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Substrate Controlled Product Divergence in CO₂ Conversion to Heterocyclic Products

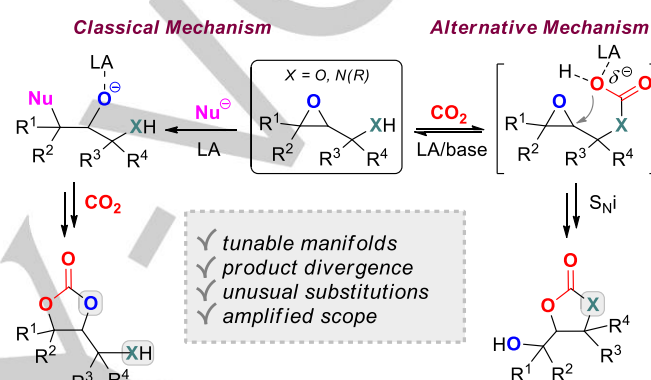
Jeroen Rintjema,^[a] Roel Epping,^[a] Giulia Fiorani,^[a] Eddy Martín,^[a] Eduardo C. Escudero-Adán^[a] and Arjan W. Kleij^{[a][b]*}

Abstract: Substituted epoxy alcohols and amines allow for substrate-controlled conversion of CO₂ into a wide range of heterocyclic structures through different mechanistic manifolds. This new approach allows for an unusual scope of CO₂ derived products by initial activation of CO₂ through the amine or alcohol unit, 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 leading towards heterocyclic scaffolds.

The global challenge regarding future fossil fuel depletion has motivated the chemical community to invent new methodologies for alternative carbon feedstock conversion into basic and fine chemical targets. While carbon dioxide is mainly considered as an environmental hazard due to 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, the progress in this area of research is still rather limited to a handful of coupling reactions prominently based on C–O and C–N bond formations.^[2] Although catalysis has been recognized as a key sustainable technology enabling more efficient CO₂ conversion,^[3] it often relies on metal-mediated activation of a co-reactant rather than CO₂ itself, thereby limiting its use in a more amplified portfolio of chemical reactions.^[4] Direct substrate involvement in the activation of the CO₂ molecule is truly scarce and typically requires the use of stoichiometric amounts of additives,^[5] or the involvement of substrates that have limited scope and/or accessibility.^[6]

To solve this challenge, the use of cheap molecular scaffolds that induce activation of CO₂ and guide alternative new mechanistic approaches towards its conversion is appealing. This approach would create a new conceptual framework for CO₂ use and valorization. Epoxides have been frequently used as high-energy reaction partners for CO₂ 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 CO₂^[8] necessitates the quest for an alternative, mechanistically distinct methodology.



Scheme 1. Mechanistic divergence in the coupling between CO₂ and epoxy alcohols or amines leading to product diversity. LA stands for Lewis acid, Nu is nucleophile.

Recently, we proposed that hydroxy- and amino-substituted oxetanes can be catalytically coupled at remarkably low temperatures with CO₂ 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 (non-catalytic) approaches using stoichiometric additives in combination with substrates having pendent hydroxyl/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 CO₂ would trigger an alternative mechanism leading to intramolecular nucleophilic attack (S_Ni) of a hemi-ester 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 Al(III)-centred aminotriphenolate complexes **A–D** (see Figure to Table 1 and S1) in the absence of an external nucleophile: these

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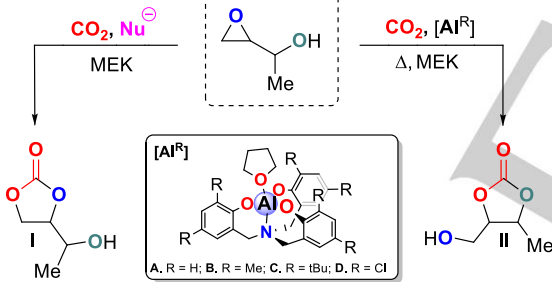
[b] Prof. Dr. A. W. Kleij, Catalan Institute of Research and Advanced Studies (ICREA), Pg. Lluís Companys 23, 08010 Barcelona, Spain

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reactions conditions are related to the hydroxy oxetane conversions reported previously.^[9] At 50°C after 14 h we found that Al-catalyst **C** (entry 3, Table S1) gives the highest conversion (89%) and selectivity (>99%). Whereas Al complex **D** shows higher reactivity (entry 4; >99% conversion), the product contained multiple components ascribed to, *inter alia*, polyether formation. The formation of carbonate **1** is sluggish at 25°C (entry 5) but is virtually complete in 1 h when raising the reaction temperature to 75°C (entry 7). Benzyl-protection of the alcohol unit in glycidol (entry 6) shuts down catalysis hinting at a key role for the free alcohol to mediate an alternative pathway towards the carbonate. Surprisingly, the formation of carbonate **1** also proceeds without any Lewis acid present (entries 9 and 10) but with significantly slower kinetics than in the presence of Al catalyst **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 organic carbonates as depicted in Scheme 1. The use of a nucleophile only (TBAB) at low temperature favours the conventional product (entry 1). A combination of both Al catalyst **C** and TBAB gives improved reactivity though a mixture of products of type **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 carbonate type **II**.^[a]



entry	Cat. [mol%]	Co-cat [mol%]	T [°C]	t [h]	Conv. [%] ^[b]	Ratio 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] Conditions: 1-(oxiran-2-yl)ethanol (1.0 mmol), $p(\text{CO}_2) = 10$ bar, 1.0 mL MEK (methyl ethyl ketone). [b] Determined by ¹H NMR (CDCl₃).

The results presented in Tables 1 and S1 suggest that organic carbonates may indeed be accessed through an alternative mechanism based on *in situ* formation of CO₂-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 Al complex **C** as catalyst. In general, the product scope of carbonates/carbamates that can be attained through this substrate-mediated CO₂ activation is diverse and the targeted

products **1–13** were obtained in good isolated yields of up to 95% and high chemo-selectivity.^[12,13] Notably, this alternative synthesis method for carbonates allows for the formation of highly challenging 4,5-di (cf., **5** and **7**) and 4,4,5-trisubstitutions (cf., **8**, **9**, **12** and the spiro compound **13**) on the cyclic carbonate ring and the use of terpene based scaffolds (cf., **6** derived from 2,3-epoxygeraniol).

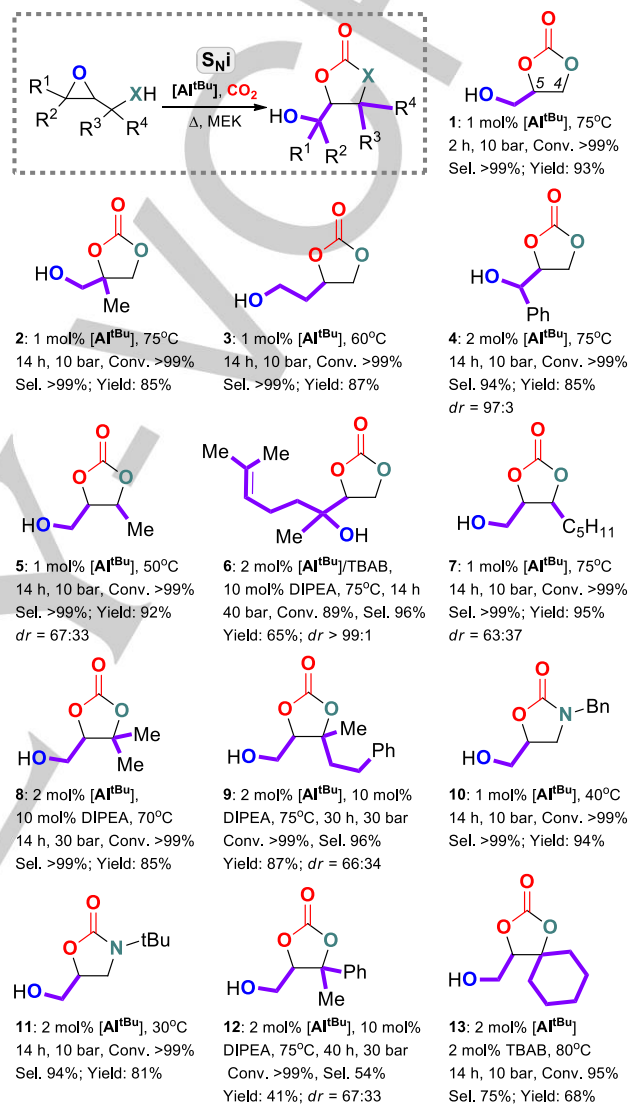


Figure 1. Synthesis of highly substituted organic carbonates and carbamates **1–13** from epoxy alcohols/amines and CO₂.^[12,13]

Interestingly, when epoxy amines are used as substrates only the 5-isomer is formed (cf., **10** and **11**) in contrast to the known (catalytic) couplings between aziridines and CO₂ which often result in the formation of regio-isomeric mixtures.^[14] The chemo-selectivity 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 tri-substituted carbonates cannot be obtained using any conventional approach in the area of catalytic

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CO₂/epoxide couplings demonstrating the added value of this new methodology.

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 (see Figure 2). In essence, the different mechanisms leading to the formation of organic carbonates should be triggered under different (temperature) conditions and using different additives. We were pleased to find that indeed access to both types of carbonate products from simple and accessible precursors (*cf.*, synthesis of **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 diastereo-isomeric mixtures arises from the sclareol epoxidation stage, with apparently some higher degree of stereo-control in the preparation of **17**.

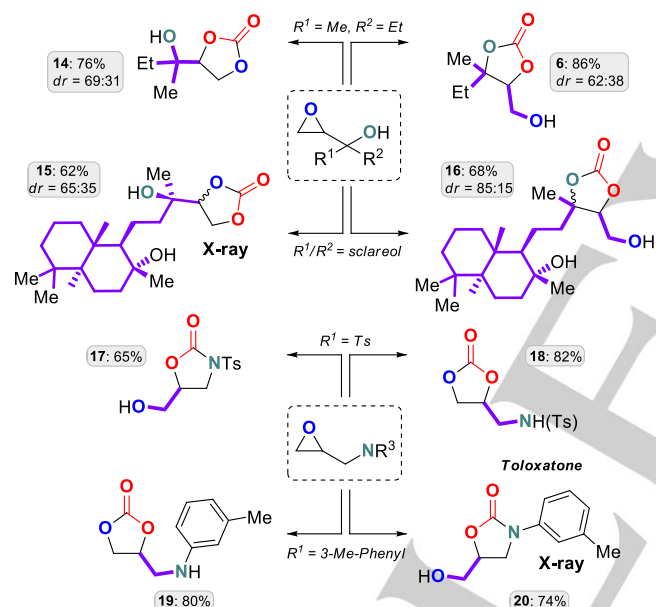


Figure 2. Product divergence from four epoxy alcohols/amines giving access to compounds **14–21**. For all reactions 2 mol% [Al^tBu] and $p(\text{CO}_2)^0 = 10$ bar were used unless indicated otherwise. Details: **14**, 5 mol% TBAB, 25°C, 60 h, conv. 95%, sel. 85%; **15**, 80°C, 40 h, 30 bar, conv. >99%, 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]

The use of epoxy amines (Figure 2, below) also gives product divergence potential (*cf.*, synthesis of **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 CO₂ (Scheme 1, alternative

pathway). However, we found that the addition of a suitable base (DIPEA) allows accessing the carbamate **19** in an appreciable yield of 65% with full selectivity towards the 5-isomer in line with the proposed intra-molecular pathway presented in Scheme 1. The presence of an N-aryl group in the epoxy amine substrate expands further on the potential of this chemistry as it gives a simple entry to pharmaceutically relevant 5-substituted oxazolidinones such as toloxatone **21** (74% yield; X-ray structure determined)^[16] which is a known anti-depressant. Interestingly, there are several structurally highly related oxazolidinone molecules that are used as anti-microbials and the easy formation of toloxatone gives promise to the synthesis of new types of bio-active compounds using CO₂ as a co-reactant.

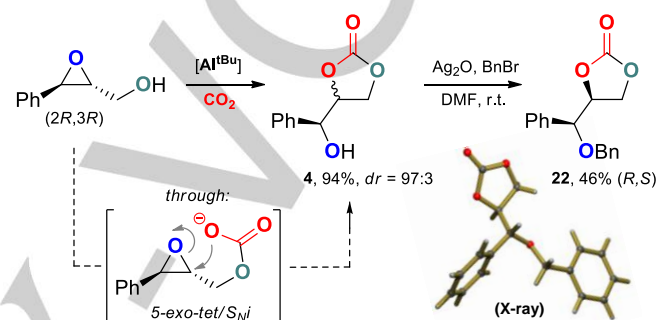


Figure 3. More detailed investigation into the diastereo-selective formation of cyclic carbonate **4** and its benzyl-protected derivative **22**.

In order to support the formation of a nucleophile derived from an epoxy alcohol and CO₂, we examined more closely the formation of carbonate product **4** (Figure 3). Enantiopure (2*R*,3*R*)-(+)-3-phenylglycidol (96%) was converted with 94% selectivity into **4** (86% yield, one diastereo-isomer). The other two components of the reaction mixture were the other diastereo-isomer (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 diastereo-selective pathway ($dr = 97:3$). The absolute configuration [(2*R*,3*S*)] of **4** was determined by X-ray crystallographic analysis of its O-benzyl protected derivative **22** (see also Supporting Information)^[16] and showed a formal inversion at one of the carbon centers. This suggests that a nucleophilic substitution had taken place prior to isolation (*cf.*, Walden inversion) being in line with the mechanistic proposal in Scheme 1 presenting a formal 5-*exo-tet* type cyclization. Moreover, the selective formation of the 5-substituted oxazolidinone products **10**, **11** and **21** further 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 CO₂ conversion process that allows for product divergence from epoxy alcohols/amines. The different carbonate/carbamate products can be accessed through different mechanistic manifolds simply triggered by tuning of the reaction temperature/pressure and use of suitable nucleophilic/base

additives. Such control allows for new, unexplored uses of CO₂ in organic synthesis using substrate-driven activation of this renewable carbon feed stock. Notably, here such reactivity 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 in order to further capitalize on the potential of this alternative raw carbon material in chemical synthesis.

Acknowledgements

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Keywords: carbon dioxide • CO₂ activation • epoxy alcohols • homogeneous catalysis • product divergence

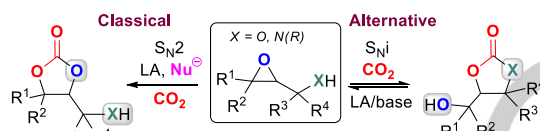
- [1] a) Q. Liu, L. Wu, R. Jackstell, M. Beller, *Nat. Commun.* **2015**, *6*, 5933; b) M. Aresta, A. Dibenedetto, A. Angelini, *Chem. Rev.* **2014**, *114*, 1709; c) N. Kielland, C. J. Whiteoak, A. W. Kleij, A. W. *Adv. Synth. Catal.* **2013**, *355*, 2115; d) B. Yu, L.-N. He, *ChemSusChem* **2015**, *8*, 52; e) M. Cokoja, C. Bruckmeier, B. Rieger, W. A. Herrmann, F. E. Kühn, *Angew. Chem. Int. Ed.* **2011**, *50*, 8510; f) Y. Tsuji, T. Fujihara, *Chem. Commun.* **2012**, *48*, 9956.
- [2] Formation of C–O bonds in polycarbonates: a) X.-B. Lu, D. J. Darensbourg, *Chem. Soc. Rev.* **2012**, *41*, 1462; b) R. Nakano, S. Ito, K. Nozaki, *Nat. Chem.* **2014**, *6*, 325; c) M. R. Kember, C. K. Williams, *J. Am. Chem. Soc.* **2012**, *134*, 15676; d) G. W. Coates, D. R. Moore, *Angew. Chem. Int. Ed.* **2004**, *43*, 6618; Formation of C–O bonds in linear/cyclic carbonates: e) J. A. Kozak, J. Wu, X. Su, F. Simeon, T. A. Hatton, T. F. Jamison, *J. Am. Chem. Soc.* **2013**, *135*, 18497; f) V. Laserna, G. Fiorani, C. J. Whiteoak, E. Martin, E. C. Escudero-Adán, A. W. Kleij, *Angew. Chem. Int. Ed.* **2014**, *53*, 10416; g) W.-M. Ren, G.-P. Wu, F. Lin, J.-Y. Jiang, C. Liu, Y. Luo, X.-B. Lu, *Chem. Sci.* **2012**, *3*, 2094; h) S. Yoshida, K. Fukui, S. Kikuchi, T. Yamada, *J. Am. Chem. Soc.* **2010**, *132*, 4072; Formation of C–N bonds affording various products: i) F. Fontana, C. C. Chen, V. K. Aggarwal, *Org. Lett.* **2011**, *13*, 3454; j) O. Jacquet, C. Das Neves Gomes, M. Ephritikhine, T. Cantat, *J. Am. Chem. Soc.* **2012**, *134*, 2934; k) K. Beydoun, G. Ghattas, K. Thenert, J. Klankermayer, W. Leitner, *Angew. Chem. Int. Ed.* **2014**, *53*, 11010; l) Y. Li, T. Yan, K. Junge, M. Beller, *Angew. Chem. Int. Ed.* **2014**, *53*, 10476; m) W.-J. Yoo, C.-J. Li, *Adv. Synth. Catal.* **2008**, *350*, 1503.
- [3] a) G. Centi, E. A. Quadrelli, S. Perathoner, *Energy Environ. Sci.* **2013**, *6*, 1711; b) *Carbon Dioxide as Chemical Feedstock*, ed. M. Aresta, Wiley-VCH, Weinheim, **2010**; c) *New and Future Developments in Catalysis: Activation of Carbon Dioxide*, ed. S. L. Suib, Elsevier, Amsterdam, **2013**.
- [4] Cantat *et al.* previously described an interesting diagonal concept towards the amplification of chemical functionality from CO₂, see: C. Das Neves Gomes, O. Jacquet, C. Villiers, P. Thuéry, M. Ephritikhine, T. Cantat, *Angew. Chem. Int. Ed.* **2012**, *51*, 187.
- [5] For seminal/illustrative examples: a) A. G. Myers, P. J. Proteau, T. M. Handel, *J. Am. Chem. Soc.* **1988**, *110*, 7212; b) A. G. Myers, K. L. Widdowson, *Tetrahedron Lett.* **1988**, *29*, 6389; c) P. Yan, X. Tan, H. Jing, S. Duan, X. Wang, Z. Liu, *J. Org. Chem.* **2011**, *76*, 2459; d) J. A. H. Inkster, I. Ling, N. S. Honson, L. Jacquet, R. Gries, E. Plettner, *Tetrahedron: Asymmetry* **2005**, *16*, 3773.
- [6] For some examples: a) S. Yoshida, K. Fukui, S. Kikuchi, T. Yamada, *J. Am. Chem. Soc.* **2010**, *132*, 4072; b) Q.-W. Song, W.-Q. Chen, R. Ma, A. Yu, Q.-Y. Li, Y. Chang, L.-N. He, *ChemSusChem* **2015**, *8*, 821; c) W. Yamada, Y. Sugawara, H. M. Cheng, T. Ikeno, T. Yamada, *Eur. J. Org. Chem.* **2007**, 2604.
- [7] For some seminal contributions: (a) M. North, R. Pasquale, *Angew. Chem. Int. Ed.* **2009**, *48*, 2946; b) A. Khan, R. Zheng, Y. Kan, J. Ye, J. Xiang, Y. Zhang, *Angew. Chem. Int. Ed.* **2014**, *53*, 6439; c) C. J. Whiteoak, N. Kielland, V. Laserna, E. C. Escudero-Adán, E. Martin, A. W. Kleij, *J. Am. Chem. Soc.* **2013**, *135*, 1228; d) W. Guo, J. González-Fabra, N. A. G. Bandeira, C. Bo, A. W. Kleij, *Angew. Chem. Int. Ed.* **2015**, *54*, 11686; e) Y.-B. Wang, Y.-M. Wang, W.-Z. Zhang, X.-B. Lu, *J. Am. Chem. Soc.* **2013**, *135*, 11996.
- [8] Note that the catalytic coupling of tri-substituted epoxides and CO₂ has been seldom reported and only examples for poly(limonene)carbonate formation have been reported: a) C. M. Byrne, S. D. Allen, E. B. Lobkovsky, G. W. Coates, *J. Am. Chem. Soc.* **2004**, *126*, 11404; b) L. Peña Carrodegua, J. González-Fabra, F. Castro-Gómez, C. Bo, A. W. Kleij, *Chem. Eur. J.* **2015**, *21*, 6115; c) O. Hauenstein, M. Reiter, S. Agarwal, B. Rieger, A. Greiner, *Green. Chem.* **2016**, DOI: 10.1039/C5GC01694K; Yoshida *et al.* reported on the use of propargylic alcohols to form highly substituted cyclic carbonates: d) M. Yoshida, M. Fujita, T. Ishii, M. Ihara, *J. Am. Chem. Soc.* **2003**, *125*, 4874.
- [9] J. Rintjema, W. Guo, E. Martin, E. C. Escudero-Adán, A. W. Kleij, *Chem. Eur. J.* **2015**, *21*, 10754.
- [10] a) N. Ishida, Y. Shimamoto, M. Murakami, *Angew. Chem. Int. Ed.* **2012**, *51*, 11750; b) S. Minakata, I. Sasaki, T. Ide, *Angew. Chem. Int. Ed.* **2010**, *49*, 1309; c) B. A. Vara, T. J. Struble, W. Wang, M. Dobish, J. N. Johnston, *J. Am. Chem. Soc.* **2015**, *137*, 7302; d) Y. Takeda, S. Okumura, S. Tone, I. Sasaki, S. Minakata, *Org. Lett.* **2012**, *14*, 4874; Tunge *et al.* have reported on CO₂-mediated alcohol activation through alkyl carbonic acid formation and using it as a leaving group in intermolecular allylation chemistry, see: e) S. B. Lang, T. M. Locascio, J. A. Tunge, *Org. Lett.* **2014**, *16*, 4308.
- [11] Epoxy alcohols are privileged scaffolds in organic synthesis and easily prepared, see: a) R. M. Hanson, *Chem. Rev.* **1991**, *91*, 437; b) A. Riera, M. Moreno, *Molecules* **2010**, *15*, 1041; For synthesis of chiral epoxy alcohols see: c) J. L. Olivares-Romero, Z. Li, H. Yamamoto, *J. Am. Chem. Soc.* **2013**, *135*, 3411; d) C. Wang, H. Yamamoto, *J. Am. Chem. Soc.* **2014**, *136*, 1222. Epoxy amines can be simply derived from epoxy alcohols or by standard nucleophilic substitution using alcohol activating groups.
- [12] Note that for some of the studied epoxy alcohol substrates further optimization was required (higher reaction temperatures and pressures) in order to achieve the best combination of chemo-selectivity and yield. In most of these cases, the conventional carbonate was formed as a side-product. See the Supporting Information for more details.
- [13] In some reactions the use of an external nucleophile was beneficial to significantly improve the reaction kinetics. See for a detailed discussion and explanation the Supporting Information.
- [14] For illustrative examples see: a) A. W. Miller, S. T. Nguyen, *Org. Lett.* **2004**, *6*, 2301; b) Z.-Z. Yang, Y.-N. Li, Y.-Y. Wei, L.-N. He, *Green Chem.* **2011**, *13*, 2351.
- [15] The lower chemo-selectivity is explained in terms of a larger steric effect in the ring-opening of the epoxide after formation of the alkyl carbonic acid intermediate. Upon reducing the steric bulk (*cf.* synthesis of **9**), the chemo-selective nature of this conversion is restored. See the SI for the optimization details of **12** and **13**.
- [16] CCDC-1441879, 1441880 and 1441881.

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Entry for the Table of Contents:

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A novel substrate-driven and divergent approach allows to access different and challenging heterocyclic products from a single epoxy alcohol/amine substrate. The different mechanisms leading to these CO₂-derived scaffolds are controlled by the reaction conditions allowing for an amplified scope of organic structures based on this C₁ feed stock. A new mechanism is proposed where the substrate activates the CO₂ molecule leading to an intramolecular process giving rise to alternative product formation.



- substrate-controlled CO₂ conversion
- product divergence from a single substrate
- good yields and selectivities
- synthesis of challenging scaffolds

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