Effect of an Al(III) Complex on the Regio- and Stereoisomeric Formation of Bicyclic Organic Carbonates

Cristina Maquilón,[§‡] Bart Limburg,[§] Victor Laserna,[§] Diego Garay,[§] Joan González Fabra,[§] Carles Bo,[§‡] Marta Martínez Belmonte,[§] Eduardo C. Escudero-Adán[§] and Arjan W. Kleij*[§†]

[§] Institute of Chemical Research of Catalonia (ICIQ), Barcelona Institute of Science & Technology (BIST), Av. Països Catalans 16, 43007 – Tarragona, Spain

[†] Catalan Institute of Research and Advanced Studies (ICREA), Pg. Lluis Companys 23, 08010 – Barcelona, Spain

[‡] Departament de Química Física i Inorgànica, Universitat Rovira i Virgili, Marcel·lí Domingo s/n, 43007 Tarragona, Spain

Supporting Information Placeholder

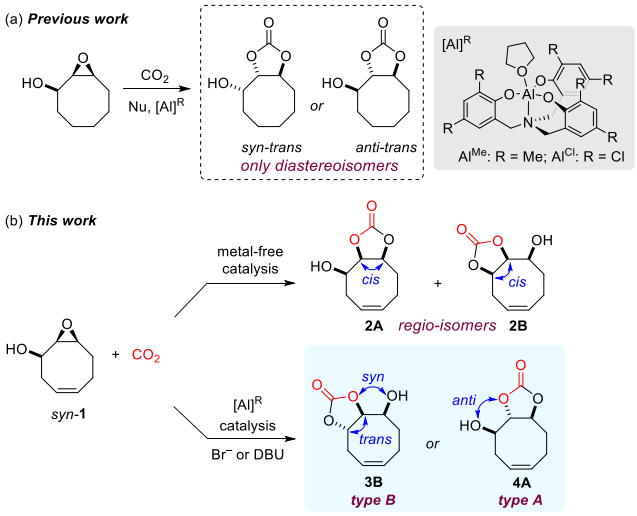
ABSTRACT: Valorization of carbon dioxide into organic molecules using catalytic approaches has witnessed an upsurge in recent years. Here, the influence of an Al(III) aminotriphenolate complex on the regio- and stereo-chemical features of the coupling between carbon dioxide and a cyclic epoxy alcohol has been studied. Three distinct bicyclic carbonate products were produced from a single starting material depending on the catalytic conditions. The proposed carbonate configurations were examined by solution and solid phase techniques including NMR spectroscopic and X-ray crystallographic analyses. Control experiments combined with DFT calculations provide a rationale for the distinct catalytic manifolds observed in the presence and absence of the Al(III) complex.

INTRODUCTION

Contemporary research focusing on the use of carbon dioxide as a readily available carbon feedstock in organic synthesis[1–8] has a major focus on the discovery of new transformations[9-14] while improving existing ones.[15-19] Whereas the vast majority of the conversions that utilize CO_2 as one of the substrates involve catalytic protocols that afford the final product in racemic form, recent work has shown an upsurge of more challenging, enantioselective or stereo-divergent transformations.[20-25] Among the most common synthetic efforts, the ones that incorporate CO_2 whilst preserving a high oxidation state of the carbon center originally present in the C1 reagent prevail. This is exemplified by the development of diverse organic transformations that result in functional compounds such as carboxylic acids,[26-29] organic carbonates[30-36] and carbamates.[37-39]

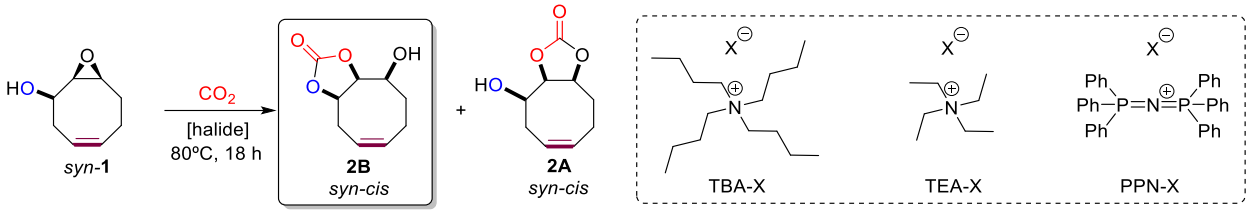
The area of cyclic carbonate synthesis has witnessed a spectacular growth over the last decade[2,3,30-32] with a primary focus on the development of improved and more sustainable catalysts for the [3+2] cycloaddition of epoxides and CO_2.[40-43] The (dia)stereoselective formation of more complex cyclic organic carbonates,[25,44,45] however, remains underdeveloped. It is generally assumed that the formation of a cyclic carbonate from epoxides and CO_2 follows a typical three-step sequence involving epoxide ring opening induced by the (binary) catalyst, subsequent activation of the CO_2 molecule by the intermediate alkoxide and termination through cyclization releasing the desired product.[46-50] However, recent work from two laboratories has illustrated that certain catalysts[51,52] or specific substrates[53,54] may alter the reaction pathway, leading to regio- and stereomeric products.

Scheme 1. Previous Formation of Bicylic Carbonates (a) and Current Regio- and Diastereodivergent Synthesis (b)



Recently we reported on a substrate-controlled conversion of cyclic epoxy alcohols with CO_2.[25] Different stereoselective routes for cyclic carbonate formation could be triggered by a judicious choice of the catalyst components derived from an Al(III) based Lewis acid and an accompanying external nucleophile (Scheme 1a). We observed the formation of rare (*syn/anti*) *trans*-configured bicyclic carbonates. However, due to the symmetric nature of the rings, we were unable to unambiguously differentiate between regio-isomers that may be produced. These latter regioisomeric carbonates would be produced via conventional [3+2] cycloaddition into the epoxide

Table 1. Screening Conditions for the Coupling of Epoxy Alcohol (*syn*-1) and CO_2 using Halide Salts as Catalysts.[a]



entry	cat. (mol%)	solvent	$p(CO_2)^0$ (bar)	conversion of **1** (%)[b]	Sel. for **2B** (%)[b]	Sel. for **2A** (%)[b]
1	TBAB (1.0)	MEK	40	20	80	20
2	TBAB (10)	MEK	40	85	88	12
3	TBAB (15)	MEK	40	85	89	11
4	TBAB (20)	MEK	40	90	87	13
5	TBAB (25)	MEK	40	>99	92	8
6	PPNBr (25)	MEK	40	>99	88	12
7	TEAB (25)	MEK	40	>99	91	9
8	NaBr (25)[c]	MEK	40	40	87	13
9	TEAI (25)	MEK	40	>99	88	12
10	PPNI (25)	MEK	40	>99	89	11
11	TBAI (25)	MEK	40	>99	88	12
12	PPNCl (25)	MEK	40	79	93	7
13	TBACl (25)	MEK	40	56	93	7
14	TBAB (25)	ACN	40	>99	88	12
15	TBAB (25)	DMSO	40	68	66	34
16	TBAB (25)	DMF	40	87	78	22
17	TBAB (25)	DEE	40	97	91	9
18	TBAB (25)	TOL	40	>99	93	7
19	TBAB (25)[d]	MEK	40	48	92	8
20	TBAB (25)[d]	MEK	30	52	90	10
21	TBAB (25)[d]	MEK	20	54	87	13
22	TBAB (25)[d]	MEK	10	56	88	12

[a]Reaction conditions: 80 °C, 18 h, substrate **1** (0.50 mmol, 70 mg, 2.5 M), MEK = methyl ethyl ketone. DEE stands for diethoxyethane. [b]Based on ^{1}H NMR integration of the crude product taking only the starting material and carbonate products into account. Sel. = selectivity. [c]The reaction mixture was heterogeneous. [d]Carried out in a different pressurized HTE system, see SI for details.

only (type **A**), or formed by substrate-controlled incorporation of the alcohol in the substrate (type **B**), see Scheme 1b. This result prompted us to consider other cyclic epoxy alcohol substrates that do not show this symmetry, by introduction of a different degree of rigidity in their backbone and to examine the influence on the regio- and stereoselective nature of the overall [3+2] cycloaddition reaction (Scheme 1b). In this work, we will demonstrate that introducing a symmetry-breaking element in the backbone of the cyclic epoxy alcohol substrate delivers new configurations that remained previously unnoticed. By using Al(III)-based catalysts, we are able to access two unexpected products, different from those produced using standard Br^--catalysis. Knowing the absolute configuration is of vital importance to design conversions that capitalize on the synthetic potential of readily available and ubiquitous epoxy alcohols delivering organic cyclic carbonates under high stereo- and/or regio-control. Such carbonates are valuable as is, or can be used as precursors to triols with absolute stereo-configuration.[25,55] Notably, these protocols allow for the selective synthesis of 3 out of 8 possible isomeric products from a single starting material, and produces 2 additional isomers in minor amounts.

RESULTS AND DISCUSSION

Halide Catalyzed Carbonation. We began to investigate the conversion of epoxy alcohol *syn*-**1** into bicyclic carbonates using a metal-free, halide-based catalyst and the results are gathered in Table 1. Based on previous work carried out by us in this area with other types of cyclic epoxy alcohols,[25] the initial reactions conditions were provisionally set at 80 °C and 40 bar initial CO_2 pressure while using an 18 h reaction time. Tetrabutylammonium bromide (TBAB) was first scrutinized (Table 1, entry 1) at a loading of 1 mol% with respect to *syn*-**1**. Under these conditions, formation of cyclic carbonate products was rather sluggish and therefore the amount of TBAB was gradually increased (Table 1, entries 2-5) revealing eventually that a virtual full conversion of *syn*-**1** could be achieved at a loading of 25 mol% TBAB. Out of the products, we identified *syn-cis* **2B** as major and *syn-cis* **2A** as minor products in 92%

to 8% selectivity, respectively. Interestingly, the selectivity seems to not depend on the type of nucleophilic catalyst (Table 1 entries 6–13), although lower conversions were obtained using poorly soluble salts (NaBr, entry 8), or chlorides (Table 1 entries 12–13). The lower potential of chloride-based nucleophiles in epoxide/CO_2 coupling reactions follows general trends typically noted in this area.[56] The selectivity was neither perturbed by the CO_2 pressure (Table 1, entries 19–22), and was only affected slightly by the choice of solvent (entries 14–18). In these cases, a lower selectivity goes accompanied by a lower conversion, and therefore MEK was selected as the solvent for further studies.

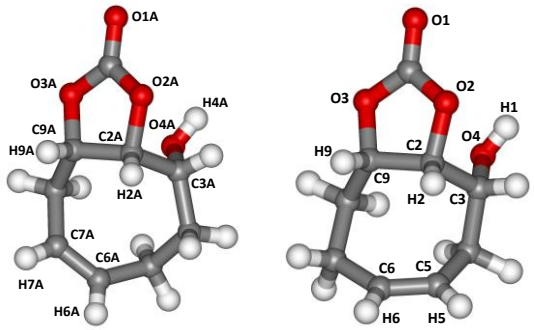


Figure 1. LEFT: X-ray molecular structure determined for *syn-cis* **2B** (major isomer). Some selected pertinent bond lengths (Å) and dihedral angles (º) with esd´s in parentheses: C(6A)-C(7A) = 1.3323(8); O(2A)-C(2A)-C(9A)-O(3A) = 27.20(5), O(2A)-C(2A)-C(3A)-O(4A) = -70.22(5). **RIGHT**: X-ray molecular structure determined for *syn-cis* **2A** (minor isomer). Some selected pertinent bond lengths (Å) and dihedral angles (º) with esd´s in parentheses: C(5)-C(6) = 1.3324(17), O(2)-C(2)-C(9)-O(3) = 22.49(9), O(2)-C(2)-C(3)-O(4) = -54.62(11).

In order to optimize the yield of *syn-cis* **2B**, reactions were then performed at a larger scale (1 mmol) and at a lower concentration of *syn*-**1** (1 M) while keeping most of the other reaction conditions constant. Some variation of the reaction temperature was applied (60-80 ºC; see Table S1 entries 1-3 in the Supporting Information, SI) showing that the preparation of *syn-cis* **2B** is best performed at 80 ºC (entry 3) affording the desired product in a 76% NMR and 65% isolated yield after chromatographic purification.[57] The afforded pure materials could be crystallized and examined in detail by X-ray crystallography (Figure 1). The crystallographic studies indisputably showed that two regio-isomeric cyclic carbonates (**2A** and **2B**) had been formed having both a *syn-cis* configuration. Surprisingly, the major isomer turned out to be *syn-cis* **2B**, *i.e*. the carbonate product of type **B**, contrary to what would be expected if a standard double inversion would have taken place.[43,48,58]

DFT Studies. The combined results collected in Table 1 seem to propose that the formation of *syn-cis* **2B** is the result of an unknown manifold that should involve an overall double inversion pathway, different from the standard mechanism. In order to shed light on the formation of the regio-isomer *syn-cis* **2B**, density functional theory (DFT) calculations were performed (see Figure 2); for further details see the Experimental section and Supporting Information, SI). In the presence of TBAB, *syn*-**1** can be converted both via α- or β-attack of the bromide onto the epoxy alcohol. Moreover, we computed both stepwise and concerted processes, with the latter thus combining epoxide ring-opening and linear carbonate formation. The stepwise formation of *syn-cis* **2A** via the β-attack has an energetic span (ΔE; relative to *syn*-**1**) of 22.6 kcal/mol, whereas the α-attack has a significantly lower ΔE (18.7 kcal/mol). The concerted pathways to the linear carbonate intermediates demonstrate that via initial β-attack the ΔE is higher (21.2 kcal/mol) compared to the stepwise manifold, while the pathway from an α-attack is favored even more (ΔE = 15.8 kcal/mol). Therefore, the formation of *syn-cis* **2A** is suggested to go through initial α-attack of the bromide nucleophile. Importantly, the calculated energies involved in the formation of the respective intermediates and transition states shows that under the experimental conditions (80 ºC, 40 bar) these steps should be reversible.

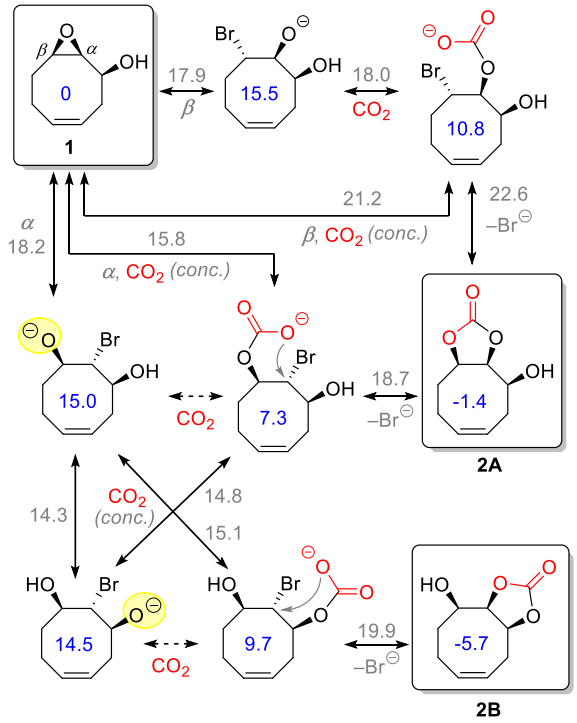
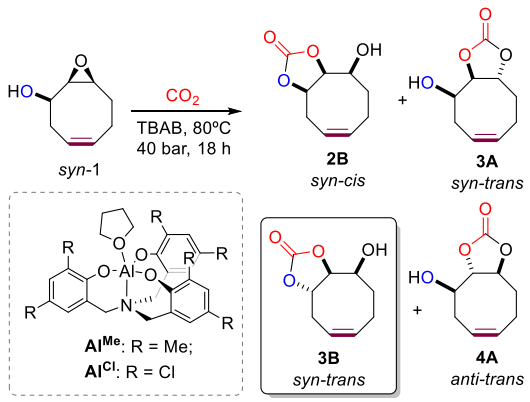


Figure 2. DFT computed pathways for the formation of **2A** through step-wise and concerted (conc.) pathways via α- and β-attack of the bromide nucleophile. Interconversion of the alkoxide species formed after initial bromide-mediated ring-opening of *syn*-epoxy alcohol **1** through intramolecular proton transfer (highlighted in yellow) leads to product **2B**. The accompanying TBA cations are omitted for clarity in all manifolds. In blue, the Gibbs free energies (in kcal/mol) of the intermediates are given; the numbers in grey refer to the calculated Gibbs free energies of the corresponding transitions states. All energies are relative to the energy of **1**.

The formation of product **2B** cannot occur through a mechanism involving a β-attack, and we therefore explored possible pathways from the alkoxide produced after initial α-attack of the bromide onto the epoxide unit in *syn*-**1** (in Figure 2). This intermediate can isomerize through an intramolecular proton transfer (the oxygen anions involved are indicated in yellow) practically without barrier. The resultant alkoxide isomer can then lead to the formation of *syn-cis* **2B** through an apparent barrierless CO_2 activation and subsequent cyclization having a barrier of 19.9 kcal/mol. Other routes leading to *syn-cis* **2** (see SI) via formation of an isomerized *syn* epoxy alcohol and subsequent stepwise/concerted ring-opening, CO_2 activation and cyclization (including α- and β-pathways) were considered, but have energetic spans (slightly) above the one computed for the stepwise conversion of the isomerized alkoxide into **2B**.

The free energy of the product **2B** (–5.7 kcal/mol) is substantially lower than that of **2A** (–1.4 kcal/mol). **2B** is therefore the expected thermodynamic product, given that there are no other thermodynamic wells in the scheme (*i.e.*, all reactions are reversible at 80 ºC). Thus, the mechanistic DFT results align well with the experimental observation that **2B** is the major product, and the final product ratio is therefore thermodynamically controlled. Microkinetic modeling was performed (see SI) showing a good fit with the experimental observations predicting a 95% selectivity for **2B** (92% observed).

Table 2. Conversion of Syn-1 in the Presence of Al(III) Complexes Al^{Me} or Al^{Cl} and a Halide based Nucleophile.[a]



entry	[Al] (mol%)	TBAB mol%	Sel.[b] **2B**:**3A**:**3B**:**4A** (%)	Yield **3B** (%)
1	$\mathbf{Al^{Me}}$ (1.0)	1.0	16:22:**34**:28	n.d.
2	$\mathbf{Al^{Me}}$ (1.0)	10	27:17:**38**:18	n.d.
3	$\mathbf{Al^{Cl}}$ (1.0)	2.5	0:15:**74**:11	n.d.
4	$\mathbf{Al^{Cl}}$ (1.0)	1.0	0:6:**81**:16	n.d.
5	$\mathbf{Al^{Cl}}$ (5.0)	5.0	4:6:**90**:0	n.d.
6	$\mathbf{Al^{Cl}}$ (7.5)	7.5	2:9:**89**:0	n.d.
7	$\mathbf{Al^{Cl}}$ (10)	10	3:6:**91**:0	n.d.
8[c]	$\mathbf{Al^{Cl}}$ (5.0)	5.0	7:13:**80**:0	42 (29)[d]
9[ce]	$\mathbf{Al^{Cl}}$ (5.0)	5.0	2:6:**92**:0	33[g]
10[cf]	$\mathbf{Al^{Cl}}$ (5.0)	5.0	0:7:**93**:0	16[g]

[a]Reaction conditions: 18 h, 80 ºC, 40 bar CO_2, *syn*-**1** (0.5 mmol, 70 mg, 2.5 M), TBAB (16 mg, 5.0 mol%), MEK. Conversion was >99% in all cases. [b]Based on ^{1}H NMR integration of the crude product; numbers refer to conversion into carbonates. [c]Reactions were carried out in an autoclave equipped with a 20 mL Teflon insert, using *syn*-**1** (1.0 mmol, 140 mg, 1.0 M) and $\mathbf{Al^{Cl}}$/TBAB (5.0 mol% each), 80 ºC, 40 bar, 24 h. [d]Overall cyclic carbonate selectivity: 55%. NMR yield for *syn-trans* **3B** was 42% using 1,3,5-trimethoxy-benzene as internal standard. In brackets the isolated yield of *syn-trans* **3B** after column purification. [e]Temperature: 70 ºC. [f]p_{CO2}: 10 bar. [g]A different unidentified product is produced is large amounts. n.d. = not determined.

Al-Catalyzed Formation of Syn-Trans 3B. With these reference data in hand, we continued to study the influence of the addition of Al(III) aminotriphenolate complexes $\mathbf{Al^{Me}}$ and $\mathbf{Al^{Cl}}$ (Scheme 1) on the outcome of the cycloaddition of CO_2 to epoxy alcohol *syn*-**1** (Table 2). We decided to first use Al(III) complex $\mathbf{Al^{Me}}$ in combination with TBAB starting with relatively low loadings of 1.0 mol% for each catalyst component (Table 3, entry 1) leading to full conversion of the substrate *syn*-**1**. Under such conditions, the reaction pathway discussed above using only TBAB is slow enough to be neglected (*cf.*, Table 1 entry 1).

These conditions led to a reaction mixture from which four major cyclic carbonate products (*syn-cis* **2B**, *syn-trans* **3A** *syn-trans* **3B** and *anti-trans* **4A**) could be identified. Whereas for *syn-cis* **2B** the NMR and structural features had already been determined (see Table 1 and Figure 1), two products were unambiguously assigned by X-ray diffraction studies (Figure 3) after they had been separated by chromatography and isolated. A fourth product was produced in minor amounts and was assigned by NMR spectroscopy (see SI) as the last remaining possible *syn*-isomer **3A**.

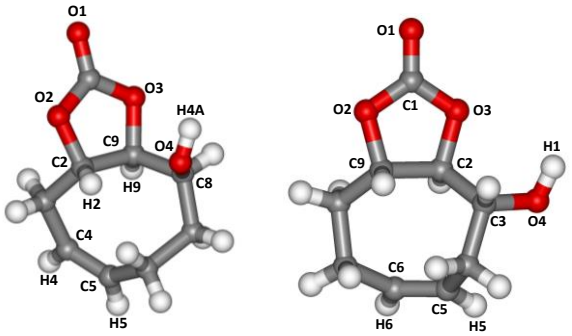


Figure 3. LEFT: X-ray molecular structure determined for *syn-trans* **3B**. Some selected pertinent bond lengths (Å) and dihedral angles (º) with esd´s in parentheses: C(4)-C(5) = 1.3384(15); O(2)-C(9)-C(2)-O(3) = 4.07(9), O(3)-C(9)-C(8)-O(4) = 71.02(9). **RIGHT**: X-ray molecular structure determined for *anti-trans* **4A**. Some selected pertinent bond lengths (Å) and dihedral angles (º) with esd´s in parentheses: C(5)-C(6) = 1.329(2), O(2)-C(9)-C(2)-O(3) = 15.56(12), O(3)-C(2)-C(3)-O(4) = -66.30(14).

Both carbonate structures **3B** and **4A** show a cyclic carbonate having a *trans* configuration (*cf.*, relative position of H2 and H9 in *syn-trans* **3B**). The OH fragment in **3B** is in a *syn*-position to the *trans*-configured carbonate ring, whereas in **4A** this position is *anti*. The configuration of **3B** suggests the involvement of the alcohol group in its formation whereas the formation of **4A** implies a different mechanism not implicating the OH fragment of the substrate *syn*-**1**.

With the major components now being identified, we sought to first increase the selectivity towards the *syn-trans* carbonate **3B** (Table 2, entries 2–10). The presence of an excess (10 equiv) of TBAB with respect to Al(III) complex $\mathbf{Al^{Me}}$ increased the production of **2B** (likely through mechanism discussed above), but did not significantly increase the selectivity for **3B** (entry 3). However, changing the Lewis acid catalyst from $\mathbf{Al^{Me}}$ to $\mathbf{Al^{Cl}}$ (entries 3-5) while increasing the amount of $\mathbf{Al^{Cl}}$:TBAB (ratio 1:1) to 5.0 mol% provided *syn-trans* **4** with a 90% selectivity (entry 5). A further increase in the amount of catalyst (entries 6 and 7) showed no beneficial effect. The higher Lewis acidity of catalyst $\mathbf{Al^{Cl}}$ is likely responsible for the suppression of the formation of **2B**, whereas a higher loading of TBAB leads to suppression of **4A**. The yield of *syn-trans* **3B** was then further optimized (Table 2 entries 8–10) using a 1.0 mmol scale and autoclave reactors operated under the optimal conditions reported in entry 5. Importantly, in these latter reactions the maximum yield of carbonate products was around 55%

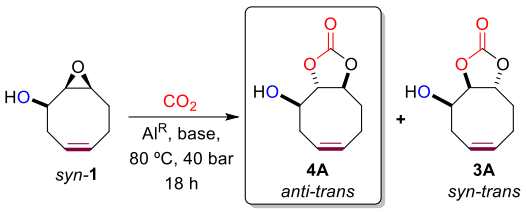
(with 42% being the desired *syn-trans* **3B**) while producing significant amounts of unidentified side-products (45%). From this reaction mixture (entry 8), pure *syn-trans* **3B** was isolated in 29% after chromatographic work-up. Lowering the temperature or the pressure led to lower yields of **3B** and an increased amount of unidentified side-products (entries 9 & 10). The rather similar R_f values for all carbonate products produced under these conditions complicated a further improvement of the isolated yield.

In order to explain the lower yield of *syn-trans* **3B** as opposed to *syn-cis* **2B**, we performed several control experiments involving the substrate *syn*-**1** and the Al(III) complex **Al^{Cl}**. First, heating a solution of *syn*-**1** and an internal standard (1,3,5-trimethoxy-benzene) dissolved in MEK to 80 ºC did not result in any observable degradation of starting material after 18 h as monitored by ^{1}H NMR. Then the experiment was repeated with a catalytic amount of **Al^{Cl}** (5.0 mol%) present. The progress of the experiment was followed by ^{1}H NMR and, with time, a gradual decrease of the original amount of *syn*-**1** was noted. After 18 h, 33% of substrate was remaining while after 3 days only trace amount of *syn*-**1** could be detected, while other possible products were not observed. The latter experiment was then repeated in d_8-toluene as medium; despite that the decrease in substrate conversion was lower, after 18 h only 60% of starting material was noted, and a significant amount of material precipitated from solution. Both the solution phase as well as the precipitated solid were scrutinized by ^{1}H NMR and IR analysis, but showed virtually identical results. Whereas the NMR spectra displayed broadened signals, the IR was more informative and pointed at the formation of an oligo/polyether compound.[59]

It appears that at elevated temperature strong Lewis acids such as **Al^{Cl}** are capable of inducing ring-opening of the oxirane. Recently we described similar Al(III) aminotriphenolate complexes that can activate epoxy alcohols following proton transfer to one of the phenolate donor atoms of the complex providing an Al-alkoxide species.[53,54] In the absence of any reagent, this nucleophilic alkoxide should be able to engage in ring-opening of a second molecule of epoxy alcohol leading eventually to a stepwise formation of an oligoether. The formation of the latter type of byproduct from sterically more congested epoxides has precedent as was recently demonstrated by Fiorani *et al*. in the synthesis of terpene-based cyclic carbonates under fairly similar reaction conditions (85 ºC, 10-40 bar; using 1.0 mol% **Al^{Cl}**).[60]

Al-Catalyzed Formation of Anti-Trans 4A. Finally, we optimized conditions in order to selectively synthesize *anti-trans* **4A** (Table 3). Since we were able to suppress the formation of **4A** entirely by increasing the concentration of TBAB in Table 3, we envisioned that omitting TBAB would favor the formation of **4A**. Instead, decomposition of *syn*-**1** was observed. The addition of a base as co-catalyst proved essential in order to steer the reaction towards **4A**. Several (N-heterocyclic) bases were probed (Table 3), and initially 4-dimethylaminopyridine (DMAP) demonstrated a selectivity for **4A** of 82% (entry 2). Further variation of the base (DBU, DIPEA), the Al(III) complex (**Al^{Me}** or **Al^{Cl}**) and the (relative/total) amounts of Al(III) complex and base finally gave an optimized selectivity of 86% (entry 7). Interestingly, using DIPEA we were unable to obtain any carbonate products, indicating that relatively nucleophilic bases are required for the reaction to occur.

Table 3. Optimization of the Reaction Conditions leading to Anti-Trans Carbonate (4A).[a]

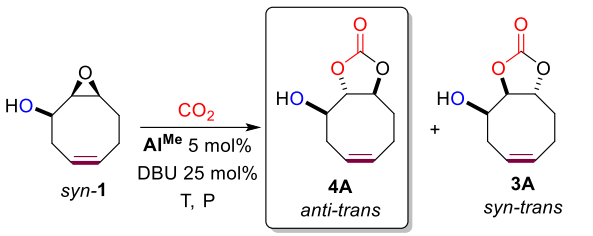


entry	[Al] (mol%)	Base (mol%)	Sel. **4A:3A** (%)[b]
1	**Al^{Me}**, 1.0	DMAP, 10	79:21
2	**Al^{Me}**, 5.0	DMAP, 20	82:18
3	**Al^{Me}**, 1.0	DBU, 10	79:21
4	**Al^{Me}**, 5.0	DBU, 5.0	76:24
5	**Al^{Me}**, 5.0	DBU, 15	82:18
6	**Al^{Me}**, 5.0	DBU, 20	85:15
7	**Al^{Me}**, 5.0	DBU, 25	86:14
8	**Al^{Cl}**, 5.0	DMAP, 5.0	84:16
9	**Al^{Cl}**, 5.0	DBU, 5.0	81:19
10	**Al^{Cl}**, 5.0	DIPEA, 5.0	0:0

[a]Reaction conditions: 80 ºC, 40 bar CO_2, *syn*-**1** (0.5 mmol, 70 mg, 2.5 M), base (type and amount indicated), MEK. Conversion was quantitative in all cases. [b]Based on ^{1}H NMR integration of the crude product. Carbonates **2A**, **2B** and **3B** could not be detected.

Again, the yield for *anti-trans* **4A** was further maximized using larger scale experiments as reported for *syn-trans* **3B** in an autoclave reactor (Table 4). The observation of substantial amounts of oligoether byproduct in the synthesis of *syn-trans* **3B** (see Table 2) prompted us to initially use lower reaction temperatures (Table 4, entries 1–3). However, the NMR yield of *anti-trans* **4A** was not positively affected and neither a change in the pressure or reaction time (in combination with a lower amount of catalyst components) gave any improvement. As expected, a lower conversion of the substrate *syn*-**1** was noted under these latter conditions. Raising the reaction temperature to 80 ºC (entry 4) increased the overall carbonate yield to 73% and produced *anti-trans* **4A** in 59% (NMR) yield. Further variations were probed including lowering the pressure or the loading of the catalyst components, eliminating purging of the reactor prior to pressurizing at 40 bar (to reduce possible loss of the volatile *syn*-**1**) and changing the solvent (entries 5, 6, 8 and 9). Notably, when the catalytic experiment was repeated using the conditions of entry 4 while elongating the reaction time to 48 h, practically the same results were obtained showing the stable character of the carbonate products once formed under the experimental conditions (80 ºC, 40 bar, in the presence of **Al^{Me}** and DBU). From the crude product produced in entry 7 the desired *anti-trans* **4A** (57% NMR yield) was isolated in 25% yield.[61] The isolation and characterization of *trans*-fused cyclic carbonates is difficult and rare, and only few examples have been reported in the literature.[25,62,63]

Table 4. Optimization of the Yield of Anti-Trans Carbonate (4A) obtained from Syn-1.[a]



entry	T/P (°C/bar)	t (h)	Conv. (%)[b]	**4A** (%)[b]	**3A** (%)[b]	Rest (%)[c]
1	70/40	24	>99	49	17	34
2	70/10	24	79	47	19	13
3[e]	70/40	18	89	45	22	22
4	80/40	24	>99	59	14	27
5	80/10	24	94	47	14	33
6[e]	80/40	24	>99	44	14	42
7	80/40	48	>99	57 (25)[d]	18	25
8[f]	80/40	24	>99	54	14	32
9[g]	80/40	24	>99	40	13	47

[a]Reaction conditions: autoclave reactors were used equipped with a 20 mL Teflon insert; temperature/pressure indicated, *syn*-**1** (1.0 mmol, 140 mg, 2.5 M), **Al^{Me}** (22 mg, 5 mol%), DBU (37 μL, 25 mol%), 1,3,5-trimethoxy-benzene (TMB, 189.2 mg, 1 equiv), MEK. [b]Determined by ^{1}H NMR ($CDCl_3$) using TMB as internal standard. [c]Remaining mass balance of all unidentified products based on ^{1}H NMR ($CDCl_3$) analysis. [d]In brackets, the isolated yield for **4A** is reported. Beside the desired product, also 16% of hydrolysed product (*i.e.*, triol) was isolated (see the SI for details). [e]Using 5.0 mol% DBU and 1.0 mol% **Al^{Me}**. [f]The reactor was not purged with CO_2 *prior to* the experiment. [g]Using toluene as solvent.

CONCLUSIONS

The introduction of a symmetry-breaking element (double bond) in the backbone of cyclic epoxy alcohol *syn*-**1** allows for its conversion into various regio- and diastereo-isomeric bicyclic carbonates. The nature of the catalytic system controls the bias towards specific cyclic carbonate products with in general good selectivity for one specific carbonate of around 90%. The use of TBAB as catalyst produces *syn-cis* **2B** as major component under thermodynamic control, whereas combining TBAB with an Al(III) aminotriphenolate complex (**Al^{Cl}**) changes the diastereoselectivity towards *syn-trans* **3B**. The replacement of the bromide based nucleophile for an N-heterocyclic base (DBU) modifies the carbonate selectivity significantly and generates regio- and diastereomer *anti-trans* **4A** as the principal carbonate product. The unusual *trans* configuration of both *syn-trans* **3B** and *anti-trans* **4A** were both confirmed by X-ray crystallography and are rare examples of such types of heterocycles. We have identified 5 out of 8 isomeric bicyclic carbonate products, and we optimized the synthesis of 3 of them. Further work is now focusing on unraveling the mechanisms leading to the formation of the *trans*-fused bicyclic carbonates while improving the overall chemo-selectivity.

EXPERIMENTAL SECTION

General Considerations. The Al complexes **Al^{Me}**[47] and **Al^{Cl}**[47] and epoxy alcohol **1**[64] were prepared according to previously reported procedures. Carbon dioxide was purchased from PRAXAIR and used without further purification. Solvents used in the synthesis of the complexes were dried using an Innovative Technology PURE SOLV solvent purification system. Solvents used in the catalytic screening were used as received. ^{1}H and ^{13}C and 2D NMR spectra were recorded on a Bruker AV-300, AV-400 or AV-500 spectrometer, and signals are referenced to the residual solvent peak. FT-IR measurements were carried out using a Bruker Optics FTIR Alpha spectrometer. Mass spectrometric analyses and X-ray diffraction analysis were performed by the Research Support Area (RSA) at ICIQ.

General Catalytic Procedure using Autoclave Reactors: The experiments reported in Table S1 (entries 1–3), Table 2 (entries 8–10) and Table 4 (entries 1–9) were carried out using this protocol; a photo of this reactor is reported in the SI. Typical conditions are as follows: epoxy alcohol **1** (1.0 mmol, 140 mg, 1.0 M), TBAB (16-82 mg, 5-25 mol%) and Al complex **Al^{Cl}** (note: only for Tables 2 and 3; 28 mg, 5.0 mol%), MEK (200 μL) and internal standard TMB (1,3,5-trimethoxy-benzene; 189.2 mg, 1 equiv) were charged into a stainless steel autoclave equipped with a 20 mL Teflon insert. After the autoclave was sealed three cycles of pressurization/depressurization were carried out. After reaching the selected reaction temperature (typically 80 °C), the autoclave was pressurized with CO_2 to the desired pressure (typically 40 bar) and left stirring. At the end of the chosen time interval, the autoclave was cooled to rt and then carefully depressurized. An aliquot of the reaction mixture was taken for analysis and the conversion/yield was determined by ^{1}H NMR spectroscopy in $CDCl_3$ to determine conversions, selectivities and NMR yields. The desired products **2–4** were then obtained by chromatographic purification as indicated below.

General Catalytic Procedure using a HEL Multi-Reactor System: The results from Table 1 (entries 1-18), Table 2 (entries 1-7) and Table 3 (entries 1-10) have been obtained with this system. A typical procedure is as follows: epoxy alcohol **1** (70 mg, 0.50 mmol, 2.5 M), Al-complex **Al^{Cl}** (5.0 mol%; only added in the experiments from Tables 3 and 4), TBAB (5.0-25 mol%) and MEK (200 μL) were added into a glass insert. The HEL system was closed and after three pressurization/depressurization cycles using 10 bar of CO_2 the reactor was charged with 40 bar CO_2 pressure. Then the reactor was heated to the desired temperature and the mixtures were stirred for 18 h. Finally the HEL reactor was cooled down to rt, carefully depressurized and opened. For each of the reaction mixtures an aliquot was taken and analyzed by ^{1}H NMR ($CDCl_3$) to determine conversions and selectivities.

General Catalytic Procedure using an AMTEC Multi-Reactor System: The results from Table 1 (entries 19-22) were performed using this multi-reactor system. Typical set up is as follows: All the solids are weight into every steel vessel in this case TBAB (25 mol%), then overnight leak test was carried out at 30 bar. When leak test is finished the epoxy alcohol **1** (140 mg, 1 mmol) dissolved in MEK (500 μL) is carefully added and the reactors are warm up to 80 °C and finally pressurized with CO_2 (10, 20, 30 and 40 bar). After the reaction time the multi-reactor was cooled down and depressurized and an aliquot was taken and analyzed by ^{1}H NMR ($CDCl_3$) to determine conversions and selectivities.

Synthesis of Syn-Cis Cyclic Carbonate (2B): The below mentioned protocol refers to those used in Table S1, entry 3: a mixture of *syn*-epoxy alcohol **1** (140 mg, 1.0 mmol) and TBAB (82 mg, 25 mol %) dissolved in 1.0 mL of MEK was introduced into a 30 mL stainless steel reactor. After three cycles of pressurization and depressurization, the reactor was charged with 40 bar of CO_2. Then the reaction mixture was heated to 80 °C and magnetically stirred for 24 h. Finally, the reactor was cooled down to rt and carefully depressurized. The crude product was purified by flash chromatography on silica gel (hexane:ethyl acetate, 2:1 v/v) affording the title compound (120 mg, 65% yield) as a white solid. Single crystals were obtained by recrystallization from CH_2Cl_2/hexane at room temperature. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.94 (dtd, *J* = 10.3, 8.0, 1.0 Hz, 1H), 5.66 – 5.48 (m, 1H),

4.73 (ddd, J = 12.6, 7.3, 4.2 Hz, 1H), 4.52 (dd, *J* = 7.4, 1.2 Hz, 1H), 4.36 – 4.30 (m, 1H), 3.41 – 3.29 (m, 1H), 2.99 – 2.84 (m, 1H), 2.80 – 2.68 (m, 1H), 2.43 (ddd, J = 11.6, 6.6, 4.2 Hz, 1H), 2.16 – 2.05 (m, 1H), 1.96 – 1.86 (m, 1H), 1.59 – 1.46 (m, 1H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 155.8, 135.8, 123.8, 84.1, 80.0, 72.9, 33.8, 26.5, 19.7 ppm. IR (neat): ν = 3456 (OH), 1758 (C=O) cm^{-1}. HRMS (ESI+, MeOH): *m/z* calcd. for $[C_9H_{12}NaO_4]^+$, 207.0623; found, 207.0628.

Synthesis of Syn-Trans Cyclic Carbonate (3B): The below mentioned protocol refers to those used in Table 2, entry 9: a mixture of *syn*-epoxy alcohol **1** (140 mg, 1.0 mmol), Al catalyst **Al^{Cl}** (16 mg, 5.0 mol %) and TBAB (28 mg, 5.0 mol %) dissolved in MEK (1.0 mL) was introduced into a 30 mL stainless steel reactor. After three cycles of pressurization and depressurization, the reactor was charged with 40 bar of CO_2. Then the reaction mixture was heated to 80 ºC and magnetically stirred for 24 h. Finally, the reactor was cooled down to rt and carefully depressurized. Flash chromatography on silica gel (hexane:ethyl acetate, 2:1 v/v) afforded the title compound as a 91:9 mixture of *syn-trans* **3B** and a minor isomer (78 mg, 42% yield) as a white solid. Note that more extensive column purification was possible (Table 3, entry 8) but due to fairly similar R_f values for the carbonate products only 29% of pure *syn-trans* **3B** was obtained, see the SI for details. Recrystallization from CH_2Cl_2/hexane at room temperature afford single crystals. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.75-5.64 (m, 1H), 5.54 (ddd, *J* = 11.8, 7.9, 5.7 Hz, 1H), 5.48-5.38 (m, 1H), 4.55 (dd, *J* = 7.9, 1.3 Hz, 1H), 4.30-4.21 (m, 1H), 3.06-2.85 (m, 1H), 2.50-2.31 (m, 1H), 2.23-2.12 (m, 1H), 2.10-1.93 (m, 2H), 1.65-1.51 (m, 1H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 154.6, 131.1, 123.6, 84.9, 74.1, 66.4, 34.1, 32.2, 20.3 ppm. IR (neat) ν = 3427 (OH), 1793 (C=O) cm^{-1}. HRMS (ESI+, MeOH): *m/z* calcd. for $[C_9H_{12}NaO_4]^+$, 207.0630; found, 207.0628.

Synthesis of Anti-Trans Cyclic Carbonate (4A): The below mentioned protocol refers to those used in Table 4, entry 7: a mixture of *syn*-epoxy alcohol **1** (140 mg, 1 mmol), Al catalyst **Al^{Me}** (22 mg, 5.0 mol %) and DBU (8.0 mg, 5.0 mol %) dissolved in 1.0 mL of MEK was introduced into a 30 mL stainless steel reactor. After three cycles of pressurization and depressurization, the reactor was charged with 40 bar of CO^2. Then the reaction mixture was heated to 80 ºC and magnetically stirred for 24 h. Finally, the reactor was cooled down to rt and carefully depressurized. Flash chromatography on silica gel (hexane:ethyl acetate, gradient from 2:1 to 1:1 v/v) afforded the title compound as a colorless oil (46 mg, 25% yield). Crystals of **4A** were obtained from a saturated solution in $CDCl_3$/Hexane at -20 ºC. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.82-5.68 (m, 2H), 4.50-4.38 (m, 2H), 3.91-3.78 (m, 1H), 2.51-2.37 (m, 2H), 2.37-2.28 (m, 1H), 2.27-2.15 (m, 2H), 1.82-1.62 (m, 1H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 154.1, 130.8, 126.1, 86.8, 79.2, 70.9, 29.8, 29.4, 21.0 ppm. IR (neat): ν = 3473 (OH), 1787 (C=O) cm^{-1}. HRMS (ESI+, MeOH): *m/z* calcd. for $[C_9H_{12}NaO_4]^+$, 207.0631; found, 207.0628.

X-ray Crystallographic Studies: The measured crystals of *syn-cis* **2A**, *syn-cis* **2B**, *syn-trans* **3B** and *anti-trans* **4A** 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 MoKα 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.[65] Structure Refinement: SHELXTL-97-UNIX VERSION.

ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.organomet.###.

Details of the experimental procedures, copies of NMR spectra and crystallographic information (PDF)

Cartesian coordinates of the calculated structures (XYZ), for details refer to https://doi.org/10.19061/iochem-bd-1-141.

Accession Codes

CCDC 1868678-1868679 and 1945737-1945738 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

AUTHOR INFORMATION

Corresponding Author

* E-mail for AWK: akleij@iciq.es

ORCID

Arjan W. Kleij: 0000-0002-7402-4764

Notes

The authors declare no competing financial interest.

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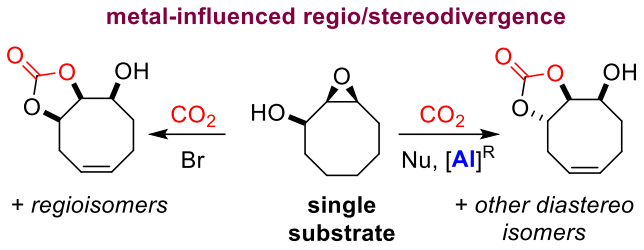

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