25 (t, $^3J_{HH}$ = 5.6 Hz, 1H), 4.84 - 4.75 (m, 1H), 4.51 – 4.47 (m, 1H), 4.28 (dd, $^2J_{HH}$ = 7.9 Hz, $^3J_{HH}$ = 5.9 Hz, 1H), 3.66 (ddd, $^2J_{HH}$ = 12.6 Hz, $^3J_{HH}$ = 5.5 Hz, $^3J_{HH}$ = 2.9, 1H), 3.50 (ddd, $^2J_{HH}$ = 12.6 Hz, $^3J_{HH}$ = 5.7 Hz, $^3J_{HH}$ = 3.4 Hz, 1H); **^{13}C NMR (101 MHz, DMSO, 298 K) δ** 155.13, 76.99, 65.84, 60.57; **IR (neat, cm^{-1})** 3418 (OH), 1763 (C=O).



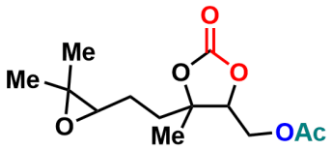
Compound 4.3b1; 4-(2-hydroxypropan-2-yl)-1,3-dioxolan-2-one; ^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ 4.52 - 4.40 (m, 3H), 2.34 (bs, 1H), 1.34 (s, 3H), 1.18 (s, 3H); **^{13}C NMR (126 MHz, $CDCl_3$, 298 K) δ** 155.37, 81.95, 70.05, 65.68, 25.50, 24.38; **IR (neat, cm^{-1})** 3459 (OH), 2980 (C-H), 1775 (C=O).



Compound 4.3b2; 4-(2-hydroxypropan-2-yl)-1,3-dioxolan-2-one; ^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ 4.52 - 4.40 (m, 3H), 2.34 (bs, 1H), 1.34 (s, 3H), 1.18 (s, 3H); **^{13}C NMR (126 MHz, $CDCl_3$, 298 K) δ** 155.37, 81.95, 70.05, 65.68, 25.50, 24.38; **IR (neat, cm^{-1})** 3459 (OH), 2980 (C-H), 1775 (C=O).

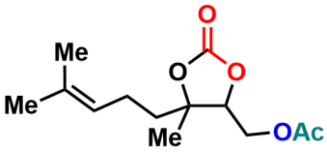


Compound 4.3c1; (5,5-dimethyl-2-oxo-1,3-dioxolan-4-yl)methyl acetate; ^{1}H NMR (500 MHz, $CDCl_3$, 298K) δ 4.46 (dd, $^3J_{HH}$ = 6.6 Hz, $^3J_{HH}$ = 4.3 Hz, 1H), 4.32 (dd, $^2J_{HH}$ = 12.3 Hz, $^3J_{HH}$ = 4.3 Hz, 1H), 4.23 (dd, $^2J_{HH}$ = 12.3 Hz, $^3J_{HH}$ = 6.6 Hz, 1H), 2.12 (s, 3H), 1.56 (s, 3H), 1.45 (s, 3H); **^{13}C NMR (126 MHz, $CDCl_3$, 298 K) δ** 170.27, 153.43, 83.00, 81.50, 61.20, 26.93, 21.13, 20.63; **IR (neat, cm^{-1})** 2985 (C-H), 1791 (C=O), 1742 (C=O); **HRMS (ESI+; MeOH):** *m/z* calcd. ($C_8H_{12}NaO_5$) 211.0577 $(M+Na)^+$; found: 211.0576.

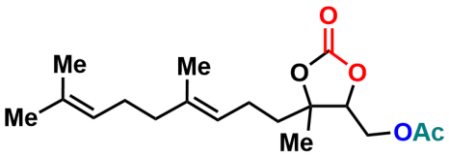


Compound 4.4c1; (5-(2-(3,3-dimethyloxiran-2-yl)ethyl)-5-methyl-2-oxo-1,3-dioxolan-4-yl)methyl acetate; dr: (69:31) **^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ** 4.53 - 4.45 (m, 1H), 4.41 - 4.22 (m, 2H), 2.77 - 2.69 (m, 1H), 2.12 (s, 3H), 2.08 - 1.59 (m, 4H), 1.58 - 1.49 (m, 3H), 1.34 - 1.26

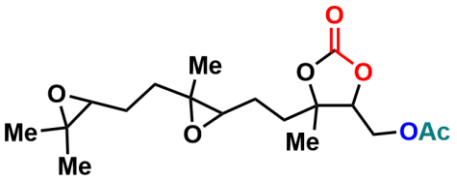
(m, 6H); **^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ** 170.39, 170.33, 153.32, 153.28, 84.68, 84.43, 82.50, 82.45, 63.75, 63.35, 60.94, 60.87, 59.07, 58.83, 31.04, 31.00, 24.91, 24.89, 24.08, 23.63, 23.29, 23.25, 20.78, 18.90, 18.85; **IR (neat, cm^{-1})** 2977 (C-H), 1794 (C=O), 1744 (C=O); **HRMS (ESI+; MeOH):** *m/z* calcd. ($C_{13}H_{20}NaO_6$) 295.1152 $(M+Na)^+$; found: 295.1156.



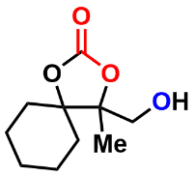
Compound 4.5c1; (5-methyl-5-(4-methylpent-3-en-1-yl)-2-oxo-1,3-dioxolan-4-yl)methyl acetate; dr (51:49); **^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ** 5.13 - 5.02 (m, 1H), 4.44 (dd, $^3J_{HH}$ = 6.9 Hz, $^3J_{HH}$ = 4 Hz, 1H), 4.33 (dd, $^3J_{HH}$ = 12.3 Hz, $^3J_{HH}$ = 4 Hz, 1H), 4.23 (dd, $^3J_{HH}$ = 12.3 Hz, $^3J_{HH}$ = 6.9 Hz, 1H), 2.24 - 2.13 (m, 1H), 2.11 (s, 3H), 1.83 - 1.73 (m, 1H), 1.58 - 1.51 (m, 8H); **^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ** 170.45, 153.58, 133.55, 122.38, 84.98, 82.58, 61.11, 34.20, 25.79, 23.87, 22.13, 20.79, 17.85; **IR (neat, cm^{-1})** 2973 - 2928 (C-H), 1795 and 1745 (C=O); **HRMS (ESI+; MeOH):** *m/z* calcd. ($C_{11}H_{15}NaO_5$) 279.1203 $(M+Na)^+$; found: 279.1192.



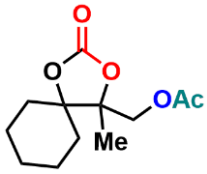
Compound 4.6c1; (*E*)-(5-(4,8-dimethylnona-3,7-dien-1-yl)-5-methyl-2-oxo-1,3-dioxolan-4-yl)methyl acetate; *dr* (>99:1) **^{1}H NMR (300 MHz, $CDCl_3$, 298 K) δ** 5.11 - 5.03 (m, 2H), 4.47 (dd, $^3J_{HH}$ = 7.0 Hz, $^3J_{HH}$ = 4.0 Hz, 1H), 4.36 (dd, $^2J_{HH}$ = 12.0 Hz, $^3J_{HH}$ = 4.0 Hz, 1H), 4.25 (dd, $^2J_{HH}$ = 12.0 Hz, $^3J_{HH}$ = 7.0 Hz, 1H), 2.22 - 2.14 (m, 1H), 2.12 (s, 3H), 2.09 - 1.95 (m, 3H), 1.87 - 1.73 (m, 1H), 1.68 (s, 3H), 1.61 (s, 3H), 1.60 (s, 3H), 1.54 (s, 3H), 1.53 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ** 170.44, 153.57, 137.16, 131.72, 124.19, 122.24, 84.99, 82.58, 61.11, 39.72, 34.16, 26.70, 25.83, 23.85, 22.01, 20.77, 17.83, 16.20; **IR (neat, cm^{-1})** 2922 (C-H), 1797 (C=O), 1747 (C=O). **HRMS (ESI+; MeOH):** *m/z* calcd. ($C_{18}H_{28}NaO_5$) 347.1829 $(M+Na)^+$; found: 347.1830.



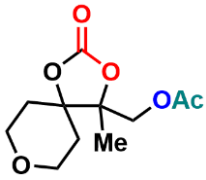
Compound 4.7c1; (5-(2-(3-(2-(3,3-dimethyl oxiran-2-yl) ethyl)-3-methyloxiran-2-yl) ethyl) -5-methyl-2-oxo- 1,3-dioxolan-4-yl) methyl acetate; ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 4.52 - 4.47 (m, 1H), 4.41 - 4.32 (m, 1H), 4.31 - 4.22 (m, 1H), 2.80 - 2.65 (m, 2H), 2.12 (s, 3H), 2.06 – 1.60 (m, 7H), 1-56 - 1.51 (m, 3H) 1.35 - 1.21 (m, 10H); **^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ** 170.56, 153.02, 84.62, 84.44, 82.55, 68.03, 63.98, 63.85, 63.07, 62.83, 62.53, 62.08, 61.09, 60.97, 60.87, 58.55, 58.36, 53.54, 35.92, 35.79, 35.22, 31.01, 30.95, 30.88, 24.95, 24.84, 24.61, 24.01, 23.64, 23.21, 20.75, 18.84, 18.75, 16.93, 16.63, 16.52.; **IR (neat, cm^{-1})** 2967 (C-H), 1798 (C=O), 1745 (C=O); **HRMS (ESI+; MeOH):** *m/z* calcd. ($C_{18}H_{28}NaO_7$) 379.1727 $(M+Na)^+$; found: 379.1733.



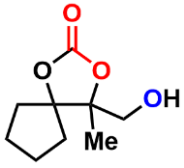
Compound 4.8b1; 4-(hydroxymethyl)-4-methyl-1,3-dioxaspiro [4.5]decan-2-one; ^{1}H NMR (300 MHz, $CDCl_3$, 298 K) δ 3.81 (dd, $^{2}J_{HH}$ = 12.0Hz, $^{3}J_{HH}$ = 5.1 Hz, 1H), 3.68 (dd, $^{2}J_{HH}$ = 12.0 Hz, $^{3}J_{HH}$ = 7.2 Hz 1H), 2.27 - 2.17 (m, 1H), 2.15 - 1.89 (m, 2H), 1.80 - 1.56 (m, 5H), 1.53 - 1.39 (m, 2H), 1.37 (s, 3H), 1.30 - 1.14 (m, 1H); **^{13}C NMR (126 MHz, $CDCl_3$, 298 K) δ** 154.15, 87.31, 86.98, 65.09, 32.16, 29.72, 25.00, 22.11, 21.79, 16.84; **IR (neat, cm^{-1})** 3298 (O-H), 2934 - 2860 (C-H), 1765 (C=O); **HRMS (ESI+; MeOH):** *m/z* calcd. ($C_{10}H_{16}NaO_4$) 223.0941 $(M+Na)^+$; found: 223.0935.



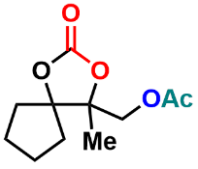
Compound 4.8c1; (4-methyl-2-oxo-1,3-dioxaspiro[4.5]decan-4-yl) methyl acetate; ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 4.24 - 4.15 (m, 2H), 2.11 (s, 3H), 2.01 - 1.93 (m, 2H), 1.81 - 1.64 (m, 5H), 1.46 - 1.35 (m, 5H), 1.27 - 1.14 (m, 1H); **^{13}C NMR (126 MHz, $CDCl_3$, 298 K) δ** 170.30, 153.48, 86.55, 85.35, 65.32, 31.91, 30.02, 24.95, 22.06, 21.78, 20.84, 17.47; **IR (neat, cm^{-1})** 2937 - 2864 (C-H), 1792 (C=O), 1744 (C=O); **HRMS (ESI+; MeOH):** *m/z* calcd. ($C_{12}H_{18}NaO_5$) 265.1046 $(M+Na)^+$; found: 265.1044.



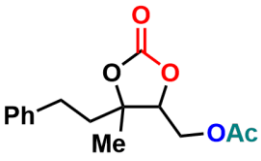
Compound 4.9c1; (4-methyl-2-oxo-1,3,8-trioxaspiro[4.5]decan-4-yl)methyl acetate; ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 4.25 (d, $^{2}J_{HH}$ = 12.1 Hz, 1H), 4.15 (d, $^{2}J_{HH}$ = 12.1 Hz, 1H), 4.01 - 3.92 m, 2H), 3.81 - 3.70 (m, 2H), 2.12 (s, 3H), 1.86 - 1.78 (m, 4H), 1.42 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ** 169.92, 152.69, 84.75, 83.86, 64.89, 63.57, 63.50, 32.11, 30.44, 20.65, 17.40; **IR (neat, cm^{-1})** 2966 - 2868 (C-H), 1798 (C=O), 1744 (C=O); **HRMS (ESI+; MeOH):** *m/z* calcd. ($C_{11}H_{16}NaO_6$) 267.0839 $(M+Na)^+$; found: 267.0827.



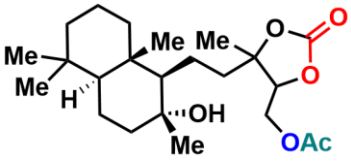
Compound 4.10b1; (4-methyl-2-oxo-1,3-dioxaspiro[4.4]nonan-4-yl) methyl acetate; ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 3.80 (d, $^{2}J_{HH}$ = 12.0 Hz, 1H), 3.70 (d, $^{2}J_{HH}$ = 12.0 Hz, 1H), 2.17 - 2.07 (m, 1H), 2.06 - 1.96 (m, 2H), 1.92 - 1.71 (m, 6H), 1.43 (m, 3H); **^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ** 153.93, 97.08, 85.84, 66.04, 34.58, 31.96, 22.68, 22.16, 18.24; **IR (neat, cm^{-1})** 3399 (OH), 2955 - 2878 (C-H), 1768 (C=O).



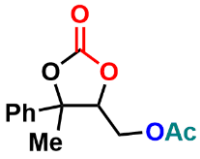
Compound 4.10c1; (4-methyl-2-oxo-1,3-dioxaspiro[4.4]nonan-4-yl) methyl acetate; ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 4.21 (s, 2H), 2.12 (s, 3H), 2.07 - 1.96 (m, 2H), 1.94 - 1.67 (m, 6H), 1.45 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ** 170.16, 96.40, 83.62, 66.16, 34.44, 31.93, 22.48, 22.16, 20.69, 18.55; **IR (neat, cm^{-1})** 2959 - 2879 (C-H), 1791 (C=O), 1744 (C=O); **HRMS (ESI+; MeOH):** *m/z* calcd. ($C_{11}H_{16}NaO_5$) 251.0890 $(M+Na)^+$; found: 251.0878.



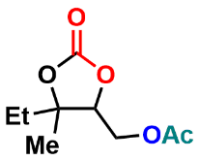
Compound 4.11c1; (5-methyl-2-oxo-5-phenethyl-1,3-dioxolan-4-yl)methyl acetate; dr (61:39) **^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ** 7.36 - 7.11 (m, 5H), 4.57 - 4.47 (m, 1H), 4.39 - 4.19 (m, 2H), 2.93 - 2.66 (m, 2H), 2.18 - 1.79 (m, 5H), 1.64 - 1.43 (m, 3H); **^{13}C NMR (126 MHz, $CDCl_3$, 298 K) δ** 170.41, 153.44, 140.45, 140.10, 128.90, 128.35, 126.66, 84.70, 82.62, 80.51, 61.60, 60.97, 42.02, 36.29, 29.75, 29.50, 23.93, 20.79, 20.76, 19.42, 17.71; **IR (neat, cm^{-1})** 3028 - 2942 (C-H), 1793 (C=O), 1742 (C=O); **HRMS (ESI+; MeOH):** *m/z* calcd. ($C_{15}H_{18}NaO_5$) 301.1046 $(M+Na)^+$; found: 301.1048.



Compound 4.12c1; sclareol trisubstituted cyclic carbonate; *dr* (55:45) **^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ** 4.62 - 4.41 (m, 1H), 4.38 - 4.17 (m, 2H), 2.15 - 2.08 (m, 3H), 2.06 - 1.93 (m, 1H), 1.90 - 1.77 (m, 1H), 1.69 - 1.57 (m, 3H), 1.56 (s, 3H), 1.48 - 1.36 (m, 6H), 1.31 - 1.23 (m, 3H), 1.20 - 1.13 (m, 3H), 1.11 - 1.01 (m, 1H), 0.96 - 0.85 (m, 5H), 0.82 - 0.76 (m, 6H); **^{13}C NMR (126 MHz, $CDCl_3$, 298 K)** δ 170.55, 153.80, 153.78, 85.39, 85.38, 82.81, 79.82, 74.51, 74.38, 61.78, 61.57, 61.40, 61.29, 56.26, 56.22, 44.86, 44.69, 43.10, 42.02, 42.01, 39.91, 39.28, 39.21, 37.74, 33.51, 33.37, 29.83, 27.05, 24.64, 24.51, 24.47, 21.58, 20.82, 20.81, 20.63, 20.60, 19.95, 19.07, 18.55, 15.58. **IR (neat, cm^{-1})** 3519 (OH) 2927 – 2850 (C-H), 1793 (C=O), 1747 (C=O). **HRMS (ESI+; MeOH):** *m/z* calcd. ($C_{23}H_{38}NaO_6$) 433.2561 $(M+Na)^+$; found: 433.2559.



Compound 4.13c1; (5-methyl-2-oxo-5-phenyl-1,3-dioxolan-4-yl) methyl acetate; dr (>99:1) **^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ** 7.49 - 7.33 (m, 5H), 4.79 (dd, $^3J_{HH}$ = 6.9 Hz, $^3J_{HH}$ = 4.1 Hz, 1H), 4.51 (dd, $^2J_{HH}$ = 12.3 Hz, $^3J_{HH}$ = 4.0 Hz, 1H), 4.39 (dd, $^2J_{HH}$ = 12.4 Hz, $^3J_{HH}$ = 6.8 Hz, 1H), 2.12 (s, 3H), 1.76 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ** 170.40, 153.25, 141.29, 129.31, 129.04, 124.04, 85.51, 82.68, 61.49, 22.27, 20.76; **IR (neat, cm^{-1})** 3041 - 2957 (C-H), 1792 (C=O), 1731 (C=O); **HRMS (ESI+; MeOH):** *m/z* calcd. ($C_{13}H_{14}NaO_5$) 273.0733 $(M+Na)^+$; found: 273.0730.



Compound 4.14c1; (5-ethyl-5-methyl-2-oxo-1,3-dioxolan-4-yl) methyl acetate; dr (58:42) **^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ** 4.55 - 4.47 (m, 1H), 4.40 - 4.32 (m, 1H), 4.29 - 4.20 (m, 1H), 2.16 - 2.12 (m, 3H), 1.93 - 1.80 (m, 1H), 1.68 - 1.57 (m, 1H), 1.55 - 1.41 (m, 3H), 1.12 - 1.02 (m, 1H); **^{13}C NMR (126 MHz, $CDCl_3$, 298 K) δ** 170.46, 153.62, 85.38, 85.28, 82.44, 80.12, 61.79, 61.04, 33.12, 27.03, 23.36, 20.78, 18.95, 7.89, 7.53; **IR (neat, cm^{-1})** 2980 (C-H), 1790 (C=O), 1742 (C=O); **HRMS (ESI+; MeOH):** *m/z* calcd. ($C_9H_{14}NaO_5$) 225.0733 $(M+Na)^+$; found: 225.0733.

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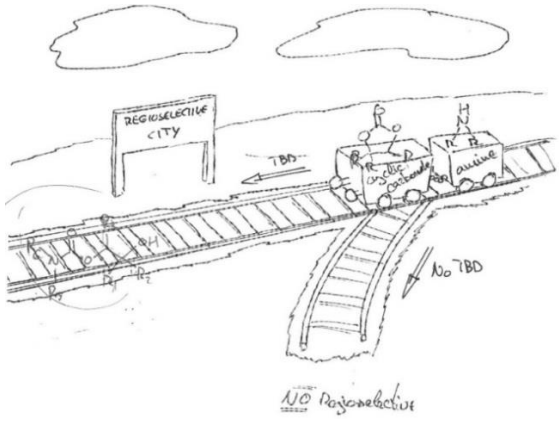
Chapter V

Regioselective organocatalytic formation of carbamates from substituted cyclic carbonates

A highly regio-selective catalytic approach has been developed towards carbamates derived from cyclic organic carbonates by reaction of the latter with amine reagents under organo-catalytic control. For various combinations of carbonate and amine substrates, an organocatalyst (TBD: triazabicyclodecene) was used to increase the reaction kinetics while exerting excellent regio-selective control. The current method is the first general approach towards the control over the regio-selectivity of this reaction using a wide variety of easily accessed substituted organic carbonates.



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UNIVERSITAT ROVIRA I VIRGILI
ORGANOCATALYTIC TRANSFORMATIONS OF CARBON DIOXIDE AND CYCLIC CARBONATES
Sergio Sopeña de Frutos

5.1 – Introduction

The use of carbon dioxide, a renewable carbon feed stock, in synthetic chemistry has witnessed a tremendous development in the last decade.[1–7] Common awareness has driven the scientific communities to develop new technologies for CO_2 storage and conversion, and undoubtedly catalysis has now become one of the key enabling strategies to access chemicals from this cheap and readily available carbon resource addressing the kinetic inertness of this small molecule.[8,9]

There exist also challenges associated with its high thermodynamic stability, and two important strategies for efficient conversion of CO_2 have become available: (1) the direct use of high-energy co-reactants to counter-balance the unfavorable thermodynamic stability of CO_2, and (2) the use of renewable wind, solar and thermal energy that can accommodate the formation of suitable reducing agents such as H_2 useful for sustainable CO_2 conversion.[10,11]

The use of small strained heterocycles, including epoxides and oxetanes, as co-reactants for CO_2 conversion has been exploited in the synthesis of cyclic[12–15] and poly-carbonates,[16–18] and this field has developed to a high level of sophistication. In particular, cyclic carbonates are among the most popular class of compounds being readily derived from CO_2 as they have commercial potential.[19–21] These cyclic carbonates may have various substitutions represented by simple mono-[22–28] up to more complex 4,5-di-[29–32] and 4,4´,5-tri-functionalized[33,34] scaffolds. The latter two categories are considered to be challenging to prepare using (catalytic) CO_2/epoxide coupling chemistry.

We have become interested in the post-modification of these cyclic carbonates as they represent interesting and modular building blocks in organic synthesis.[35–39] Cyclic organic carbonates are amenable towards ring opening by suitable nucleophiles, and their reaction with amines (aminolysis) has been used to prepare their corresponding carbamates,[40–43] which are interesting pharmaceutical scaffolds.[44] A recent and rational catalytic screening study by Andrioletti and coworkers[45] provided valuable insight into the type of catalyst and reaction conditions needed for high conversion in the aminolysis reaction of mono-substituted cyclic carbonates. Although this organocatalysis approach proved to be highly efficient, a general noted drawback was the lack of regio-control in the aminolysis step, *i.e.*

mixtures of two regio-isomeric carbamates were formed. As far as we know, there are only a few reports that show complete regiocontrol in the aminolysis of cyclic carbonates[46,47] and examples of such exquisite selectivity thus remain extremely limited.

The regio-selective ring-opening of cyclic carbonates is indeed an important feature. Recently the interest in the formation of more sustainable, non-isocyanate based polyurethanes (NIPUs) using bis-cyclic carbonates as intermediates and diamines as nucleophilic reagents has grown significantly.[48–55] In order to be able to control the polyurethane properties through the formation of a regio-regular polymer backbone, new synthetic methodology addressing the regio-selectivity in the aminolysis step is warranted. Thus, we set out to investigate this aspect in more detail in order to unravel the key features that help to increase regio-control.

Inspired by the use of TBD (triazabicyclodecene) as an efficient proton-relay catalyst in organic transformations,[36,45,56] we found that the combination of substituted organic carbonates and amine reagents in the presence of TBD as catalyst promotes the regio-selective cleavage of one of the C–O bonds. The presence of this organocatalyst also significantly enhances the overall kinetics, and gives access to a series of regio-pure carbamate structures in high isolated yields. This newly developed procedure towards these attractive scaffolds may hence provide a useful entry into regio-regular urethane based polymers.

5.2 – Results and discussion

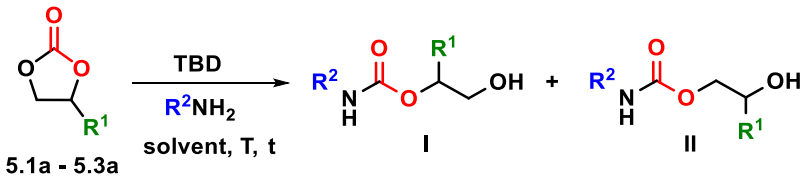
5.2.1 – Monosubstituted cyclic carbonates

First, we examined the aminolysis step in more detail and under various reaction conditions (Table **5.1**) using primarily mono-substituted cyclic carbonates and amines as reactants. Propylene carbonate (**5.1a**, PC) undergoes facile aminolysis in the presence of various amines (Table **5.1**, entries 1–9) using different amine reagents including *n*-butyl amine, cyclohexyl amine and morpholine. The influence of the addition of a known organocatalyst (TBD)[36,44] was also probed (Table **5.1**, entries 2, 4 and 6) and basically inverted the regioselectivity.[a] For the combination of PC and various amines the regioselectivity was virtually independent of the reaction temperature (Table **5.1**, entries 1, 3 and 5).

When styrene carbonate (**5.2a,** SC) was investigated (Table **5.1**, entries 10–13), the presence of TBD improved the preference towards formation of isomer **II**, but in neither of the cases very high regioselectivity was achieved. Next, we further studied the use of epichlorohydrin carbonate **5.3a** as substrate (Table **5.1**, entries 14–23). Aminolysis by *n*-butyl amine provided at 25 ºC already a high **II:I** isomer ratio of 87:13 (Table **5.1**, entry 14), which could be further improved to up to 95:5 by lowering the reaction temperature (Table **5.1**, entries 16 and 18). The presence of TBD did not exert a positive effect on the isomer ratio, which was slightly lower in the reactions utilizing this additive. The reaction times at –40 ºC had to be extended to 6 h to achieve quantitative conversion. Though the highest isomer ratio (**II**:**I**; 95:5) was achieved under different reaction conditions using a pre-isolated cyclic carbonate as substrate, it implies that electron-withdrawing groups (EWGs) help to favor the selective cleavage of the C–O bond adjacent to the position where the substituent is anchored onto the carbonate ring. This means that isomer **II** is formed preferentially, and this observation was further supported by changing the nature of the amine reagent from *n*-butyl to cyclohexyl amine (Table **5.1**, entries 20–23) giving a similar optimal result at –40 ºC (**II**:**I**; 93:7).

[a] **Note 1**; reactions were carried out under anhydrous conditions, but despite these precautions the formation of diol product could not be fully avoided.

Table 5.1: Screening of the aminolysis of mono-substituted cyclic carbonates under various reaction conditions.



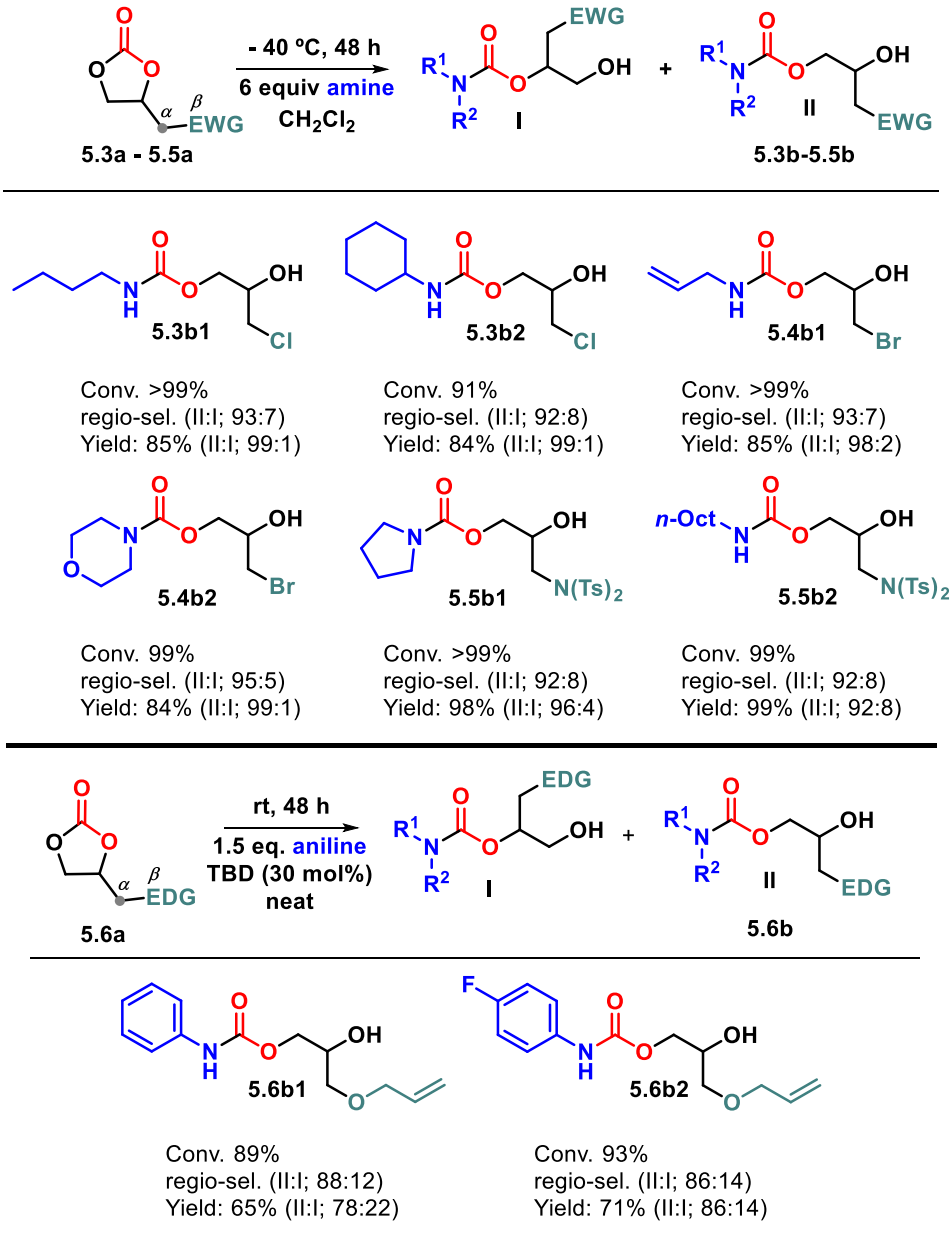
Entry	R^1	R^2	T [ºC]	t / Conv[h] / [%]	Cat.	II:I[a]
1	Me	Bu	50	2, >99	–	38:62
2	Me	Bu	50	2, >99	TBD	62:38
3	Me	Bu	25	2, >99	–	38:62
4	Me	Bu	25	2, >99	TBD	53:47
5	Me	Bu	–40	24, 5	–	37:63
6	Me	Bu	–40	24, 82	TBD	55:45
7	Me	Cy	25	2, >99	–	39:61
8	Me	Morph[b]	25	12, >99	–	34:66
9	Me	Allyl	25	2, >99	–	35:65
10	Ph	Bu	25	2, >99	–	66:34
11	Ph	Bu	25	2, >99	TBD	73:27
12	Ph	Bu	–40	24, >99	–	63:37
13	Ph	Bu	–40	24, >99	TBD	66:34
14	CH_2Cl	Bu	25	2, >99	–	87:13
15	CH_2Cl	Bu	25	2, >99	TBD	83:17
16	CH_2Cl	Bu	0	3, 99	–	91:9
17	CH_2Cl	Bu	0	3, >99	TBD	85:15
18	CH_2Cl	Bu	–40	6, >99	–	95:5
19	CH_2Cl	Bu	–40	6, >99	TBD	88:12
20	CH_2Cl	Cy	25	18, >99	–	82:18
21	CH_2Cl	Cy	25	18, >99	–	89:11[c]
22	CH_2Cl	Cy	–40	24, >99	–	90:10
23	CH_2Cl	Cy	–40	48, 92	–	93:7[c]

General reaction conditions: Cyclic carbonate (1.0 mmol), amine (2.0 mmol), neat. Reactions performed at –40 ºC were done in CH_2Cl_2 (2.0 mL), catalyst loading (5.0 mol%), Bu = *n*-butyl, Cy = cyclohexyl. [a] Determined by ^{1}H NMR ($CDCl_3$). [b] Morpholine used as amine reagent. [c] Using 6 equiv of amine reagent.

These optimal conditions for the aminolysis of mono-substituted cyclic carbonates having EWGs were then applied towards a small series of carbamate products **5.3b1** – **5.6b2** (Scheme **5.1**; top) with a focus on optimizing their isolated yield and regio-preference. In all cases, high selectivity towards isomer **II** was noted and excellent isolated yields were achieved.

In turn, when electron-donating groups (EDGs) are present in the cyclic carbonate substrate, we found that aminolysis can also be accomplished with high regio-control when combining glycidol-ether based cyclic carbonates and anilines as reaction partners at rt.[33] Anilines are poorly nucleophilic and therefore require a suitable catalyst to mediate the aminolysis process.[36] Carbamates **5.6b1** and **5.6b2** were thus obtained in appreciable yields and with moderately high regio-isomeric excess (Scheme **5.1**; below).

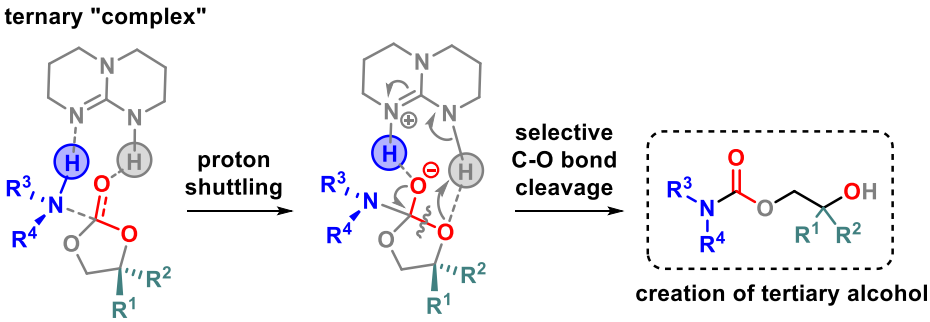
Scheme 5.1: Regioselective carbamate formation from monosubstituted cyclic carbonates with a pending EWG (top) or EDG (below) in the β position.



5.2.2 – Catalyst effect and kinetic profile

Previous computational studies related to the formation of *N*-aryl carbamates by aminolysis of mono-substituted cyclic carbonates using aromatic amines in the presence of TBD[36] revealed a ternary complex as intermediate involving the catalyst, cyclic carbonate and amine reagent interacting via H-bonding. Further, a subtle proton-shuttling mechanism between the three components allowed to deliver the carbamate target under mild reaction conditions (25 ºC).

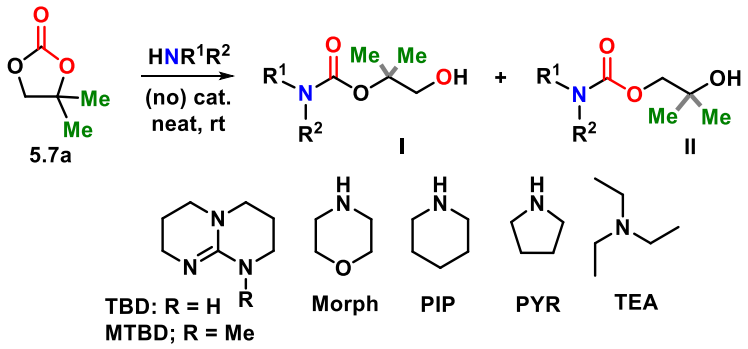
Figure 5.1: Proposed regioselective C-O bond breaking in *gem*-disubstituted cyclic carbonates by TBD using amine reagents.



We envisioned that an appropriate substitution of the cyclic carbonate substrate could enforce the TBD to direct the amine nucleophile to attack from the least hindered face resulting in site-selective C–O bond cleavage and thus regio-selective formation of the carbamate product (Figure **5.1**). With this idea in mind, we selected *gem*-disubstituted cyclic carbonate **5.7a** (Table **5.2**) as substrate to challenge this hypothesis and treated cyclic carbonate **5.7a** with three different amines (morpholine, piperidine, pyrrolidine and triethylamine) in the presence or absence of TBD (Table **5.2**; entries 1–8). These aminolysis reactions, in the absence of TBD, typically lead to mixtures of carbamates **I** (major product) and **II** having a primary and tertiary alcohol fragment, respectively (Table **5.2**; entries 1, 3 and 5). Remarkably, when TBD is added as a catalyst, exclusive formation of carbamate type **II** is observed (regio-selectivity >99:1) in all three cases (Table **5.2**; entries 2, 4 and 6). Whereas the catalyst-free reactions require longer time and larger excess of the amine reagent, the TBD-mediated processes are significantly faster in the presence of only two equivalents of the amine reagent. Finally, the use of MTBD underwent lower conversions

and loss of regiocontrol compared to TBD (Table 5.2; entry 7) while the use of a tertiary amine showed no formation of carbamates even in the presence of TBD (Table 5.2; entry 8)

Table 5.2: Screening studies towards the regioisomeric formation of carbamates I and II using cyclic carbonate 5.7a and various amines as substrates, and TBD as catalyst.



Entry	Cat.	Amine/equiv	t [h]	Conv. [%][a]	I [%][a]	II [%][a]
1	–	Morph, 6.0	18	>99	63	37
2	**TBD**	Morph, 2.0	0.5	>99	<1	>99
3	–	PIP, 6.0	18	>99	60	40
4	**TBD**	PIP, 2.0	6	>99	<1	>99
5	–	PYR, 6.0	18	>99	46	54
6	**TBD**	PYR, 2.0	6	>99	<1	>99
7	**MTBD**	Morph, 2.0	6	85	17	83
8	**TBD**	TEA, 2.0	6	<1	-	-

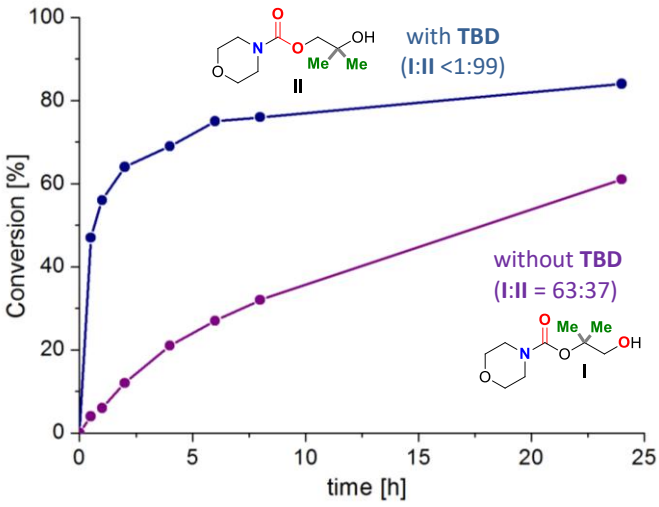
General reaction conditions: Cyclic carbonate (1.0 mmol), catalyst loading (TBD, 20 mol%), neat, amine quantity indicated. [a] Conversion and percentage of isomers **I** and **II** determined by ^{1}H NMR ($CDCl_3$)

The kinetic profiles of the catalyst-free process and the TBD-mediated aminolysis of cyclic carbonate **5.7a** by morpholine were then studied[b] in more detail (Figure **5.2**). From the conversion profiles it is clear that the TBD mediated aminolysis reaction (5.0 mol%, neat conditions) is much faster and exclusively delivers the carbamate type **II** whereas in the absence of TBD the other regio-isomer **I** is formed in excess (**II**:**I** = 37:63). The regio-

[b] **Note 2**; general reaction conditions: cyclic carbonate (1.0 mmol), morpholine (1.0 mmol), TBD (5.0 mol%), neat, rt.

selectivities were checked by ^{1}H NMR throughout the entire time span of these studies (0–24 h), and we found that for both the non-catalyzed and TBD-catalyzed processes these do not change with time.

Figure 5.2: Kinetic profiles for the aminolysis of cyclic carbonate 5.7a by morpholine in the absence or presence of TBD.

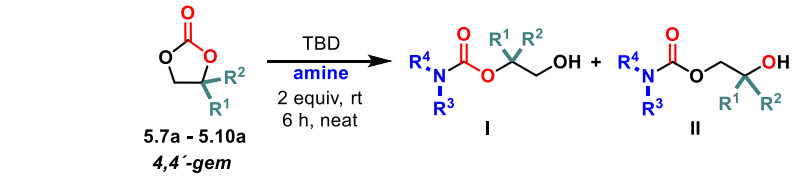


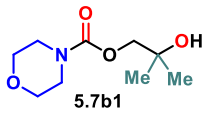
5.2.3 – Substrate scope

5.2.3.1 – Disubstituted cyclic carbonates

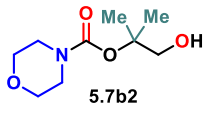
Inspired by these results, we decided to investigate the scope of reaction partners in more detail focusing first on the use of various *gem*-disubstituted cyclic carbonates and various amines (Scheme **5.2**) using TBD as catalyst. The morpholine based carbamate **5.7b1** was isolated in high yield (95%, isomer **II**), whereas the other isomer (**I**, carbamate **5.7b2**) was conveniently separated by column chromatography (after 18 h; **note:** in the absence of TBD) and isolated in an appreciable yield of 63%. These examples provided a (spectroscopic) reference for the synthesis and analysis of other carbamates (Scheme **5.2**; Carbamates **5.7b3 – 5.9b3**) derived from different *gem*-disubstituted cyclic carbonates and amine reagents.

Scheme 5.2: Regioselective carbamate formation from disubstituted cyclic carbonates using TBD (20 mol%) as catalyst.

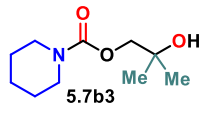



5.7b1

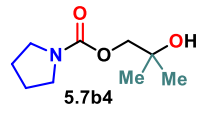
Conv. >99%
regio-sel. (II:I; 99:1)
Yield: 95% (II:I; 99:1)


5.7b2

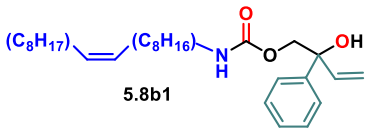
Conv. >99% (**no TBD**)
regio-sel. (II:I; 1:99)
Yield: 95% (II:I; 1:99)


5.7b3

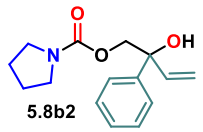
Conv. >99%
regio-sel. (II:I; 99:1)
Yield: 90% (II:I; 99:1)


5.7b4

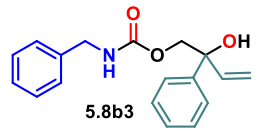
Conv. >99%
regio-sel. 99:1
Yield: 97% (99:1)


5.8b1

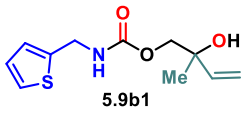
Conv. >99%
regio-sel. (II:I; >99:1)
Yield: 92% (II:I; >99:1)


5.8b2

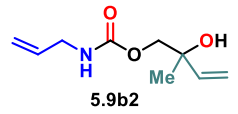
Conv. >99%
regio-sel. (II:I; >99:1)
Yield: 85% (II:I; >99:1)


5.8b3

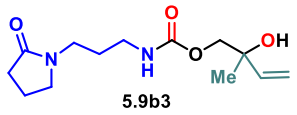
Conv. >99%
regio-sel. (II:I; >99:1)
Yield: 85% (II:I; >99:1)


5.9b1

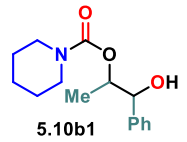
Conv. >99%
regio-sel. (II:I; >99:1)
Yield: 89% (II:I; >99:1)


5.9b2

Conv. >99%
regio-sel. (II:I; >99:1)
Yield: 96% (II:I; 99:1)


5.9b3

Conv. >99%
regio-sel. (II:I; >99:1)
Yield: 73% (II:I; 99:1)

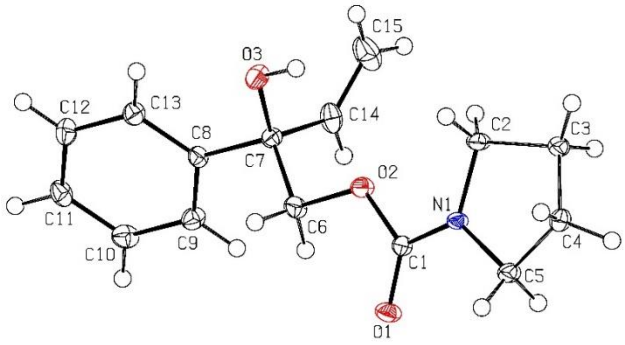

5.10b1

Conv. >99%
regio-sel. (II:I; 66:34)
Yield: 51% (II:I; >99:1)

The TBD-mediated aminolysis of cyclic carbonate **5.7a** and piperidine and pyrrolidine provided the carbamate products **5.7b3** (90%) and **5.7b4** (97%) in excellent yields and with high regio-selectivity. Other *gem*-disubstituted carbonates were also probed to examine the generality of the approach. The combination of a vinyl and phenyl group at the 4–position of the cyclic carbonate precursor (cyclic carbonate **5.8a**) also provided smooth access to various carbamate products of type **II** in high yield (**5.8b1 – 5.8b3**; 85-92%) incorporating useful olefin groups with post-synthetic modification potential. The carbamates **5.9b1 – 5.9b3** obtained from a *gem*-methyl-vinyl-substituted carbonate (cyclic carbonate **5.9a**) were also isolated in high yields and under excellent regio-control.

In order to test whether the *gem*-disubstitution in the carbonate precursor plays an important role, we probed the aminolysis of a *syn*-methyl-phenyl based cyclic carbonate **5.10a** by piperidine in the presence of TBD (*cf.*, formation of carbamate **5.10b1**). Interestingly, a much lower regio-selectivity was noted (**II**:**I**; 66:34). Thus, it seems that under these conditions no exclusive formation of a single ternary complex comprising TBD, the carbonate and the amine reagent is possible. The *syn*-disubstitution here does not provide enough steric differentiation between both sides of the carbonate scaffold to induce exclusive H-bonding with the TBD/amine scaffolds on the least hindered face.

Figure 5.3: X-ray molecular structure of carbamate 5.8b2.

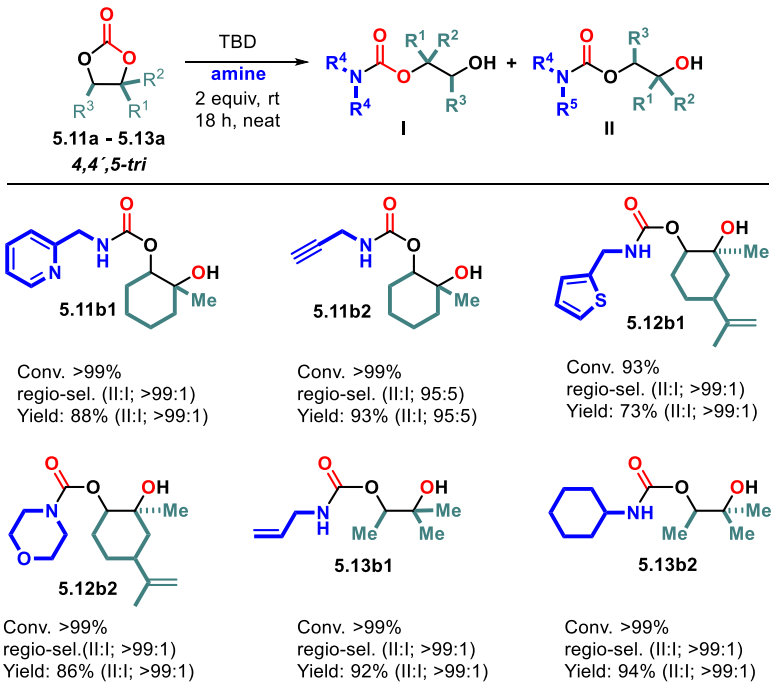


Fortunately, we were able to get unambiguous confirmation for the formation of the carbamate type **II** by single crystal X-ray diffraction studies carried out for compound **5.8b2** (Scheme **5.2**). The molecular structure (Figure **5.3**) has the proposed connectivity pattern with a diagnostic tertiary alcohol group as anticipated from the 1D/2D NMR spectroscopic analyses carried out for all the isolated carbamate species **5.7b1 – 5.9b3**.

5.2.3.2 – Trisubstituted cyclic carbonates

Motivated by the results obtained for the TBD-catalyzed aminolysis of *gem*-disusbtituted cyclic carbonates, we then examined the use of more complex carbonates including 4,4´,5-*tri*-substitutions (Scheme **5.3**). We first probed 1-methyl-cyclohexene carbonate (Scheme **5.3**; cyclic carbonate **5.11a**) as substrate and performing the aminolysis using 2-aminomethyl-pyridine and propargylic amine, respectively, in the presence of TBD (Scheme **5.3**; carbamates **5.11b1** and **5.11b**).

Scheme 5.3: Regioselective formation of carbamates derived from trisubstituted cyclic carbonates using TBD as catalyst.



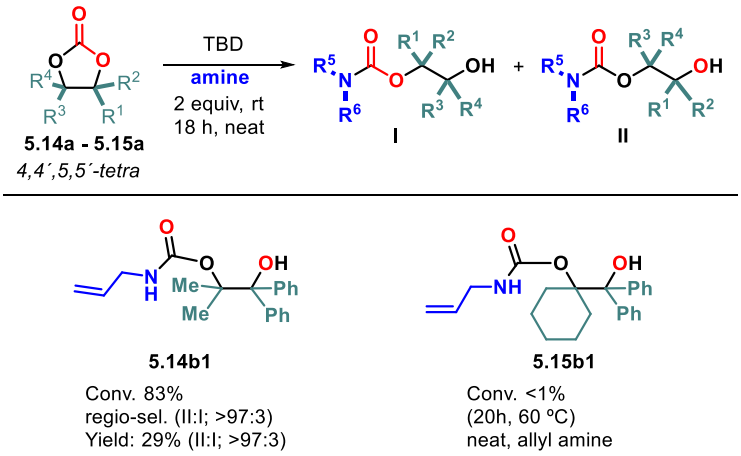
We were pleased to find that installation of a third substituent in the carbonate precursor also provides clean access to regio-isomeric carbamates of type **II** in good yields and excellent regio-selectivities. The use of other trisubstituted cyclic carbonates (limonene carbonate **5.12a** and a trimethyl-substituted one **5.13a**; syntheses of carbamates **5.12b1** – **5.13b2**) gave similar results producing the targeted molecules in high isolated yields and regio-selectivity. Apparently, also here the catalytic system is able to direct the C–O bond

cleavage process with high accuracy despite a smaller difference in steric impediment of both faces compared to the *gem*-disubstituted carbonate substrates.

5.2.3.3 – Tetrasubstituted cyclic carbonates

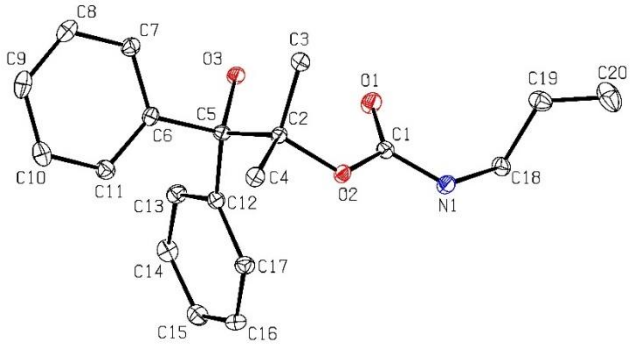
Finally, tetra-substituted carbonate precursors were studied as potential reaction partners and treated with allyl amine under TBD catalysis with the aim to produce carbamates **5.14b1** and **5.15b1** (Scheme **5.4**).

Scheme 5.4: Regioselective formation of carbamates derived from tetrasubstituted cyclic carbonates using TBD as catalyst.



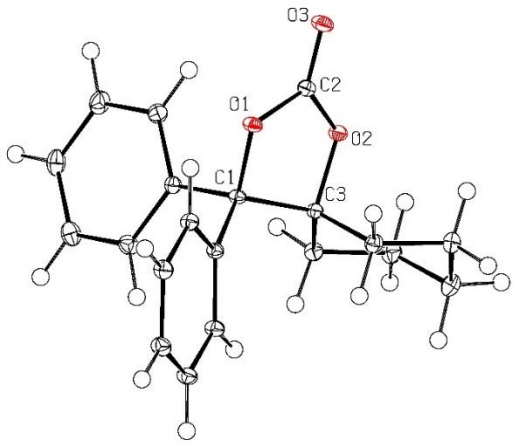
Although regio-control towards the formation of the carbamate type **II** product was again noted, the isolation by chromatographic methods turned out to be difficult resulting in low isolated yields. In these reactions we observed about 10% diol formation (attributed to hydrolysis of the carbonate precursor by adventitious water), and both the diol as well as the carbonate precursor have very similar R_f values compared to the carbamate product. Longer reaction times indeed gave higher conversion of the carbonate precursor but unfortunately an increasing amount of diol side-product was noted. To our delight, the molecular structure of carbamate **5.14b1** could also be confirmed by X-ray analysis (Figure **5.4**), showing unambiguously the preference of formation of carbamate type **II**.

Figure 5.4: X-ray molecular structure of carbamate 5.14b1.



The use of tetrasubstituted cyclic carbonate **5.15a** (Scheme **5.4**) did not result in any observable conversion into carbamate **5.15b1** not even at elevated temperature and in the presence of a large excess of allyl amine. Inspection of the molecular structure determined by X-ray analysis (Figure **5.5**) shows the steric impediment around the carbonate fragment to be a likely cause for this sluggish reactivity as the formation of the necessary ternary complex does not seem feasible.

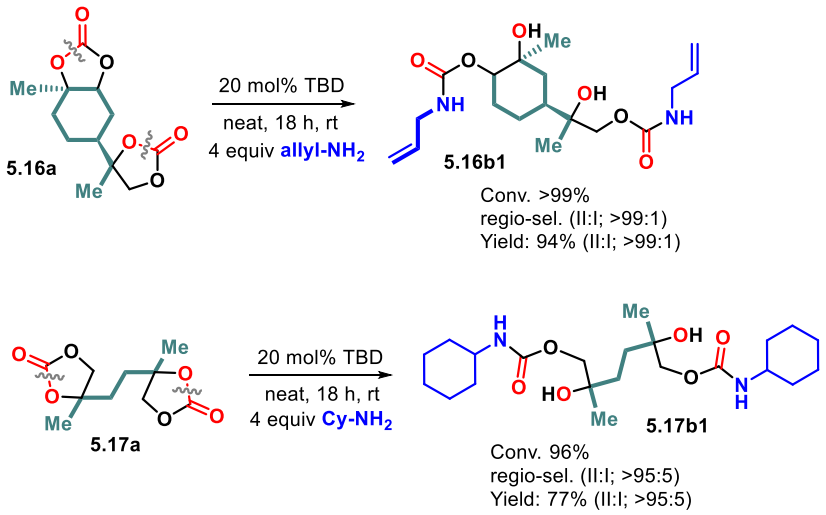
Figure 5.5: X-ray molecular structure of carbonate 5.15a.



5.2.3.4 – Bis-cyclic carbonates and oligourethanes

In order to further assess the applicability of this regio-selective carbamate formation in oligourethane formation, the bis-cyclic carbonate of limonene **5.16a** (*trans*-isomer)[33] was treated with allyl amine under similar conditions as reported for the *gem*-disubstituted and trisubstituted cyclic carbonates, and this gave the regio-isomerically pure bis-carbamate **5.16b1** in high yield (94%, Scheme **5.5**). The bis-carbamate **5.17b1** was prepared in 77% yield under high regio-control (**II**:**I**; >95:5) using cyclohexyl amine and the bis-carbonate **5.17a**: the latter was simply prepared from the corresponding bis-olefin in two steps. The regio-controlled formation of both these bis-carbamates **5.16b1** and **5.17b1** may hold promise for the development of regio-regular polyurethanes.

Scheme 5.5: Synthesis of bis-carbamates derived from the corresponding bis-cyclic carbonates in the presence of TBD as catalyst.



5.3 – Conclusions

In summary, we here describe the first general, catalytic approach towards the regio-selective aminolysis of cyclic carbonates yielding synthetically valuable carbamate scaffolds. The procedure leading to these latter compounds combines high regio-control, high isolated yields and operational simplicity (rt, no inert atmosphere needed) using readily available starting materials. Additional experiments have disclosed potential towards the regio-selective formation of oligourethanes, a feature that can be of use in the preparation of regio-regular polymers and fine-tuning the materials properties.

5.4 – Experimental section

5.4.1 – General information and instrumentation

General information

Commercially available epoxides, amines, solvents, co-catalysts and oxidants were purchased from various commercial sources (Acros, Aldrich and TCI) and used without further purification. The non-commercial epoxides and cyclic carbonates were synthesized according to reported literature procedures unless otherwise stated. Carbon dioxide (purchased from PRAXAIR) was used without further purification or drying prior to its use. ^{1}H NMR, ^{13}C 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. The regioisomeric ratio (**II**:**I**) of the carbamates mixtures and isolated products was measured by ^{1}H NMR spectroscopy and supported by 1D/2D NMR experiments. 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 – Synthesis of cyclic carbonates

General procedure for the synthesis of cyclic carbonates from epoxides

The general procedure for the synthesis cyclic carbonates (**5.1a** – **5.7a**, **5.10a - 5.13a**, **5.16a** and **5.17a**) following this synthetic protocol consists in the reaction of CO_2 and the corresponding epoxides. All reactions were performed in a 30 ml stainless steel reactor. In a typical experiment, a solution of catalyst [tannic acid (0.5 %) for compounds **5.1a** – **5.7a** and **5.17a**; Al-complex (1 mol%) for compounds **5.10a - 5.13a** and **5.16a**], TBAI/TBAB (5 %), epoxide (8.3 mmol) in MEK (5 mL) was added to a stainless steel reactor. Three cycles of pressurization and depressurization of the reactor (with pCO_2^0 = 5 bar) were carried out before finally stabilizing the pressure at 15 bar. The reactor was then heated to the required

temperature and left stirring for a further 18 hours. Then the reactor was cooled down, depressurized and an aliquot of the solution was analyzed by means of ^{1}H NMR spectroscopy using $CDCl_3$ as the solvent. The reaction mixture was purified by flash chromatography column affording the desired compound.

General procedure for the synthesis of cyclic carbonates from diols

A solution of diol (1 equiv.) and pyridine (4 equiv.) in CH_2Cl_2 (20 mL) was added triphosgene (0.5 equiv., 1.0 M in CH_2Cl_2) at 0 °C. The reaction was stirred under N_2 atmosphere at room temperature for 2 h. The reaction mixture was then quenched with saturated aqueous NH_4Cl, and extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography on silica to afford corresponding cyclic carbonates (**5.8a**, **5.9a**, **5.14a** and **5.15a**) in 85–95% yields.

General procedure for the synthesis of epoxides

Non-commercially available epoxides precursors of cyclic carbonates **5.11a** – **5.13a**, **5.16a** and **5.17a** were synthetized from the corresponding alkene by reaction with *m*-CPBA. To a solution of epoxide (100 mmol) in CH_2Cl_2 (250 mL) at 0 ºC was added *m*-CPBA (1.33 eq/monoepoxides; 2.5 eq/diepoxides). The mixture was stirred at room temperature 3 – 24 h. Then a NaOH (2M) solution was added until reach basic pH. The organic layer was separated and washed with $NaHCO_3$ saturated solution and brine. Finally the organic layer was dried, concentrated under vacuum and purified by flash column chromatography.

General method 1 for the synthesis of diols

Cyclic carbonates **5.8a** and **5.9a** were synthesized from the corresponding diol precursors obtained following this methodology. To a solution of hydroxyl methyl ketone (1 equiv.) in THF (20 mL) was added Vinyl/Phenyl-magnesium bromide (1.0 M in THF, 2.5 equiv.) at 0 °C. The reaction was stirred under N_2 atmosphere at room temperature for 2 h. The reaction mixture was then quenched with saturated aqueous NH_4Cl, and extracted with EtOAc. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and

concentrated. The residue was purified by flash chromatography on silica to afford corresponding diols in 77–86% yields.

General method 2 for the synthesis of diols: Retropinacol/Cross-Pinacol-Coupling reaction method.

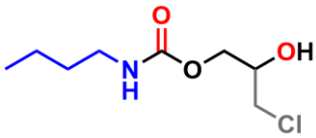
Cyclic carbonates **5.14a** and **5.15a** were synthesized from the corresponding diols precursors obtained following this methodology. Benzopinacol (1.0 mmol) and 4 eq of the corresponding ketone were solved in 3 ml dry DCM. 1 ml of a separately prepared solution containing 1 mol / L $Ti(O^tBu)_4$ and Et_3SiCl was added. The resulting solution was stirred at ambient temperature in a sealed reaction tube. The reaction was continuously monitored by thin layer chromatography (hexane / acetone). When no more Benzopinacol was detectable (7 days) the resulting mixture was extracted with CH_2Cl_2 and successively by saturated aq. NH_4Cl- and $NaHCO_3$ solution. The organic layers were separated, dried ($MgSO_4$) and the solvent was removed in vacuo. The residue was purified by flash column chromatography affording the desired diol.

5.4.3 – General procedure for catalysed aminolysis experiments

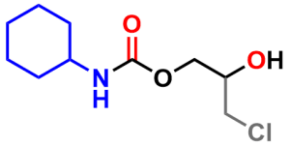
Typical catalytic experiment

A mixture of cyclic carbonate (1 mmol), TBD (20 mol%) and amine (2 equivalents per cyclic carbonate unit) was stirred for 6 - 18 hours at room temperature under neat conditions. Then the reaction mixture was purified by flash column chromatography affording the desired carbamate. The regioisomeric ratio (**II**:**I**) of the carbamates mixtures and isolated products was measured by ^1H NMR spectroscopy and supported by 1D/2D NMR experiments.

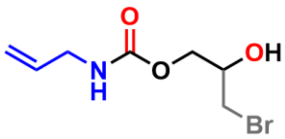
5.4.4 – Spectroscopic data for all compounds



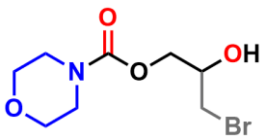
Compound 5.3b1; 3-chloro-2-hydroxypropyl butyl carbamate; ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 4.8 (m, 1H), 4.35 – 4.17 (m, 2H), 4.10 – 3.99 (m, 1H), 3.64 – 3.54 (m, 2H), 3.25 – 3.09 (m, 2H), 1.54 – 1.44 (m, 2H), 1.40 – 1.29 (m, 2H), 0.93 (t, $^{3}J_{HH}$ = 7.3 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$, 298 K) *δ*** 156.97. 70.58, 66.17, 45.64, 41.09, 32.04, 20.01, 13.84; **IR (neat, cm^{-1})** 3329 (O-H), 2959 – 2862 (C-H) 1696 (C=O).1522 (N-H), 1243 (C-O); **HRMS (ESI+; MeOH):** *m/z* calcd. ($C_8H_{16}ClNNaO_3$) 232.0711; $(M+Na)^+$ found: 232.0715.



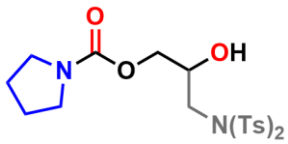
Compound 5.3b2; 3-chloro-2-hydroxypropyl cyclohexyl carbamate; ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 4.72 (bs, 1H), 4.34 - 4.16 (m, 2H), 4.09 - 3.98 (m, 1H), 3.63 - 3.54 (m, 2H), 3.53 - 3.40 (m, 1H), 3.19 (d, $^{3}J_{HH}$ = 5.2 Hz, 1H), 2.00 - 1.87 (m, 2H), 1.77 – 1.66 (m, 2H), 1.65 - 1.52 (m, 1H), 1.43 - 1.28 (m, 2H), 1.23 - 1.07 (m, 3H); **^{13}C NMR (126 MHz, $CDCl_3$, 298 K) δ** 156.11, 70.63, 66.08, 50.27, 45.65, 33.42, 25.57, 24.88; **IR (neat, cm^{-1})** 3342 (O-H), 3271 (N-H), 2938 – 2855 (C-H), 1689 (C=O), 1546 (N-H), 1239 (C-O); **HRMS (ESI+; MeOH):** *m/z* calcd. ($C_{10}H_{18}ClNNaO_3$) 258.0867; $(M+Na)^+$ found: 258.0874.



Compound 5.4b1; 3-bromo-2-hydroxypropyl allyl carbamate; ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 5.90 - 5.77 (m, 1H), 5.20 (dd, $^{2}J_{HH}$ = 17.2 Hz, $^{3}J_{HH}$ = 1.4 Hz, 1H) 5.15 (dd, $^{2}J_{HH}$ = 10.3 Hz, $^{3}J_{HH}$ = 1.3 Hz, 1H), 4.91 (bs, 1H), 4.34 - 4.20 (m, 2H), 4.09 - 4.00 (m, 1H), 3.85 - 3.77 (m, 2H), 3.52 - 3.41 (m, 2H), 3.08 (m, 1H); **^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ** 156.57, 133.99, 116.49, 69.95, 66.73, 43.60, 34.41; **IR (neat, cm^{-1})** 3331 (O-H), 1692 (C=O), 1523 (N-H), 1243 (C-O); **HRMS (ESI+; MeOH):** *m/z* calcd. ($C_7H_{12}BrNNaO_3$) 259.9893; $(M+Na)^+$ found: 259.9887.

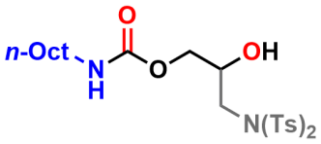


Compound 5.4b2; 3-bromo-2-hydroxypropyl morpholine-4-carboxylate; ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 4.30 (dd, $^{2}J_{HH}$ = 4.5 Hz, $^{3}J_{HH}$ = 0.4 Hz, 2H), 4.10 - 4.01 (m, 1H), 3.67 - 3.51 (m, 4H), 3.41 - 3.26 (m, 6H), 3.26 (d,$^{3}J_{HH}$ = 5.4 Hz, 1H); **^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ** 155.89, 70.17, 67.59, 66.62, 66.54, 44.56, 44.19, 34.50; **IR (neat, cm^{-1})** 3420 (O-H), 1677 (C=O), 1239 (C-O); **HRMS (ESI+; MeOH):** *m/z* calcd. ($C_8H_{14}BrNNaO_4$) 289.9998; $(M+Na)^+$ found: 289.9998.

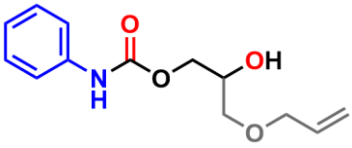


Compound 5.5b1; 2-hydroxy-3-((4-methyl-N-tosylphenyl) sulfonamido)propyl pyrrolidine-1-carboxylate; ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 7.95 (d, $^{3}J_{HH}$ = 8.4 Hz, 4H), 7.35 (d, $^{3}J_{HH}$ = 8.1Hz, 4H), 4.23 - 4.11 (m, 3H), 3.84 - 3.73 (m, 2H),

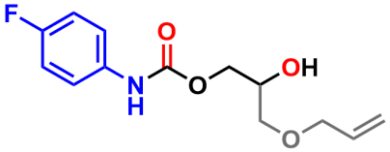
3.39 (dt, $^2J_{HH}$ = 6.5 Hz, $^3J_{HH}$ = 6.4 Hz, 4H), 3.19 (d, $^3J_{HH}$ = 5.3 Hz, 1H), 2.46 (s, 6H_{CH3}), 1.93 - 1.82 (m, 4H); **^{13}C NMR (101 MHz, CDCl$_3$, 298 K) δ** 155.09, 145.28, 136.52, 129.79, 128.64, 77.36, 69.41, 66.52, 51.11, 46.48, 46.00, 25.86, 25.04, 21.81; **IR (neat, cm^{-1})** 3411 (O-H), 2955 – 2878 (C-H), 1681 (C=O), 1369 (S=O); **HRMS (ESI+; MeOH):** *m/z* calcd. ($C_{22}H_{29}N_2O_7S_2$) 497.1411; $(M+Na)^+$ found: 497.1424.



Compound 5.5b2; 2-hydroxy-3-((4-methyl-N-tosyl phenyl)sulfonamido)propyl octylcarbamate; ^{1}H NMR (400 MHz, CDCl$_3$, 298 K) δ 7.94 (d, $^3J_{HH}$ = 8.4 Hz, 4H), 7.35 (d, $^3J_{HH}$ = 8.2 Hz, 4H), 4.77 (bs, 1H), 4.21 - 4.05 (m, 3H), 3.83 - 3.69 (m, 2H), 3.17 (dt, $^2J_{HH}$ = 6.8 Hz, $^3J_{HH}$ = 6.8 Hz, 2H), 2.93 (d, $^3J_{HH}$ = 2.7 Hz, 1H), 2.46 (s, 6H), 1.54 - 1.50 (m, 2H), 1.34 - 1.20 (m, 10H), 0.87 (t, $^3J_{HH}$ = 6.6 Hz, 3H); **^{13}C NMR (126 MHz, CDCl$_3$, 298 K) δ** 156.50, 145.37, 136.51, 129.86, 128.65, 69.34, 66.36, 51.24, 41.37, 31.92, 30.02, 29.37, 29.33, 26.88, 22.77, 21.84, 14.22; **IR (neat, cm^{-1})** 3408 (O-H), 2926 – 2855 (C-H), 1702 (C=O), 1370 (S=O); **HRMS (ESI+; MeOH):** *m/z* calcd. ($C_{26}H_{39}N_2O_7S_2$) 555.2193; $(M+Na)^+$ found: 555.2198.

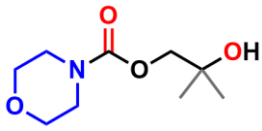


Compound 5.6b1; 3-(allyloxy)-2-hydroxypropyl phenylcarbamate; Mixture of isomers. **^{1}H NMR (400 MHz, CDCl$_3$, 298 K) δ** 6.74 (bs, 1H) 5.99 – 5.83 (m, 1H), 5.33 – 5.18 (m, 2H) 5.04 - 4.98 (m, 1H), 3.91 (d, $^3J_{HH}$ = 4.5 Hz, 2H), 3.72 (dd, $^2J_{HH}$ = 4.8Hz, $^3J_{HH}$ = 1.5 Hz, 2H); **^{1}H NMR (400 MHz, CDCl$_3$, 298 K) δ** 7.43 - 7.27 (m, 4H), 7.11 - 7.05 (m, 1H), 6.70 (bs, 1H) 5.99 - 5.83 (m, 2H), 5.33 - 5.18 (m, 2H), 4.31 (dd, $^2J_{HH}$ = 11.6 Hz, $^3J_{HH}$ = 3.9 Hz, 1H),4.23 (dd, $^2J_{HH}$ = 11.6 Hz, $^3J_{HH}$ = 6.3 Hz, 1H), 4.12 - 4.00 (m, 3H;), 3.57 (dd, $^2J_{HH}$ = 9.7 Hz, $^3J_{HH}$ = 4.4 Hz, 1H), 3.50 (dd, $^2J_{HH}$ = 9.7 Hz, $^3J_{HH}$ = 6.3 Hz, 1H) 2.6 (bs, 1H); **^{13}C NMR (101 MHz, CDCl$_3$, 298 K) δ** 137.71, 134.37, 129.25, 123.85, 72.58, 70.90, 69.37, 66.59. **IR (neat, cm^{-1})** 3319 (O-H), 3196 – 2864 (C-H), 2400 – 2000 (arm), 1713 (C=O), 1601 (C=C); **HRMS (ESI+; MeOH):** *m/z* calcd. ($C_{13}H_{17}NNaO_4$) 274.1050; $(M+Na)^+$ found: 274.1045.

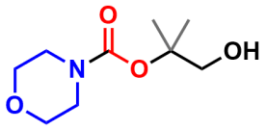


Compound 5.6b2; 3-(allyloxy)-2-hydroxypropyl (4-fluorophenyl)carbamate; Mixture of regioisomers. **^{1}H NMR (300 MHz, CDCl$_3$, 298 K) δ**; 7.38 – 7.28 (m, 2H), 7.05 – 6.95 (m, 3H), 6.72 (bs, 1H), 6.01 - 5.81 (m, 1H), 5.35 - 5.16 (m, 2H), 5.05 - 4.96 (m, 1H), 3.90 (dd, $^2J_{HH}$ = 5.9 Hz, $^3J_{HH}$ = 4.7 Hz, 2H), 3.71 (dd, $^2J_{HH}$ = 4.7 Hz, $^3J_{HH}$ = 0.8 Hz, 2H), 2.30 (t, $^3J_{HH}$ = 6.1 Hz, 1H); **^{1}H NMR (300 MHz, CDCl$_3$, 298 K) δ**; 7.38 – 7.28 (m, 2H), 7.05 – 6.95 (m, 3H), 6.67 (bs, 1H), 6.01 - 5.81 (m, 1H), 5.35 - 5.16 (m, 2H), 4.30 (dd, $^2J_{HH}$ = 11.6 Hz, $^3J_{HH}$ = 4.0 Hz, 1H), 4.21 (dd, $^2J_{HH}$ = 11.6 Hz, $^3J_{HH}$ = 6.2 Hz, 1H), 4.10 – 4.00 (m, 2H), 4.04 (dt, $^2J_{HH}$ = 5.6 Hz, $^3J_{HH}$ = 1.4 Hz, 1H), 3.57 (dd, $^2J_{HH}$ = 9.7 Hz, $^3J_{HH}$ = 5.0 Hz, 1H), 3.50 (dd, $^2J_{HH}$ = 9.7 Hz, $^3J_{HH}$ = 6.3 Hz, 1H), 2.65 (d, $^3J_{HH}$ = 4.6 Hz, 1H); **^{19}F NMR**

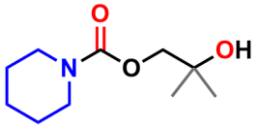
(376 MHz, $CDCl_3$, 298 K) δ -119.25; **IR (neat, cm^{-1})** 3305 (O-H), 3153 - 2866 (C-H), 1704 (C=O); **HRMS (ESI+; MeOH):** *m/z* calcd. ($C_{13}H_{16}FNNaO_4$) 292.0956; $(M+Na)^+$ found: 292.0958.



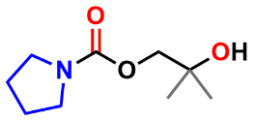
Compound 5.7b1; 2-hydroxy-2-methylpropyl morpholine-4-carboxylate; ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 4.02 (s, 2H), 3.73 - 3.64 (m, 4H), 3.54 - 3.47 (m, 4H), 2.23 (s, 1H), 1.25 (s, 6H); **^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ** 155.82, 73.50, 70.31, 66.64, 44.36, 26.38; **IR (neat, cm^{-1})** 3437 (O-H), 2972 - 2859 (C-H), 1679 (C=O); **HRMS (ESI+; MeOH):** *m/z* calcd. ($C_9H_{17}NNaO_4$) 226.1050; $(M+Na)^+$ found: 226.1052.



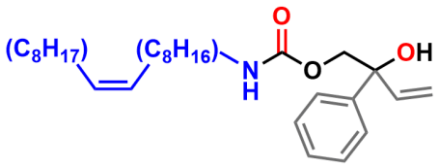
Compound 5.7b2; 1-hydroxy-2-methylpropan-2-yl morpholine-4-carboxylate; ^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ 3.67 - 3.57 (m, 6H), 3.45 - 3.37 (m, 4H), 1.37 (s, 6H); **^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ** 155.76, 84.26, 69.90, 66.63, 44.90, 43.77, 23.92; **IR (neat, cm^{-1})** 3484 (O-H), 2979 - 2863 (C-H), 1657 (C=O); **HRMS (ESI+; MeOH):** *m/z* calcd. ($C_9H_{17}NNaO_4$) 226.1050; $(M+Na)^+$ found: 226.1043.



Compound 5.7b3; 2-hydroxy-2-methylpropylpiperidine-1-carboxylate; ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 3.99 (s, 2H), 3.47 - 3.41 (m, 4H), 2.47 (s, 1H), 1.66 - 1.49 (m, 6H), 1.24 (s, 6H); **^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ** 155.91, 73.31, 70.37, 45.14, 26.36, 24.48; **IR (neat, cm^{-1})** 3434 (O-H), 2973 - 2856 (C-H), 1672 (C=O); **HRMS (ESI+; MeOH):** *m/z* calcd. ($C_{10}H_{19}NNaO_3$) 224.1257; $(M+Na)^+$ found: 224.1257.

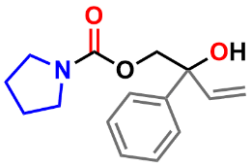


Compound 5.7b4; 2-hydroxy-2-methylpropyl pyrrolidine-1-carboxylate; ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 3.99 (s, 2H), 3.40 (dt, $^2J_{HH}$ = 6.6 Hz, $^3J_{HH}$ = 6.5 Hz, 4H), 2.53 (s, 1H), 1.95 - 1.83 (m, 4H), 1.24 (s, 6H); **^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ** 155.48, 73.11, 70.31, 46.46, 45.99, 26.30, 25.89, 25.09; **IR (neat, cm^{-1})** 3427 (O-H), 2973 - 2877 (C-H), 1676 (C=O); **HRMS (ESI+; MeOH):** *m/z* calcd. ($C_9H_{17}NNaO_3$) 210.1101; $(M+Na)^+$ found: 210.1100.

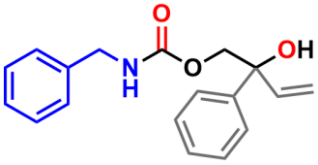


Compound 5.8b1; 2-hydroxy-2-phenylbut-3-en-1-yloleylcarbamate; ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 7.52 - 7.46 (m, 2H), 7.39 - 7.32 (m, 2H), 7.30 - 7.24 (m, 1H), 6.16 (dd, $^2J_{HH}$ = 17.2 Hz, $^3J_{HH}$ = 10.7 Hz, 1H), 5.41 (m, 1H), 5.35 (s, 2H), 5.25 (m, 1H), 4.73 (bs, 1H), 4.44 – 4.29 (m, 2H), 3.31 (s, 1H), 3.14 (dt, $^2J_{HH}$ = 6.8 Hz, $^3J_{HH}$ = 6.6 Hz, 2H), 2.09 - 1.91 (m, 4H), 1.53 - 1.39 (m, 2H), 1.38 - 1.16 (m, 22H), 0.88 (t, $^3J_{HH}$ = 6.7 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ** 156.86, 142.45, 140.54, 130.13, 129.91, 128.44, 127.54, 125.85, 115.28, 76.73, 70.99, 41.31, 32.75, 32.05, 29.95,

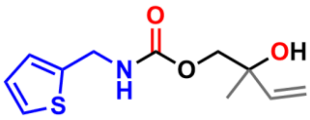
29.91, 29.88, 29.84, 29.80, 29.72, 29.67, 29.57, 29.46, 29.36, 27.37, 27.33, 26.81, 22.83, 14.26; **IR (neat, cm^{-1})** 3341 (O-H), 2923 - 2853 (C-H), 1698 (C=O), 699 (C=C); **HRMS (ESI+; MeOH):** *m/z* calcd. ($C_{29}H_{47}NNaO_3$) 480.3448; $(M+Na)^+$ found: 480.3447.



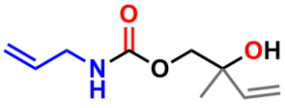
Compound 5.8b2; 2-hydroxy-2-phenylbut-3-en-1-yl pyrrolidine-1-carboxylate; ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 7.56 - 7.47 (m, 2H), 7.39 - 7.31 (m, 2H), 7.31 - 7.23 (m, 1H), 6.1 (dd, $^2J_{HH}$ = 17.2 Hz, $^3J_{HH}$ = 10.7 Hz 1H), 5.43 (dd, $^2J_{HH}$ = 17.2 Hz, $^3J_{HH}$ = 1.3 Hz, 1H), 5.26 (dd, $^2J_{HH}$ = 10.7 Hz, $^3J_{HH}$ = 1.3 Hz, 1H), 4.44 - 4.34 (m, 2H), 3.63 (bs, 1H) 3.43 - 3.32 (m, 2H), 3.29 - 3.17 (m, 2H), 1.89 - 1.77 (m, 4H); **^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ** 155.51, 142.65, 140.67, 128.37, 127.45, 125.93, 115.18, 71.54, 46.46, 45.93, 25.79, 25.05; **IR (neat, cm^{-1})** 3480 (O-H), 2979 - 2890 (C-H), 1676 (C=O) 697 (C=C); **HRMS (ESI+; MeOH):** *m/z* calcd. ($C_{15}H_{19}NNaO_3$) 284.1257; $(M+Na)^+$ found: 284.1254.



Compound 5.8b3; 2-hydroxy-2-phenylbut-3-en-1-yl benzylcarbamate; ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 7.55 - 7.42 (m, 2H), 7.40 - 7.19 (m, 8H), 6.16 (dd, $^2J_{HH}$ = 17.1 Hz, $^3J_{HH}$ = 10.7 Hz, 1H), 5.47 – 5.38 (m, 1H), 5.29 – 5.22 (m, 1H), 5.04 (bs, 1H), 4.49 - 4.31 (m, 4H); **^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ** 156.85, 142.32, 140.48, 138.21, 128.85, 128.49, 127.74, 127.61, 125.85, 115.38, 71.21, 45.32; **IR (neat, cm^{-1})** 3411 (O-H), 3348 (N-H), 3087 - 2929 (C-H), 1696 (C=O), 697 (C=C); **HRMS (ESI+; MeOH):** *m/z* calcd. ($C_{18}H_{19}NNaO_3$) 320.1257; $(M+Na)^+$ found: 320.1259.

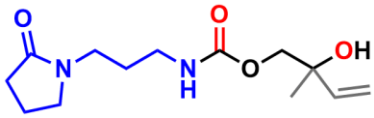


Compound 5.9b1; 2-hydroxy-2-methylbut-3-en-1-yl(thiophen-2-ylmethyl)carbamate; ^{1}H NMR (300 MHz, $CDCl_3$, 298 K) δ 7.25 - 7.21 (m, 1H), 7.00 - 6.92 (m, 2H), 5.90 (dd, $^2J_{HH}$ = 17.3 Hz, $^3J_{HH}$ = 10.8 Hz, 1H), 5.41 - 5.07 (m, 3H), 4.54 (d, $^2J_{HH}$ = 5.8 Hz, 2H), 4.17 - 3.99 (m, 2H), 2.39 (s, 1H), 1.28 (s, 3H); **^{13}C NMR (126 MHz, $CDCl_3$, 298 K) δ** 156.49, 141.45, 141.13, 126.96, 125.89, 125.22, 114.20, 72.68, 71.52, 39.98, 24.46; **IR (neat, cm^{-1})** 3324 (O-H), 3087 - 2938 (C-H), 1694 (C=O); **HRMS (ESI+; MeOH):** *m/z* calcd. ($C_{16}H_{23}NNaO_3S$) 332.1291; $(M+Na)^+$ found: 332.1292.

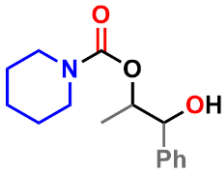


Compound 5.9b2; 2-hydroxy-2-methylbut-3-en-1-yl allyl carbamate; ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 5.90 (dd, $^2J_{HH}$ = 17.3 Hz, $^3J_{HH}$ = 10.8 Hz, 1H), 3.89 (m, 1H), 5.36 (dd, $^2J_{HH}$ = 17.3 Hz, $^3J_{HH}$ = 1.2 Hz, 1H), 5.20 (dd, $^2J_{HH}$ = 17.2 Hz, $^3J_{HH}$ = 1.4 Hz, 1H), 5.16 (dd, $^2J_{HH}$ = 10.8 Hz, $^3J_{HH}$ = 1.2 Hz, 1H), 5.14 (dd, $^2J_{HH}$ = 10.2 Hz, $^3J_{HH}$ = 1.4 Hz, 1H), 4.84 (bs, 1H), 4.15 - 3.97 (m, 2H), 3.87 - 3.73 (m, 2H), 2.45 (s, 1H), 1.29 (s, 3H); **^{13}C NMR (126 MHz, $CDCl_3$, 298 K) δ** 156.71, 141.51, 134.34, 116.00, 113.97, 72.55, 71.26, 43.41, 24.35;

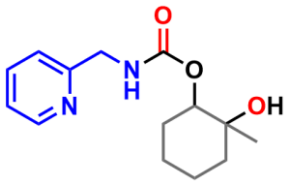
IR (neat, cm^{-1}) 3334 (O-H), 3086 - 2933 (C-H), 1696 (C=O); **HRMS (ESI+; MeOH):** *m/z* calcd. ($C_9H_{15}NNaO_3$) 208.0944; $(M+Na)^+$ found: 208.0945.



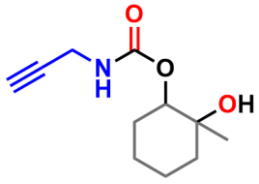
Compound 5.9b3; 2-hydroxy-2-methylbut-3-en-1-yl(3-(2-oxopyrrolidin-1-yl)propyl) carbamate; ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 5.90 (dd, $^2J_{HH}$ = 17.3 Hz, $^3J_{HH}$ = 10.8 Hz, 1H), 5.75 (bs, 1H), 5.36 (dd, $^2J_{HH}$ = 17.3 Hz, $^3J_{HH}$ = 1.0 Hz, 1H), 5.14 (dd, $^2J_{HH}$ = 10.8 Hz, $^3J_{HH}$ = 1.2 Hz, 1H), 4.13 – 3.93 (m, 2H), 3.44 - 3.30 (m, 4H), 3.13 (dt, $^2J_{HH}$ = 6.3 Hz, $^3J_{HH}$ = 6.2 Hz, 2H), 2.75 (bs, 1H), 2.40 (t, $^2J_{HH}$ = 7.9 Hz, 2H), 2.05 (tt, $^2J_{HH}$ = 15.4 Hz, $^3J_{HH}$ = 7.7 Hz, 2H), 1.69 (tt, $^2J_{HH}$ = 12.5 Hz, $^3J_{HH}$ = 6.2 Hz, 2H), 1.28 (s, 3H); **^{13}C NMR (126 MHz, $CDCl_3$, 298 K) δ** 175.49, 156.77, 141.63, 113.56, 72.15, 71.06, 47.09, 39.44, 37.56, 30.74, 26.75, 24.20, 17.72; **IR (neat, cm^{-1})** 3339 (O-H), 2976 - 2875 (C-H), 1664 (C=O); **HRMS (ESI+; MeOH):** *m/z* calcd. ($C_{13}H_{19}N_5O_3$) 293.1482; $(M+Na)^+$ found: 293.1478.



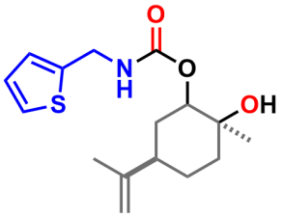
Compound 5.10b1; 1-hydroxy-1-phenylpropan-2-ylpiperidine-1-carboxylate; ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 7.39 - 7.27 (m, 5H), 4.98 (dq, $^2J_{HH}$ = 7.4 Hz, $^3J_{HH}$ = 6.4 Hz, 1H), 4.61 (dd, $^2J_{HH}$ = 7.5 Hz, $^3J_{HH}$ = 3.5 Hz, 1H), 3.44 (t, $^3J_{HH}$ = 5.8 Hz, 4H), 3.35 (d,$^3J_{HH}$ = 4 Hz, 1H), 1.66 - 1.47 (m, 6H), 1.08 (d, $^3J_{HH}$ = 6.5 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ** 155.90, 140.89, 128.46, 128.09, 127.17, 77.97, 76.00, 45.05, 25.74, 24.44, 17.06; **IR (neat, cm^{-1})** 3423 (O-H), 2935 - 2855 (C-H), 1668 (C=O); **HRMS (ESI+; MeOH):** *m/z* calcd. ($C_{15}H_{21}NNaO_3$) 286.1414; $(M+Na)^+$ found: 286.1411.



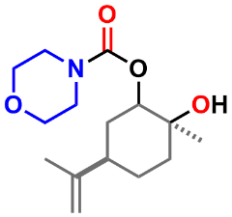
Compound 5.11b1; 2-hydroxy-2-methylcyclohexyl(pyridin-2-ylmethyl)carbamate; ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 8.60 - 8.52 (m, 1H), 7.74 - 7.63 (m, 1H), 7.32 - 7.26 (m, 1H), 7.25 - 7.18 (m, 1H), 6.00 (bs, 1H), 4.66 - 4.57 (m, 1H), 4.52 (d, $^2J_{HH}$ = 4.5 Hz, 2H), 2.06 (bs, 1H), 1.85 - 1.28 (m, 8H), 1.23 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ** 156.91, 156.39, 149.16, 136.96, 122.53, 121.91, 78.39, 71.13, 46.11, 37.62, 27.65, 27.07, 23.73, 21.28; **IR (neat, cm^{-1})** 3294 (O-H), 3065 - 2859 (C-H), 1683 (C=O); **HRMS (ESI+; MeOH):** *m/z* calcd. ($C_{14}H_{21}N_2O_3$) 265.1547; $(M+Na)^+$ found: 265.1543.



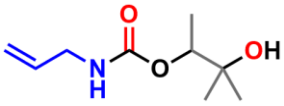
Compound 5.11b2; 2-hydroxy-2-methylcyclohexylprop-2-yn-1-ylcarbamate; ^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ 4.92 (bs, 1H), 4.62 - 4.55 (m, 1H), 4.03 - 3.95 (m, 2H), 2.25 (s, 1H), 1.81 - 1.64 (m, 4H), 1.47 - 1.28 (m, 4H), 1.27 - 1.24 (m, 2H), 1.21 (s, 3H); **^{13}C NMR (75 MHz, $CDCl_3$, 298 K) δ** 155.85, 78.62, 71.68, 71.14, 37.55, 31.80, 30.91, 27.54, 26.94, 23.62, 21.18; **IR (neat, cm^{-1})** 3304 (N-H), 2935 - 2863 (C-H), 1692 (C=O); **HRMS (ESI+; MeOH):** *m/z* calcd. ($C_{11}H_{14}N_4O_2$) 234.1111; $(M+Na)^+$ found: 234.1104.



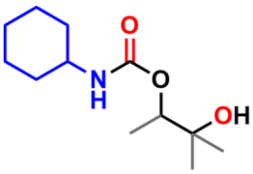
Compound 5.12b1; 2-hydroxy-2-methyl-5-(prop-1-en-2-yl)cyclohexyl(thiophen-2-yl methyl)carbamate; ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 7.22 (m, 1H), 6.99 - 6.92 (m, 2H), 5.18 (bs, 1H), 4.72 - 4.68 (m, 2H), 4.67 - 4.63 (m, 1H), 4.57 - 4.52 (m, 2H), 2.10 - 1.97 (m, 1H), 1.88 - 1.78 (m, 2H), 1.72 (s, 3H), 1.69 - 1.36 (m, 5H), 1.21 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ** 155.80, 148.76, 141.33, 127.04, 125.86, 125.30, 109.23, 78.49, 70.66, 43.59, 40.12, 37.54, 32.36, 27.31, 26.09, 20.94; **IR (neat, cm^{-1})** 3332 (N-H), 3077 (C-H; S) 2966 - 22864 (C-H), 1693 (C=O); **HRMS (ESI+; MeOH):** *m/z* calcd. ($C_{11}H_{15}NNaO_3S$) 264.0665; $(M+Na)^+$ found: 264.0665.



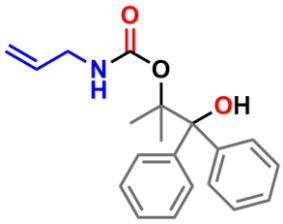
Compound 5.12b2; (2-hydroxy-2-methyl-5-(prop-1-en-2-yl)cyclohexylmorpholine-4-carboxylate; ^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ 4.74 - 4.69 (m, 2H), 4.65 (dd, $^{2}J_{HH}$ = 11.7 Hz, $^{3}J_{HH}$ = 4.6 Hz, 1H), 3.73 – 3.63 (m, 4H), 3.53 – 3.45 (m, 4H), 2.09 - 1.99 (m, 1H) 1.89 - 1.82 (m, 2H,) 1.72 (s, 3H), 1.71 - 1.40 (m, 5H), 1.21 (s, 3H);. **^{13}C NMR (126 MHz, $CDCl_3$, 298 K) δ** 155.00, 148.74, 109.26, 79.12, 70.74, 66.71, 43.61, 37.57, 32.49, 27.45, 26.12, 20.96; **IR (neat, cm^{-1})** 3503 (O-H), 2969 - 2861 (C-H), 1667 (C=O); **HRMS (ESI+; MeOH):** *m/z* calcd. ($C_{15}H_{25}NNaO_4$) 306.1676; $(M+Na)^+$ found: 306.1675.



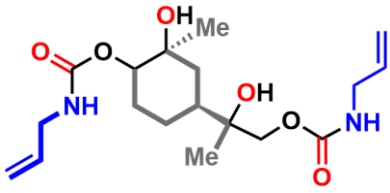
Compound 5.13b1; 3-hydroxy-3-methylbutan-2-ylallyl carbamate; ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 5.92 - 5.79 (m, 1H), 5.20 (dd, $^{2}J_{HH}$ = 17.1 Hz, $^{3}J_{HH}$ = 1.2 Hz, 1H), 5.15 (dd, $^{2}J_{HH}$ = 10.3 Hz, $^{3}J_{HH}$ = 1.2 Hz, 1H), 4.78 (bs, 1H), 4.72 (q, $^{2}J_{HH}$ = 13.0 Hz, $^{3}J_{HH}$ = 6.4 Hz, 1H), 3.86 - 3.77 (m, 2H), 1.95 (bs, 1H), 1.23 (d, $^{3}J_{HH}$ = 6.6 Hz, 3H), 1.21 (s, 3H), 1.19 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ** 156.49, 134.55, 116.01, 77.29, 72.31, 43.48, 26.43, 24.59, 15.30; **IR (neat, cm^{-1})** 3335 (O-H), 2981 - 2941 (C-H), 1690 (C=O); **HRMS (ESI+; MeOH):** *m/z* calcd. ($C_9H_{17}NNaO_3$) 210.1101; $(M+Na)^+$ found: 210.1105.



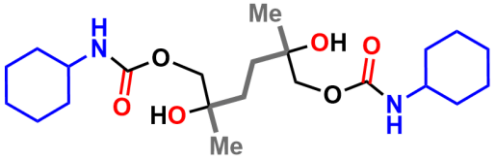
Compound 5.13b2; 3-hydroxy-3-methylbutan-2-ylcyclohexyl carbamate; ^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ 4.71 (bs, 1H), 4.68 - 4.61 (m, 1H), 3.50 - 3.39 (m, 1H), 2.32 - 2.19 (m, 1H), 1.97 - 1.85 (m, 2H), 1.73 - 1.63 (m, 2H), 1.61 - 1.53 (m, 1H), 1.38 - 1.25 (m, 2H), 1.24 - 1.03 (m, 12H); **^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ** 155.74, 76.97, 72.41, 49.96, 33.47, 26.56, 25.57, 24.88, 24.63, 15.36; **IR (neat, cm^{-1})** 3422 – 3269 (N-H), 2973 - 2854 (C-H), 1687 (C=O); **HRMS (ESI+; MeOH):** *m/z* calcd. ($C_{10}H_{18}N_7O$) 252.1567; $(M+Na)^+$ found: 252.1580.



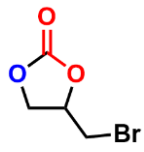
Compound 5.14b1; 1-hydroxy-2-methyl-1,1-diphenyl propan-2-ylallylcarbamate; ^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ 7.61 - 7.49 (m, 5H), 7.30 - 7.18 (m, 5H), 5.70 - 5.60 (m, 1H), 5.04 – 4.89 (m, 2H), 4.73 (bs, 1H), 3.68 - 3.60 (m, 2H), 1.57 (s, 6H); **^{13}C NMR (126 MHz, $CDCl_3$, 298 K) δ** 156.44, 145.47, 134.24, 128.65, 127.48, 126.96, 115.87, 89.06, 82.33, 43.30, 29.86; **IR (neat, cm^{-1})** 3294 (O-H), 3330 – 3210 (N-H), 3059 - 2923 (C-H), 1675 (C=O); **HRMS (ESI+; MeOH):** *m/z* calcd. ($C_{20}H_{23}NNaO_3$) 348.1570; $(M+Na)^+$ found: 348.1569.



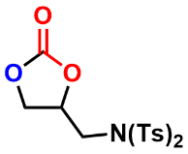
Compound 5.16b1; (1R,2S,4S)-4-((S)-1-((allylcarbamoyl)oxy)-2-hydroxypropan-2-yl)-2-hydroxy-2-methylcyclohexyl allylcarbamate; ^{1}H NMR (300 MHz, $CDCl_3$, 298 K) δ 5.95 - 5.75 (m, 2H), 5.28 - 5.10 (m, 4H), 5.08 (bs, 2H), 4.63 - 4.54 (m, 1H), 4.16 - 3.93 (m, 2H), 3.87 - 3.73 (m, 4H), 2.07 - 1.22 (m, 9H), 1.20 (s, 3H), 1.13 (d, $^{4}J_{HH}$ = 5 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ** 156.95, 156.83, 155.97, 134.53, 134.39, 116.41, 116.24, 78.36, 78.18, 73.44, 73.41, 70.68, 70.62, 43.69, 43.63, 43.35, 43.28, 37.43, 37.35, 28.47, 27.49, 27.18, 21.98, 21.30, 20.80; **IR (neat, cm^{-1})** 3328 (O-H), 2937 (C-H), 1687 (C=O); **HRMS (ESI+; MeOH):** *m/z* calcd. ($C_{18}H_{31}N_2O_6$) 371.2177; $(M+H)^+$ found: 371.2184.



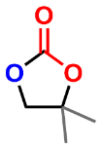
Compound 5.17b1; 2,5-dihydroxy-2,5-dimethylhexane-1,6-diyl bis(cyclohexyl carbamate); ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 4.83 (bs, 2H), 4.13 - 3.90 (m, 4H), 3.60 - 3.36 (m, 2H), 2.85 (bs, 2H), 2.04 - 1.85 (m, 4H), 1.81 - 1.48 (m, 10H), 1.45 - 1.27 (m, 4H), 1.25 - 1.00 (m, 12H); **^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ** 156.04, 74.23, 71.62, 71.58, 71.39, 71.20, 69.33, 49.97, 33.32, 32.33, 32.16, 31.57, 29.68, 29.13, 25.73, 25.46, 24.78, 24.51, 24.00, 23.87, 23.63, 18.77; **IR (neat, cm^{-1})** 3325 (N-H), 2932 - 2854 (C-H), 1687 (C=O); **HRMS (ESI+; MeOH):** *m/z* calcd. ($C_{22}H_{41}N_2O_6$) 429.2959; $(M+H)^+$ found: 429.2965.



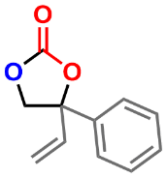
Compound 5.4a; 4-(bromomethyl)-1,3-dioxolan-2-one;[57] **^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ** 4.99 - 4.89 (m, 1H), 4.60 (dd, $^{2}J_{HH}$ = 8.9 Hz, $^{3}J_{HH}$ = 8.2 Hz, 1H), 4.35 (dd, $^{2}J_{HH}$ = 8.9 Hz, $^{3}J_{HH}$ = 5.9 Hz, 1H), 3.61 - 3.51 (m, 2H); **^{13}C NMR (75 MHz, $CDCl_3$, 298 K) δ** 154.15, 74.07, 68.27, 31.17; **IR (neat, cm^{-1})** 1789 (C=O).



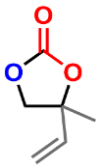
Compound 5.5a; 4-methyl-N-((2-oxo-1,3-dioxolan-4-yl)methyl)-N-tosylbenzenesulfonamide; ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) *δ* 7.96 (d, $^{3}J_{HH}$ = 8.5 Hz, 4H), 7.39 (d, $^{3}J_{HH}$ = 8.1 Hz, 4H), 5.03 – 4.93 (m, 1H), 4.51 (dd, $^{2}J_{HH}$ = 9.2 Hz, $^{3}J_{HH}$ = 8.1 Hz, 1H), 4.29 – 4.16 (m, 2H), 3.79 (dd, $^{2}J_{HH}$ = 16.0 Hz, $^{3}J_{HH}$ = 5.2 Hz, 1H), 2.49 (s, 6H); **^{13}C NMR (101 MHz, $CDCl_3$, 298 K) *δ*** 153.90, 145.94, 135.89, 130.05, 128.76, 75.36, 67.44, 50.11, 21.89; **IR (neat, cm^{-1})** 2900 - 2848 (C-H), 1797 (C=O), 1155 (S=O).



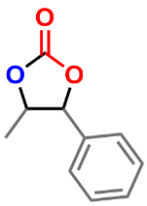
Compound 5.7a; 4,4-dimethyl-1,3-dioxolan-2-one;[58] **^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ** 4.14 (s, 2H), 1.52 (s, 6H); **^{13}C NMR (75 MHz, $CDCl_3$, 298 K) δ** 154.70, 81.79, 75.52, 26.21; **IR (neat, cm^{-1})** 2984 (C-H), 1784 (C=O).



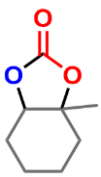
Compound 5.8a; 4-phenyl-4-vinyl-1,3-dioxolan-2-one;[59] **^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ** 7.48 - 7.33 (m, 5H), 6.16 (dd, $^{2}J_{HH}$ = 17.1 Hz, $^{3}J_{HH}$ = 10.8 Hz, 1H), 5.44 - 5.41 (m, 2H), 4.65 (d, $^{2}J_{HH}$ = 8.5 Hz, 1H), 4.58 (d, $^{2}J_{HH}$ = 8.5 Hz, 1H); **^{13}C NMR (126 MHz, $CDCl_3$, 298 K) δ** 154.05, 138.43, 136.54, 129.01, 124.87, 117.63, 85.50, 74.54, 67.98, 25.62; **IR (neat, cm^{-1})** 3031 (C-H), 1796 (C=O).



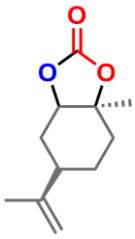
Compound 5.9a; 4-methyl-4-vinyl-1,3-dioxolan-2-one;[59] **^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ** 5.94 (dd, $^{2}J_{HH}$ = 17.30 Hz, $^{3}J_{HH}$ = 10.90 Hz; 1H), 5.54 (d, $^{2}J_{HH}$ = 17.30 Hz, 1H), 5.33 (d, $^{3}J_{HH}$ = 10.90 Hz, 1H), 4.27 (d, $^{2}J_{HH}$ = 8.3 Hz, 1H), 4.18 (d, $^{2}J_{HH}$ = 8.4 Hz, 1H), 1.60 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ** 154.52, 137.02, 116.71, 82.67, 74.51, 24.25; **IR (neat, cm^{-1})** 2985 (C-H), 1788 (C=O).



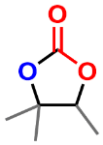
Compound 5.10a; 4-methyl-5-phenyl-1,3-dioxolan-2-one;[22] **^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ** 7.49 - 7.40 (m, 3H), 7.38 - 7.33 (m, 2H), 5.13 (d, $^{3}J_{HH}$ = 8.0 Hz, 1H), 4.65 - 4.56 (m, 1H), 1.56 (d, $^{3}J_{HH}$ = 6.2 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ** 154.41, 135.18, 129.88, 129.33, 126.11, 85.04, 80.88, 18.48; **IR (neat, cm^{-1})** 3038 – 2988 (C-H), 1787 (C=O).



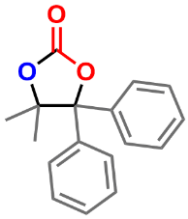
Compound 5.11a; 3a-methylhexahydrobenzo[d][1,3]dioxol-2-one;[60] **^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ** 4.35 (t, $^{3}J_{HH}$ = 4.1 Hz, 1H), 2.11 - 2.03 (m, 1H), 1.86 - 1.81 (m, 2H), 1.76 - 1.66 (m, 2H), 1.62 - 1.50 (m, 2H), 1.48 (s, 3H), 1.37 - 1.27 (m, 1H); **^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ** 154.93, 82.91, 81.19, 33.80, 26.01, 23.43, 20.52, 18.81; **IR (neat, cm^{-1})** 2949 – 2871 (C-H), 1778 (C=O).



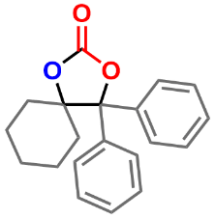
Compound 5.12a; (3aS,6S)-3a-methyl-6-(prop-1-en-2-yl)hexahydrobenzo [d][1,3]dioxol-2-one; ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 4.79 – 4.74 (m, 1H), 4.74 – 4.70 (m, 1H), 4.36 (m, 1H), 2.36 – 2.21 (m, 2H), 1.91 (m, 1H), 1.72 (t, $^{4}J_{HH}$ = 1.1 Hz, 3H), 1.70 – 1.64 (m, 1H), 1.64 – 1.55 (m, 1H), 1.52 – 1.39 (m, 5H); **^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ** 154.9, 147.4, 110.3, 82.2, 80.7, 40.1, 34.1, 33.2, 26.3, 25.8, 20.7; **IR (neat, cm^{-1})** 1776 (C=O). **HRMS (ESI^{+}, CH_3OH):** *m/z* calcd. ($C_{11}H_{16}NaO_3$) 219.0992 $(M+Na)^{+}$, found: 219.0987.



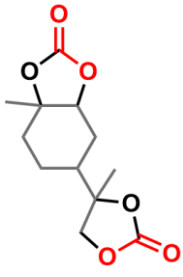
Compound 5.13a; 4,4,5-trimethyl-1,3-dioxolan-2-one;[61]. **^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ** 4.45 (q, $^{3}J_{HH}$ = 6.6 Hz, 1H), 1.49 (s, 3H), 1.37 - 1.35 (m, 6H); **^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ** 154.11, 84.11, 81.47, 25.75, 20.98, 14.49; **IR (neat, cm^{-1})** 2990 – 2950 (C-H), 1777 (C=O).



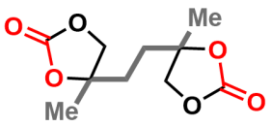
Compound 5.14a; 4,4-dimethyl-5,5-diphenyl-1,3-dioxolan-2-one; ^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ 7.45 - 7.32 (m, 10H), 1.42 (s, 6H); **^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ** 153.89, 137.97, 128.62, 128.57, 126.58, 92.32, 89.06, 25.73; **IR (neat, cm^{-1})** 3060 – 2938 (C-H), 1792 (C=O); **HRMS (ESI+; MeOH):** *m/z* calcd. ($C_{17}H_{16}NaO_3$) 291.0992; $(M+Na)^{+}$ found: 291.1000.



Compound 5.15a; 4,4-diphenyl-1,3-dioxaspiro[4.5]decan-2-one; ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 7.49 - 7.29 (m, 10H), 1.77 - 1.48 (m, 10H); **^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ** 153.89, 137.62, 128.51, 127.72, 126.80, 92.45, 90.47, 33.86, 25.01, 22.34; **IR (neat, cm^{-1})** 2957 – 2858 (C-H), 1807 (C=O); **HRMS (ESI+; MeOH):** *m/z* calcd. ($C_{20}H_{20}NaO_3$) 331.1305; $(M+Na)^{+}$ found: 331.1317.



Compound 5.16a; 3a-methyl-6-(4-methyl-2-oxo-1,3-dioxolan-4-yl)hexahydrobenzo [d][1,3]dioxol-2-one; ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 4.46 - 4.37 (m, 1H), 4.31 - 4.26 (m, 1H), 4.14 – 4.12 (m, 1H), 2.43 - 2.33 (m, 2H), 2.20 - 2.10 (m, 1H), 1.89 - 1.72 (m, 2H), 1.70, - 1.60 (m, 2H), 1.51 (s, 3H), 1.49 (d, $^{3}J_{HH}$ = 3.5 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ** 154.18, 154.13, 154.07, 154.04, 84.67, 84.64, 82.00, 81.88, 79.68, 79.57, 73.22, 73.05, 40.88, 40.81, 32.67, 32.59, 29.09, 29.00, 26.12, 21.49, 21.10, 20.99, 20.83; **IR (neat, cm^{-1})** 2982 – 2940 (C-H), 1776 (C=O); **HRMS(ESI+; MeOH):** *m/z* calcd. ($C_{12}H_{16}NaO_6$) 279.0839; $(M+Na)^{+}$ found: 279.0849.



Compound 5.17a; 4,4'-(ethane-1,2-diyl)bis(4-methyl-1,3-dioxolan-2-one); ^{1}H NMR (300 MHz, $CDCl_3$, 298 K) δ 4.25 - 4.14 (m, 4H), 1.90 – 1.86 (m, 4H), 1.54 (s, 6H); **^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ** 154.17, 82.55, 74.40, 32.93, 24.60; **IR (neat, cm^{-1})** 2984 (C-H), 1771 (C=O); **HRMS(ESI+; MeOH):** *m/z* calcd. ($C_{10}H_{14}NaO_6$) 253.0683; $(M+Na)^+$ found: 253.0688.

5.4.5 – Crystallographic information

General comments and crystallographic data

The measured crystals 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 = −173 °C). 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.[c] Structure Refinement: SHELXTL-97-UNIX VERSION.

Crystal data for carbamate 5.8b2: $C_{15}H_{19}NO_3$, M_r = 261.31, monoclinic, *C*2/c, a = 29.6567(12) Å, b = 5.7377(2) Å, c = 17.2274(7) Å, α = 90º, β = 114.1204(10)º, γ = 90º, V = 2675.49(18) Å^3, Z = 8, ρ = 1.297 mg·M^{-3}, μ = 0.090 mm^{-1}, λ = 0.71073 Å, T = 100(2) K, F(000) = 1120, crystal size = 0.40 × 0.20 × 0.20 mm, θ (min) = 1.505°, θ (max) = 32.06°, 18631 reflections collected, 4466 reflections unique (R_{int} = 0.0273), GoF = 1.080, R_1 = 0.0490 and wR_2 = 0.1327 [$I > 2\sigma(I)$], R_1 = 0.0531 and wR_2 = 0.1363 (all indices), min/max residual density = −0.309/0.625 [e·Å^{-3}]. Completeness to θ (32.06°) = 95.4%. CCDC number 1458049.

[c] **Note 3;** G. M. Sheldrick, *SHELXTL Crystallographic System*, version 6.10; Bruker AXS, Inc.: Madison, WI, **2000**.

Crystal data for carbamate 5.14b1: $C_{20}H_{23}NO_3$, M_r = 325.39, orthorhombic, *P*bca, a = 13.1420(3) Å, b = 10.8641(3) Å, c = 23.6246(5) Å, α = 90º, β = 90º, γ = 90º, V = 3373.03(14) Å^3, Z = 8, ρ = 1.282 mg·M^{-3}, μ = 0.086 mm^{-1}, λ = 0.71073 Å, T = 100(2) K, F(000) = 1392, crystal size = 0.40 × 0.20 × 0.20 mm, θ (min) = 1.72°, θ (max) = 30.53°, 24833 reflections collected, 4983 reflections unique (R_{int} = 0.0336), GoF = 1.045, R_1 = 0.0407 and wR_2 = 0.1010 [$I > 2\sigma(I)$], R_1 = 0.0525 and wR_2 = 0.1083 (all indices), min/max residual density = −0.221/0.381 [e·Å^{-3}]. Completeness to θ (30.53°) = 96.4%. CCDC number 1458050.

Crystal data for cyclic carbonate 5.14a: $C_{20}H_{20}O_3$, M_r = 308.36, monoclinic, *P*2(1)/n, a = 9.0867(9) Å, b = 16.4872(11) Å, c = 10.9948(9) Å, α = 90º, β = 109.094(10)º, γ = 90º, V = 1556.5(2) Å^3, Z = 4, ρ = 1.316 mg·M^{-3}, μ = 0.087 mm^{-1}, λ = 0.71073 Å, T = 100(2) K, F(000) = 656, crystal size = 0.45 × 0.40 × 0.40 mm, θ (min) = 2.32°, θ (max) = 36.97°, 27836 reflections collected, 7473 reflections unique (R_{int} = 0.0185), GoF = 1.029, R_1 = 0.0322 and wR_2 = 0.0999 [$I > 2\sigma(I)$], R_1 = 0.0352 and wR_2 = 0.1018 (all indices), min/max residual density = −0.237/0.555 [e·Å^{-3}]. Completeness to θ (36.97°) = 94.6%. CCDC number 1458051.

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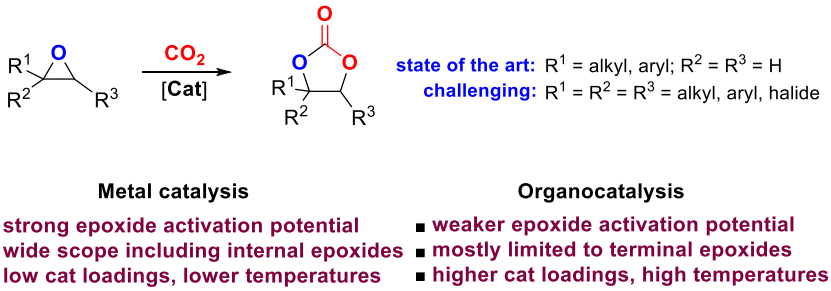
General conclusions

Carbon dioxide is necessary to life to advance, but on the other hand, it is also one of the main contributors of the greenhouse effect and constitutes a result of anthropogenic activities (i.e., the effect humans have on the environment). On a positive note, CO_2 offers a renewable carbon-based raw material for organic transformations with potential for industrial applications considering the versatility of cyclic carbonates and polyurethanes.

The quest for new low-energy demanding and selective small-molecule activation processes (including carbon dioxide) through the use of catalysis remains a major objective in chemical sciences. Initially, catalysis processes focused on the use of metal-based systems developing new transformations and improving process selectivities where possible. Metal catalysts in general terms offer excellent control over the activation of CO_2 and the process outcomes (chemoselectivity, conversion kinetics) but on the other hand are often (too) sensitive (cf., long-term stability) and require specific precautions (Scheme **C.1**).

Scheme C.1: Comparison of organocatalytic and metal-based approaches in cyclic carbonate formation with the typical pros and cons.

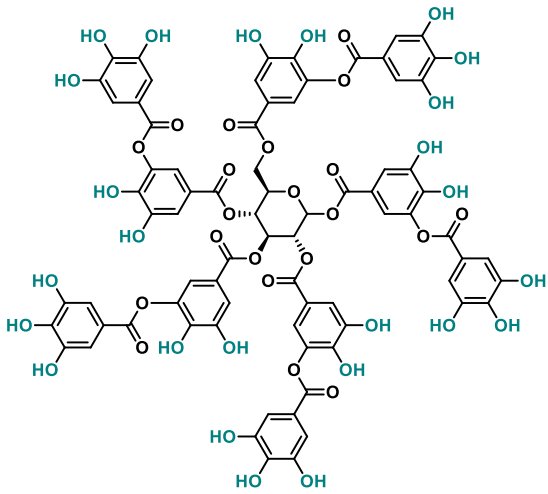


For this reason, catalysts based on organic molecules (organocatalysis) is considered an interesting alternative as it may offer a metal-free route to CO_2 valorization. A major drawback of organocatalysis, however, is that it shows significantly lower substrate activation potential compared to metal catalysis though generally speaking no special requirements are needed. The valorization of carbon dioxide continues to be an important example of the

conversion of waste-to-value, and the thesis work has been specifically focusing on the development of new organocatalytic strategies for the transformation of CO_2 and cyclic carbonates.

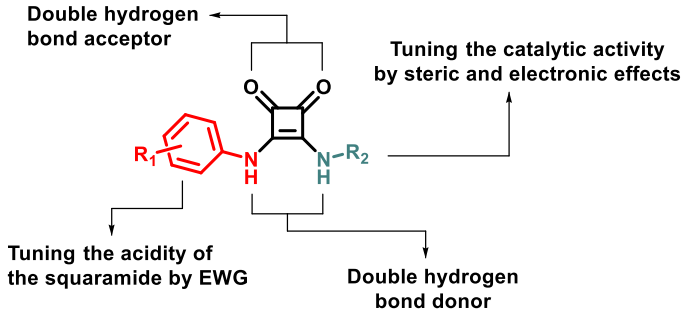
The field of organocatalysis involves organic molecules (including naturally occurring ones) that are able to catalyze a chemical reaction. Tannic acid (Scheme **C.2**), which is a natural compound and cheap polyphenol, was used as a component of a novel binary catalytic system. This combination shows excellent catalytic reactivity at attractively low catalyst loadings (0.50 mol%). The catalytic activity of the system was compared to other polyphenol based binary catalysts indicating some degree of synergy between the various poly(phenol) units within the tannic acid structure. This feature helps to increase catalyst lifetime (cf., turnover number) providing conceptually an interesting approach to improve the potential of organocatalysis in this area. The previously reported recycling problems for a related and much smaller polyphenol based binary system was addressed by the tannic acid system. The development of a new recycling protocol was successfully probed showing great potential, especially in terms of catalyst regeneration by acid treatment. The substrate scope shows excellent results in the case of terminal epoxide conversion under mild conditions and low catalyst loadings with excellent functional group diversity. However, the transformation of internal epoxides remained troublesome and therefore, for these more challenging substrates other strategies are thus warranted towards the formation of their respective cyclic carbonates.

Scheme C.2: Chemical structure of tannic acid showing five triphenol and five diphenol units.



By using an alternative approach and a different hydrogen bond donor in the binary catalytic system, we were able to improve the aforementioned results in the coupling reaction of epoxides and CO_2. Squaramides (Scheme **C.3**), which are small molecules whose properties can be easily tuned both electronically and sterically, in combination with halide-based nucleophiles provide interesting new potential for the coupling of both terminal and internal epoxides with CO_2 to prepare cyclic carbonates. In this case, the reaction mechanism is not based on the initial activation of the epoxide but rather on the stabilization of the different oxoanionic species (i.e., alkoxide, alkyl carbonate) generated during the catalytic event. The potential of the squaramides as versatile catalyst components was illustrated by the conversion of 10 internal epoxides which are known to be challenging substrates for organocatalytic systems.

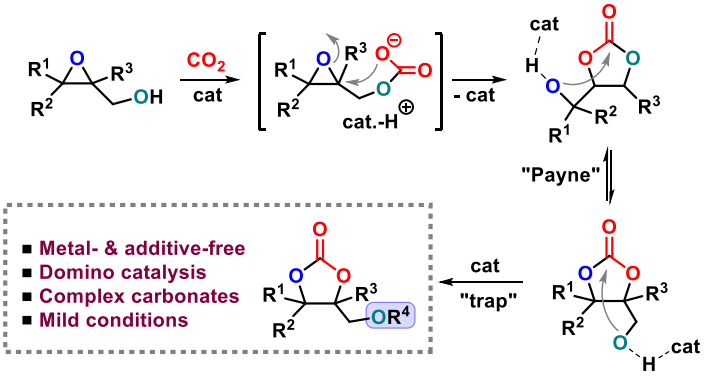
Scheme C.3: Modular synthesis and tunable properties of the squaramide structure.



The reaction mechanism for the coupling reaction of epoxides and carbon dioxide using a binary catalytic system comprising of a hydrogen bond donor in combination with a halide source usually starts with the ring opening of the epoxide by the halide. This strategy is not very successful when sterically more hindered epoxides are involved (i.e., for tri- and tetra-substituted congeners). Therefore, new strategies for the synthesis of cyclic carbonates with challenging tri- or tetrasubstitution patterns are required that go beyond the current potential of nearly all reported binary catalyst systems including metal- and organocatalytic protocols. The use of 1,2- or 2,3-epoxyalcohols (Scheme **C.4**) as starting materials allowed to develop a new conceptual approach towards these challenging carbonate targets, and is based on the initial generation of a cyclic carbonate species through base-mediated CO_2 activation followed by ring opening of the epoxy group. In the presence of the same organocatalytic base, this initial cyclic carbonate can equilibrate to a more substituted cyclic carbonate product

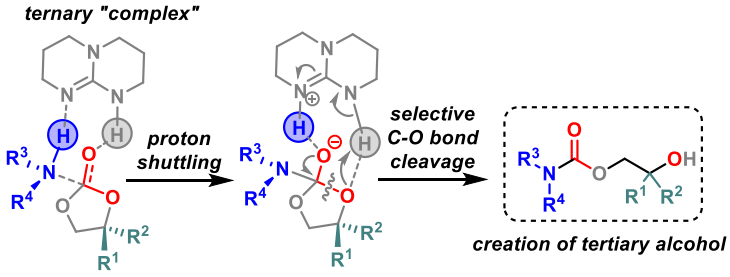
under thermodynamic control. The most substituted carbonate can be conveniently trapped *in situ* under mild reaction conditions thereby displacing the equilibrium to the desired target. The substrate scope of tri- and tetrasubstituted cyclic carbonates that could be achieved with this domino process consisting of a [3+2] cycloaddition and a Payne-type rearrangement constitutes the first example of an organocatalytic synthesis of tri- and tetra-substituted cyclic carbonates.

Scheme C.4: A domino process for the formation of highly substituted cyclic carbonates through a consecutive [3+2] cycloaddition reaction and a Payne-type carbonate rearrangement.



The use of cyclic carbonates for the formation of functionalized carbamates *via* aminolysis reactions between cyclic carbonates and amines constitutes a greener alternative to the use of harmful chemicals such us phosgene or isocyanates involved in the synthesis of polyurethanes. The aminolysis reaction typically delivers two different regioisomers (*i.e.*, the final C–O bond scission is not fully selective), but when TBD (Scheme **C.5**) is involved in the reaction not only the overall reaction kinetics but also the regioselectivity of the process is significantly improved. Our newly developed protocol combines high regio-control, high isolated yields and operational simplicity (rt, no inert atmosphere needed) using readily available starting materials. The scope presented in our study is based on a wide range of cyclic carbonates with different substitution patterns. Additional experiments using bis-cyclic carbonates have disclosed potential towards the regio-selective formation of oligourethanes, a feature that can be of great use in the preparation of regio-regular polymers and fine-tuning materials properties.

Scheme C.5: Proposed regioselective C-O bond breaking in *gem*-disubstituted cyclic carbonates by TBD using amine reagents.



Overall, this thesis summarizes previously unexplored potential for organocatalysis in the area of CO_2 conversion into challenging cyclic carbonate structures, and their regio-selective conversion into functional carbamates. Simple though highly effective organocatalysts based on polyphenols, squaramides and organic superbases such as TBD and DBU were used and shown to mediate conversions that were thought to be not feasible due to the generally lower activation potential of organocatalysis compared against metal-based approaches. However, the results in this thesis demonstrate that new conceptual designs that make clever use of synergistic effects (polyphenol based catalyst), oxoanion stabilization effects (squaramides) or Payne-like rearrangement potential (combination of epoxy alcohols and DBU/TBD) provide new synthetic opportunities in the area of CO_2 valorization. Furthermore, by properly fine-tuning the substitution of the cyclic carbonate and using hydrogen-bond activation (TBD), regioselective C–O bond breaking in the cyclic carbonate substrate can be achieved affording value-added carbamate scaffolds. These new approaches can be of high use in other types of CO_2 conversion reactions thus offering a blueprint for further development of metal-free strategies in this highly active area of small molecule activation.

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Currículum Vitae

Sergio Sopeña de Frutos was born on November 9, **1988** in Palencia (Castilla y León, Spain). In **2006** he started his undergraduate at the University of Valladolid obtaining his BSc degree in June **2012** presenting his final research projects in the field of organocatalysis in the group of Professor Rafael Pedrosa. In June **2013** he finished his MSc in "Industrial and Synthetic Chemistry" at the same university under the supervision of Professor Alicia Maestro. In January **2014**, he moved to Tarragona where he started his PhD studies under the supervision of Professor Arjan W. Kleij at the Institute of Chemical Research of Catalonia (ICIQ) where he performed the research that is described in this thesis. His research was financially supported with a predoctoral fellowship from Covestro, and the results described in this thesis have been communicated at the "*3rd International Symposium on Green Chemistry - ISGC*" (**2015**, La Rochelle, France). "*XXXV Reunión Bienal RSEQ*" (**2015**, A Coruña. Spain), "*International Conference on Carbon Dioxide Utilization – ICCDU*" (**2016**, Sheffield, United Kingdom), "*Cost Action CARISMA CM1205*" (**2017**, Lisbon, Portugal), "*Aportando Valor al CO_2*" (**2017**, Tarragona, Spain), and the "*3rd EuCheMS Congress on Green and Sustainable Chemistry – EuGSC*" (**2017**, York, United Kingdom), and published in high impact international scientific journals.

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List of Publications

1. "Highly efficient organocatalyzed conversion of oxiranes and CO_2 into organic carbonates". Sergio Sopeña, Giulia Fiorani, Carmen Martín and Arjan W. Kleij, *ChemSusChem* **2015**, *8*, 3248-3254.

2. "Regioselective organocatalytic formation of carbamates from substituted cyclic carbonates". Sergio Sopeña, Víctor Laserna, Wusheng Guo, Eddy Martín, Eduardo C. Escudero-Adán and Arjan W. Kleij, *Adv. Synth. Catal*. **2016**, *358*, 2172-2178.

3. "Pushing the limits with squaramide-based organocatalysts in cyclic carbonate synthesis". Sergio Sopeña, Eddy Martín, Eduardo C. Escudero-Adán and Arjan W. Kleij, *ACS Catal*. **2017**, *7*, 3532-3539.

4. "Organocatalyzed Domino [3+2] Cycloaddition/Payne-Type Rearrangement using Carbon Dioxide". Sergio Sopeña, Mariachiara Cozzolino, Eduardo C. Escudero-Adán, Marta Martínez Belmonte and Arjan W. Kleij, *Angew. Chem. Int. Ed*. **2018**, *submitted*.

5. "Metal Complexes Catalyzed Cyclization with CO_2". Jeroen Rintjema, Leticia Peña Carrodeguas, Victor Laserna, Sergio Sopeña and Arjan W. Kleij, *Top. Organomet. Chem.* **2016**, *53*, 39-71.

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