CO_2 Fixation

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Substrate-Controlled Product Divergence: Conversion of CO_2 into Heterocyclic Products

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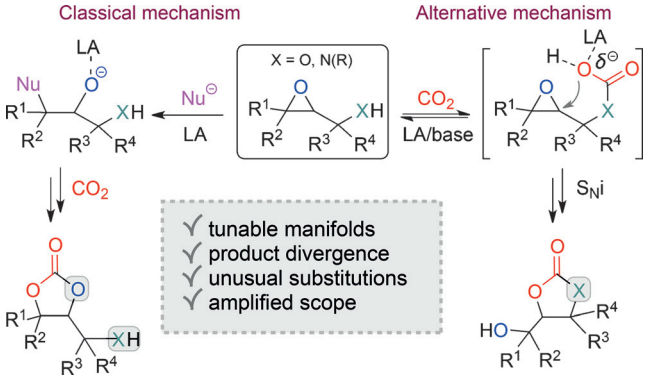
Abstract: *Substituted epoxy alcohols and amines allow substrate-controlled conversion of CO_2 into a wide range of heterocyclic structures through different mechanistic manifolds. This new approach results in an unusual scope of CO_2-derived products by initial activation of CO_2 through either the amine or alcohol unit, thus providing nucleophiles for intramolecular epoxy ring opening under mild reaction conditions. Control experiments support the crucial role of the amine/alcohol fragment in this process with the nucleophile-assisted ring-opening step following an S_Ni pathway, and a 5-exo-tet cyclization, thus leading to heterocyclic scaffolds.*

The global challenge regarding future fossil fuel depletion has motivated the chemical community to invent new methodologies for alternative conversions of carbon feedstocks into basic and fine-chemical targets. While CO_2 is mainly considered an environmental hazard because of the ever-increasing emissions from human activities into our atmosphere, it also represents a cheap and accessible carbon-based building block with great potential in organic synthesis.[1] Despite this potential, progress in this area of research is still rather limited to a handful of coupling reactions which are prominently based on C–O and C–N bond formations.[2] Although catalysis has been recognized as a key sustainable technology enabling more efficient CO_2 conversion,[3] it often relies on metal-mediated activation of a co-reactant rather than CO_2 itself, thereby limiting its use in a more amplified portfolio of chemical reactions.[4] Direct substrate involvement in the activation of the CO_2 molecule is truly scarce and typically requires the use of stoichiometric amounts of additives,[5] or the involvement of substrates which have limited scope and/or accessibility.[6]

To solve this challenge, the use of cheap molecular scaffolds which induce activation of CO_2 and guide alternative new mechanistic approaches towards its conversion is appealing. This approach would create a new conceptual framework for CO_2 use and valorization. Epoxides have been frequently used as high-energy reaction partners for CO_2-based synthesis, and considerable achievement in the preparation of organic carbonates and derived molecules has been achieved in the last decade.[7] However, the challenging coupling of highly substituted epoxides and CO_2[8] necessitates the quest for an alternate and mechanistically distinct methodology.

Recently, we proposed that hydroxy- and amino-substituted oxetanes can be catalytically coupled at remarkably low temperatures with CO_2 through elusive alkyl carbonic acid intermediates to afford five- or six-membered carbonates/carbamates in the absence of external nucleophiles.[9] Further to this, other groups have communicated on (noncatalytic) approaches using stoichiometric additives in combination with substrates having pendent hydroxy/amine groups.[10] We envisioned that epoxy alcohols and amines would serve as ideal substrates to develop an efficient substrate-controlled catalytic approach, as these scaffolds combine high accessibility, easy synthesis, and a broad molecular diversity (Scheme 1, right).[11] This new catalytic approach towards the coupling of epoxy alcohols and CO_2 would trigger an alternative mechanism leading to intramolecular nucleophilic attack (S_Ni) of a hemiester of a carbonic acid, thus accessing a wider scope of potential products. Since the conventional mechanism (Scheme 1, left) would be initiated by an external nucleophile and require different reaction conditions, both mechanistic routes would be accessible and provide a conceptually new approach towards product diversity from a single epoxy alcohol or amine substrate.

We first established general reaction conditions using the simplest epoxy alcohol (i.e., glycidol) and a Lewis acid based on aluminium(III)-centred aminotriphenolate complexes (**A**–



Scheme 1. Mechanistic divergence in the coupling between CO_2 and ither epoxy alcohols or amines leading to product diversity. LA = Lewis acid, Nu = nucleophile.

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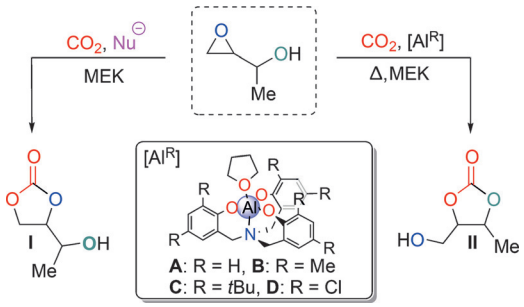
D; see Table 1 and Table S1 in the Supporting Information) in the absence of an external nucleophile: these reactions conditions are related to the hydroxy oxetane conversions reported previously.[9] At 50 °C after 14 hours we found that the aluminium-catalyst **C** (Table S1, entry 3) gives the highest conversion (89 %) and selectivity (> 99 %). Whereas the complex **D** shows higher reactivity (Table S1, entry 4; > 99 % conversion), the reaction mixture was complex, possibly resulting from polyether formation. The formation of the carbonate **1** is sluggish at 25 °C (Table S1, entry 5) but is virtually complete in 1 hour when raising the reaction temperature to 75 °C (Table S1, entry 7). Benzyl protection of the alcohol unit in glycidol (Table S1, entry 6) shuts down catalysis, thus hinting at a key role for the free alcohol to mediate an alternative pathway towards the carbonate. Surprisingly, the formation of **1** also proceeds without any Lewis acid present (Table S1, entries 9 and 10) but with significantly slower kinetics than in the presence of **C**.

Next we examined reaction conditions to trigger the alternative mechanism using 1-(oxiran-2-yl)ethanol (Table 1): if successful this would give direct evidence for an alternative pathway leading to structurally divergent organic carbonates as depicted in Scheme 1. The use of a nucleophile only (TBAB) at low temperature favors the conventional product **I** (Table 1, entry 1). A combination of both **C** and TBAB gives improved reactivity, but a mixture of products of the types **I** and **II** (entry 2) was observed. Delightedly, complete selectivity towards the alternative carbonate product (**II**) is achieved at 50 °C in the absence of an external nucleophile (entry 3).

Table 1: Screening of suitable reaction conditions to trigger an alternative mechanism leading to formation of the carbonate type **II**.[a]



Entry	Cat. [mol %]	Co-cat. [mol %]	T [°C]	t [h]	Conv. [%][b]	I/II[b]
1	–	TBAB (5.0)	25	40	55	81:19
2	**C** (1.0)	TBAB (5.0)	25	14	> 99	22:78
3	**C** (1.0)	–	50	14	> 99	0:100

[a] Reaction conditions: 1-(oxiran-2-yl)ethanol (1.0 mmol), $p(CO_2)$° = 10 bar, 1.0 mL MEK (methyl ethyl ketone). [b] Determined by ^{1}H NMR ($CDCl_3$) spectroscopy. TBAB = tetra-*n*-butylammonium iodide.

The results presented in Table 1 and Table S1 suggest that organic carbonates may indeed be accessed through an alternative mechanism based on in situ formation of CO_2-derived nucleophiles (Scheme 1). Therefore, we decided to expand the scope of carbonates/carbamates by examination of epoxy alcohols and amines with more challenging substitution patterns, using **C** as the catalyst. In general, scope, with respect to the carbonates/carbamates, which can be attained through this substrate-mediated CO_2 activation is diverse and the targeted products **1**–**13** (Figure 1) were obtained in good yields of up to 95 % upon isolation, and with high chemoselectivity.[12,13] Notably, this alternative synthetic method for carbonates allows formation of highly challenging 4,5-di- (**5** and **7**) and 4,4,5-trisubstitutions (**8**, **9**, **12** and the spirocompound **13**) on the cyclic carbonate ring, including the use of terpene-based scaffolds (**6** derived from 2,3-epoxy-geraniol). Interestingly, when epoxy amines are used as substrates only the 5-substituted isomer is formed (**10** and **11**), and is in contrast to the known (catalytic) couplings between aziridines and CO_2 which often result in the formation of regioisomeric mixtures.[14] The chemoselectivity for both **12** (54 %) and **13** (75 %) was compromised by the competitive formation of the carbonate product mediated through the conventional mechanism (Scheme 1).[15] To the best of our knowledge, the trisubstituted carbonates cannot be obtained by using a conventional approach for catalytic CO_2/epoxide couplings, thus demonstrating the added value of this new methodology.

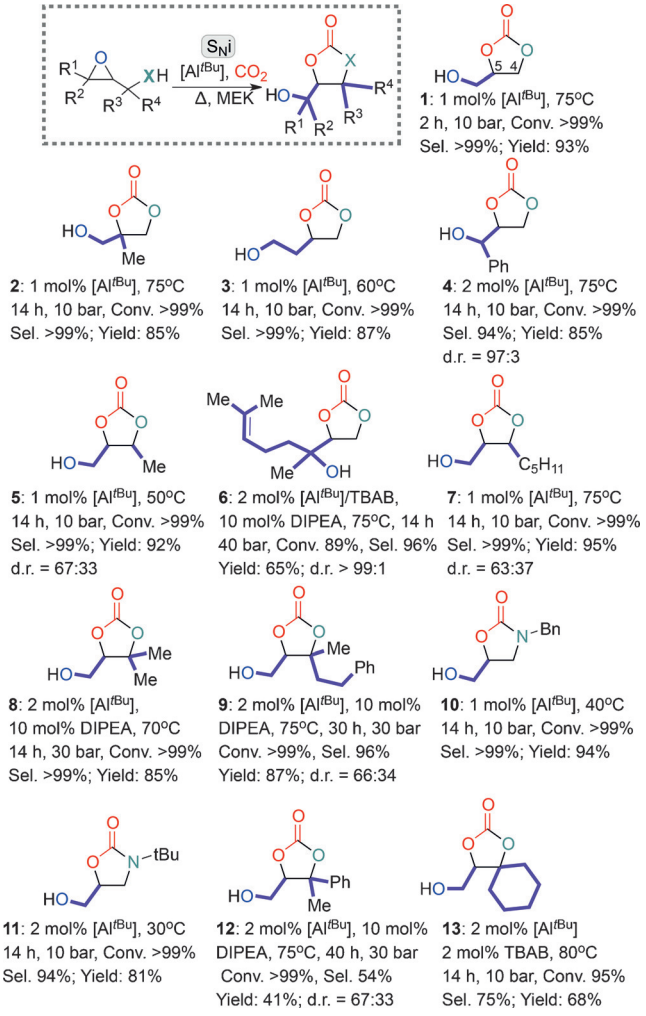


Figure 1. Synthesis of highly substituted organic carbonates and carbamates (**1**–**13**) from epoxy alcohols/amines and CO_2.[13]

Having validated that an alternative mechanism towards organic carbonate formation through the use of epoxy alcohols/amines can be selectively induced, we next set out to explore the possibility of an unprecedented product divergence from a single epoxy alcohol/amine substrate (Figure 2). In essence, the different mechanisms leading to the formation of organic carbonates should be triggered under different reaction (temperature) conditions and by using different additives. We were pleased to find that indeed access to both types of carbonate products from simple and accessible precursors (**14**–**17**) could be achieved in good yields. Notably, the use of a natural product (sclareol, a bicyclic diterpenol) shows that the approach is also feasible with more complicated scaffolds. For both sclareol carbonates **16** (X-ray structure determined)[16] and **17** the formation of diastereoisomeric mixtures arises from the sclareol epoxidation stage, with apparently some higher degree of stereocontrol in the preparation of **17**.

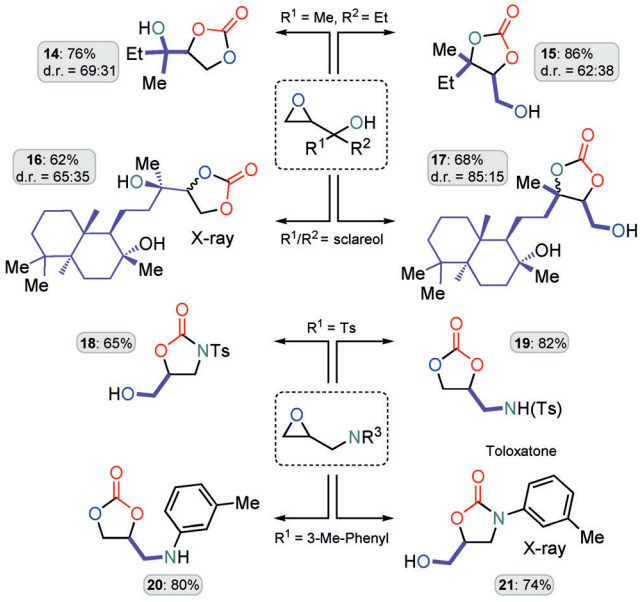


Figure 2. Product divergence from four epoxy alcohols/amines, thus giving access to the compounds **14**–**21**. For all reactions 2 mol% [Al$^{t\mathrm{Bu}}$] and $p(CO_2)$° = 10 bar were used unless indicated otherwise. Details: **14**, 5 mol% TBAB, 25 °C, 60 h, conv. 95%, sel. 85%; **15**, 80 °C, 40 h, 30 bar, conv. > 99%, sel. 93%; **16**, 5 mol% TBAB, 50 °C, 14 h, 30 bar, conv. > 99%, sel. 79%; **17**, 10 mol% TBACl, 75 °C, 14 h, conv. > 99%, sel. 79%; **18**, 5 mol% TBAB, 75 °C, 14 h, conv. > 99%, sel. 97%; **19**, 10 mol% DIPEA, 50 °C, 40 h, 30 bar, conv. > 99%, sel. 77%; **20**, 5 mol% TBAB, 30 °C, 40 h, conv. > 99%, sel. 81%; **21**, 2 mol% TBAB, 75 °C, 14 h, conv. > 99%, sel. 81%.[13] Ts = 4-toluenesulfonyl.

The use of epoxy amines (Figure 2, below) also gives product divergence potential (**18**–**21**), and leads to the formation of either cyclic carbonate or carbamate scaffolds. The use of tosyl-protected epoxy amines is challenging since the amine will be rather unreactive toward the formation of a nucleophilic intermediate based on CO_2 (Scheme 1, alternative pathway). However, we found that the addition of a suitable base (DIPEA) allows access to the carbamate **18** in an appreciable yield of 65% with full selectivity towards the 5-substituted isomer, and is in line with the proposed intramolecular pathway presented in Scheme 1. The presence of an N-aryl group in the epoxy amine substrate expands upon the potential of this chemistry as it provides a simple entry to pharmaceutically relevant 5-substituted oxazolidinones such as toloxatone (**21**; 74% yield; X-ray structure determined),[16] which is a known antidepressant. Interestingly, there are several structurally highly related oxazolidinone molecules which are used as antimicrobials and the easy formation of **21** gives promise to the synthesis of new types of bioactive compounds using CO_2 as a co-reactant.

To support the formation of a nucleophile derived from an epoxy alcohol and CO_2, we closely examined the formation of the carbonate product **4** (Figure 3). Enantiopure (2*R*,3*R*)-(+)-3-phenylglycidol (96%) was converted with 94% selectivity into **4** (86% yield, one diastereoisomer). The other two

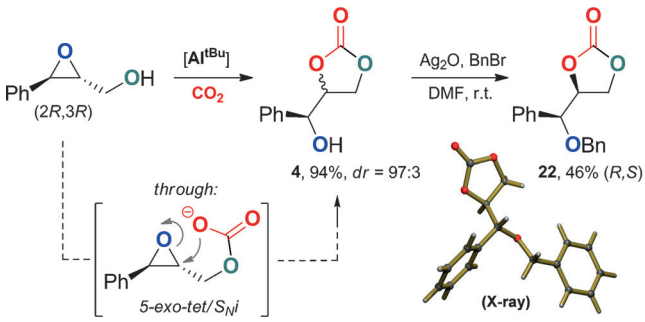


Figure 3. More detailed investigation into the diastereoselective formation of cyclic carbonate **4** and its benzyl-protected derivative **22**.

components of the reaction mixture were the other diastereoisomer (3%) and the standard carbonate product (3%), which were separated from **4** by chromatography. Note that this reaction also proceeds in the presence of cesium carbonate, though with preferential formation of the expected, disubstituted carbonate product.[5b] Overall the reaction follows a diastereoselective pathway (d.r. = 97:3). The absolute configuration [(2*R*,3*S*)] of **4** was determined by X-ray crystallographic analysis of its O-benzyl-protected derivative **22** (see the Supporting Information)[16] and showed a formal inversion at one of the carbon centers. This inversion suggests that a nucleophilic substitution takes place prior to isolation (Walden inversion), and is in line with the mechanistic proposal in Scheme 1 which presents a formal *5-exo-tet*-type cyclization. Moreover, the selective formation of the 5-substituted oxazolidinone products **10**, **11**, and **21** additionally supports the involvement of an intramolecular nucleophilic attack on the epoxide prior to product formation.

In summary, we report a simple and practical method for a new substrate-controlled CO_2 conversion process which allows product divergence from epoxy alcohols/amines. The different carbonate/carbamate products can be accessed through different mechanistic manifolds which are simply triggered by tuning of the reaction temperature/pressure and use of suitable nucleophilic/base additives. Such control allows new, unexplored uses of CO_2 in organic synthesis through substrate-driven activation of this renewable carbon

feedstock. Notably, such reactivity herein has proven to be useful to access extremely challenging substitution patterns on the cyclic carbonate/carbamate ring. Further work is in progress to expand this principle to other readily available organic scaffolds to further capitalize on the potential of this alternative raw carbon material in chemical synthesis.

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[16] CCDC 1441879, 1441880, and 1441881 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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