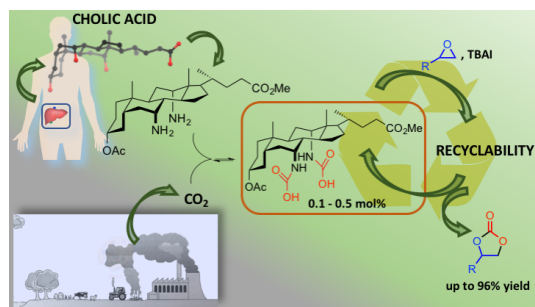


Broadening the scope of steroidal scaffolds: the umpolung of a bis-primary amine pre-catalyst for the insertion of CO₂ into epoxides

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Supporting Information Placeholder



ABSTRACT: A cholic acid-based bis-primary amine is capable of promoting the insertion of CO₂ into epoxides with the cooperative aid of an iodide anion. This framework is transformed *in situ* into a bis-carbamic acid. The later is the active catalytic species, operating through H-bonding interactions. Our system works with complete atom economy, under solvent-free, metal-free and mild conditions. Also, it can be recycled.

The production of carbon dioxide as a consequence of anthropogenic activities has been signalled out as one of the main responsible for the greenhouse effect and the concomitant global warming. Different strategies for transforming CO₂ into different added-value products of synthetical and/or industrial interest have emerged during the last decades.^[1] Particularly well studied is the insertion of CO₂ into epoxides **1** to render cyclic carbonates **2** (heading of Table 1). This reaction can be assisted by heterogeneous or homogeneous catalytic systems, in most of the cases with the synergistic participation of halide anions.^[2] Products **2** are widely used in many different applications.^[3]

Recently we have disclosed a cholic acid-based organocatalyst for the asymmetric Michael-type addition reaction.^[4] Expanding the scope and applicability of these scaffolds in organic synthesis, herein we introduce a steroidal diamino pre-catalyst, which is capable of promoting the insertion of CO₂ into epoxides with a significantly low loading and under rather mild conditions. Additionally, this catalyst presents a novel mode of action.

Most of the organocatalysts reported on the transformation **1**→**2** are equipped with an ordered array of motifs capable of acting as H-bond donors,^[5] and are accompanied by a halide anion.^[6] Based on that, we designed the bis-ammonium salt **4** (Figure 1), derived from cholic acid, **3**, as a potential candidate for catalyzing this process. Compound **4** can be accessed easily from bis-amine **5**, previously reported in the literature.^[7]

Platform **4** bears preorganized and co-directed H-bond donor motifs, which, in addition, define and configure a reactive cavity amenable for catalysis.^[4] Also, it incorporates two iodide anions. It is worth remarking that converting cholic acid into a successful catalyst of any type implies the reevaluation of an inexpensive and readily bio-available resource.

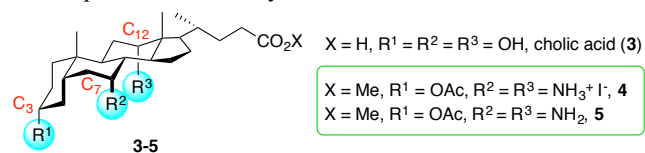
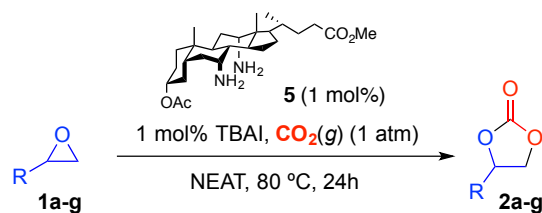


Figure 1. Structure of cholic acid, **3**, and derivatives **4** and **5**.

Initially, the steroidal derivative **4** was investigated on the insertion reaction of CO₂ into styrene oxide, **1a**, to afford the corresponding five-membered cyclic carbonate **2a** (Table 1, entry 1). Pursuing a green methodology, we decided to avoid the use of any organic solvent apart from the epoxide, which was employed as reagent and reaction media. To begin with, **5** mol% of catalyst **4** was used, under rather mild reaction conditions: 1 atm of CO₂ (a standard balloon) at 70 °C for 3 h. Disappointingly, a maximum conversion of 4% was observed. Alternatively, we decided to test steroid **5**. In this case 5 mol% of tetrabutylammonium iodide (TBAI) was also added. To our surprise, **5**, consisting of two primary amine groups, afforded promising preliminary results (Table 1, entry 2). This observation was somehow puzzling considering that primary amines

have been consistently reported as poor catalysts for the insertion of CO₂ into epoxides. For instance, the group of Tsang studied some primary amines, with varied pK_a values, as sole catalyst for the insertion of CO₂ into propylene oxide (PO).^[8] Only under harsh conditions (T=150 °C, P=5 MPa) acceptable conversions were achieved. Subsequent studies point towards the same direction.^[9] Intrigued by this fact, and looking for the limits of the bis-amine **5**, next we carried out a careful optimization of the reaction parameters involved on the transformation **1a**→**2a** (see the SI for details).

Table 1. Preparation of cyclic carbonates **2a-g catalyzed by the binary system **5**/TBAI.^a**



entry	R	conv. (%) ^b	yield (%) ^c
1 ^d	1a : C ₆ H ₅	4	-
2 ^e	1a : C ₆ H ₅	67	-
3	1a : C ₆ H ₅	99	96
4 ^f	1a : C ₆ H ₅	47	-
5 ^g	1a : C ₆ H ₅	0	-
6	1b : ⁿ C ₆ H ₁₃	99	82
7	1c : ⁿ C ₄ H ₉	99	64
8	1d : CH ₂ -O-allyl	93	92
9	1e : CH ₂ -O-Bn	99	95
10	1f : CH ₂ Cl	99	71
11	1g : CH ₂ OH	89	70

^a Reaction conditions: catalyst **5** (1 mol%) and TBAI (1 mol%) were suspended in the corresponding epoxide **1a-g** (200 μL); ^b Determined by ¹H NMR spectroscopy on crude reaction mixtures; ^c Isolated yield of analytically pure products **2a-g**; ^d Bis-ammonium salt **4** (5 mol%) was used as catalyst. No TBAI was added. The reaction mixture was vigorously stirred for 3h at 70 °C; ^e Steroid **5** (5 mol%) and TBAI (5 mol%) were used as catalysts. The reaction mixture was vigorously stirred for 3h at 70 °C; ^f TBAI (1 mol%) was used as the sole catalyst; ^g Bis-amine **5** (1 mol%) was used as the sole catalyst.

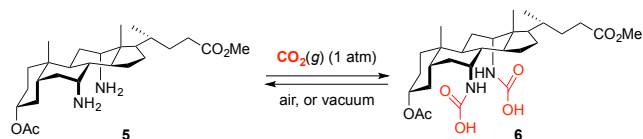
Delightfully, a slight increase in temperature and a longer reaction time allowed reducing the catalyst loading to 1 mol% for both **5** and TBAI. By this means a 99% of epoxide **1a** was converted into product **2a**, which could be readily isolated in 96% yield (Table 1, entry 3).^[10] The sole participation of TBAI under similar reaction conditions afforded significantly lower conversion, 47% (Table 1, entry 4), while steroid **5** itself was ineffective (Table 1, entry 5). Also, other primary amines and control experiments proved to be unsuccessful (see SI). With this set of conditions in hand a collection of epoxides **1b-1g**, bearing different functionalities, were investigated as substrates. In all cases the corresponding cyclic carbonates could be isolated in good to excellent yields, ranging from 64 to 96% (Table 1, entries 6–11). It is worth highlighting the low catalyst loading of steroid **5** necessary for these reactions.

Also, our methodology is solvent-free, metal-free and operationally straightforward. Moreover, steroid **5** can be compared, in terms of performance, to other organocatalytic systems known to operate under related conditions (see SI for details).^[11]

In addition, the system **5**/TBAI was recycled and it could be reutilized further, employing epoxide **1c** as a substrate (see SI). Six runs were accomplished without jeopardizing the performance of the catalysts. After the sixth run an accumulative turn over number (TON) of 565 units was displayed. Also, the turn over frequency (TOF) of the catalyst **5** was above 23 h⁻¹.^[12] These numbers, markedly high for an organocatalyzed process, demonstrate the reliability and robustness of steroid **5**.

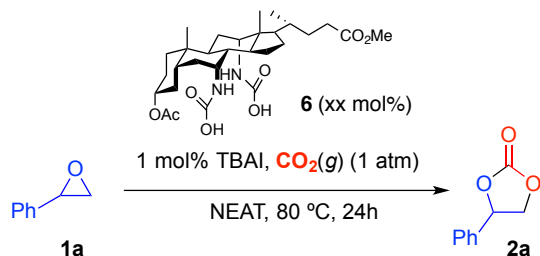
Next, we decided to concentrate our efforts on shedding some light on the action mode of bis-amine **5**. Some primary and secondary amines are known to scavenge CO₂ to form fairly stable carbamates in a reversible manner.^[13] Additionally, CO₂ is absorbed easily into superbases such as DBU,^[14] TBD,^[14] and *N*-methyl TBD,^[15] forming stabilized zwitterionic carbamates. Other guanidines behave analogously.^[16] These species are thought to be involved in the activation of CO₂ and its coupling with epoxides. We contemplated steroidal bis-amine **5** forming the same type of adducts with CO₂, which, ultimately, would give an account for its enhanced reactivity. In this sense, we found that when a saturated solution of steroid **5** in freshly distilled and degassed THF was stirred overnight under 1 atm of CO₂ a bulky white precipitate crashed out. It was filtered off, washed, dried and stored under CO₂ atmosphere, to be characterized as bis-carbamic acid **6** (Scheme 1). A maximum of 47% yield was isolated. Exposing product **6** to air for few hours, or subjecting it to vacuum, results in the recovery of pristine bis-amine **5**. The transformation of steroid **5** into **6** implies an umpolung on the reactivity of the primary amine functions, where the N–H motifs become fairly acidic and are available for participating in H-bonding events.

Scheme 1. CO₂ trapping by steroidal bis-amine **5.**



Steroid **5** was replaced by bis-carbamic acid **6** in the transformation **1a**→**2a**. This allowed reducing the loading of the organocatalyst to 0.5 mol% without compromising the reactivity of the system (Table 2, entry 1). A further drop to 0.25 or 0.1 mol% still afforded significant conversion figures (Table 2, entries 3 and 4). Considering the mild reaction conditions utilized by our system, and its markedly low catalyst loading, steroid **6** approaches some monometallic-based catalysts described to date.^{[27],[17]}

Table 2. Study of the reactivity of bis-carbamic acid **6.^a**



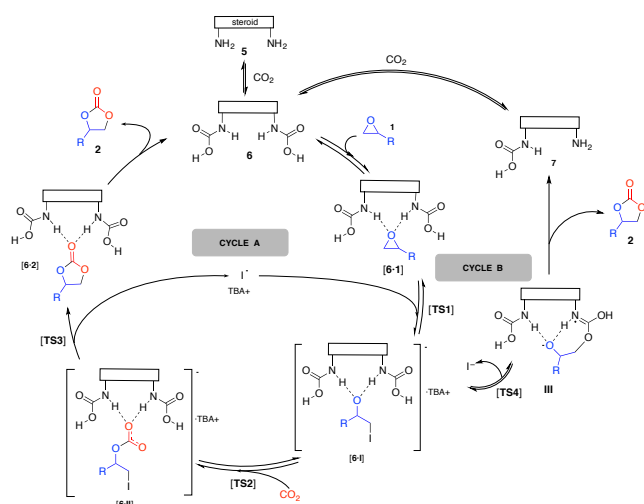
entry	6 (mol %)	conv. (%) ^b
1	0.50	96
2 ^c	0.50	61
3	0.25	72
4	0.10	68

^a Reaction conditions: catalyst **6** and TBAI (6.5 mg, 17.5 μmol , 1 mol%) were suspended in styrene oxide (200 μL , 211 mg, 1.75 mmol); ^b Determined by ¹H NMR spectroscopy on crude reaction mixtures; ^c Blank reaction: bis-amine **5** was used instead of bis-carbamic acid **6**.

The transformation **1a**→**2a** was examined further through kinetic studies (see SI). When TBAI was used as the sole catalyst the reaction obeyed pseudo-first-order kinetics.^[18] The reaction catalyzed by the binary system **6** + TBAI was significantly faster. Interestingly, for the first 25 min the reaction catalyzed by **5** + TBAI followed a course similar to that of the reaction promoted by TBAI alone. After this time an increment in the reaction rate was observed. This lag period was attributed to the formation of bis-carbamic acid **6** *in situ* from the precursor **5**. Steroid **6** is the active catalytic specie for the insertion of CO₂ into the epoxides.

Considering all the above we tentatively suggest the following mechanism for our reaction (Scheme 2).

Scheme 2. Mechanistic proposal.



Bis-carbamic acid **6**, formed *in situ* from precursor **5**, is capable of complexing epoxide **1** through cooperative and simultaneous H-bonding interactions, established between the N–H units of the carbamic acid moieties and the lone pairs of the oxygen atom of the epoxide. An iodide anion, from TBAI, attacks on the less substituted carbon of the epoxide within the complex **[6·1]** to render the iodoalkoxide-type intermediate **I**, stabilized by H-bond contacts as the anionic complex **[6·I]**.

Subsequently, CO₂ inserts into the labile C–I bond of **I** to give rise to intermediate **II**, also stabilized by supramolecular contacts (**[6·II]**). The last evolves towards the desired five-membered cyclic carbonate **2** with the release of the iodide anion, reinserted into the catalytic manifold (Scheme 2, Cycle A).

Alternatively, the incorporation of CO₂ in the intermediate **[6·1]** can also occur in a pseudo-intramolecular manner. In this respect, an experiment was set up with styrene oxide **1a**, TBAI (1 mol%) and bis-carbamic acid **6** (25 mol%), under air, at 80 °C for 24 h. Strikingly 30% of **1a** was converted into cyclic carbonate **2a** (see SI for details). It implies a formal delivery of CO₂ from the preloaded organocatalyst **6**. We suggest the participation of intermediate **III**, which evolves towards the desired five-membered cyclic carbonate **2** and specie **7**. Steroid **7**, in the presence of more CO₂, regenerates bis-carbamic acid **6** (Scheme 2, Cycle B).

The above mechanistic proposal is in agreement with DFT molecular modelling studies carried out on the slightly simplified bis-carbamic acid **6***^[19] and PO.^[20] Geometry optimizations of the different conformers of **6*** revealed that the most stable one features both N–H groups pointing towards the inner part of the cavity defined by the steroid scaffold, while the carboxylic groups are directed outwards. As it was expected, this conformation is well preorganized to interact with an epoxide inside the cavity with the simultaneous formation of two optimum H-bonds with each of the N–Hs of the carbamic acid functionalities (Figure 2). Such a complexation activates the epoxide towards the nucleophilic attack of the iodide anion.

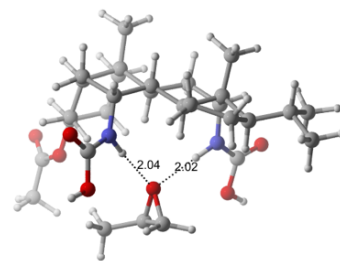


Figure 2. Three-dimensional structure of the complex **[6*·PO]** with H-bonds highlighted, at the b3lyp/6-31+G** level.

Starting from the complex **[6*·PO]** the complete reaction pathway for the formation of carbonate **2** depicted in Scheme 2, Cycle A, could be identified. According to our calculations, the rate determining step would be the CO₂ insertion ($\Delta G(\text{TS2}) - \Delta G([\mathbf{6}^* \cdot \mathbf{1}]) = +21 \text{ kcal} \cdot \text{mol}^{-1}$), and the driving force of the process the higher thermodynamic stability of the cyclic carbonate **2** (SI, Figure SI-8). Also, on the light of our observations regarding the ability of **6** to promote the formation of the carbonate even in the absence of a CO₂ atmosphere, Cycle B (Scheme 2) was explored. In this case the transition state for the first step of this alternative pathway through transition state **TS4** featured a quite higher Gibbs free energy barrier than the pathway through **TS2**, [$\Delta\Delta G = \Delta G(\text{TS4}) - \Delta G(\text{TS2}) - \Delta G(\text{CO}_2) = +5.8 \text{ kcal} \cdot \text{mol}^{-1}$], which is the rate determining step in the initially proposed catalytic cycle. Therefore, this type of intramolecular CO₂ transfer does not seem to operate in the presence of external CO₂, although it might eventually work in its absence. A mechanism such as that of Cycle B opens new opportunities for this and other reactions where CO₂ is used as reagent.

To conclude, we have implemented a cholic acid-based bis-primary amine pre-catalyst for the insertion of CO₂ into epoxides. Before, these functions had been described as modest for this transformation. The unusual activity of our bis-amine platform relies on the *in situ* formation of a stable preorganized bis-carbamic acid specie, identified experimentally as the active catalyst. Our system operates with a significantly low catalyst loading, under solvent-free, metal-free and mild conditions, and with complete atom economy. Moreover, it can be recycled a minimum of six times displaying high accumulative TON and TOF figures. This work, along with our previous contribution,^[4] allow envisioning steroidal platforms as privileged scaffolds for building up novel catalysts.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. It includes experimental procedures, characterization of the products, NMR data, and quantum chemical calculations.

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Author Contributions

All authors have given approval to the final version of the manuscript. / ‡These authors contributed equally.

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(19) Structure **6***, missing the alkyl chain at C₂₂, which is not likely to participate in the catalytic process, was used as a simplified model for the calculations. See the SI for details.

(20) The calculations were carried out with the Gaussian09 package of programs employing the b3lyp functional and the 6-31+G** basis set for H, C, O and N atoms, and lanl2dz effective core potential for I.

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