Substrate Triggered Stereoselective Preparation of Highly Substituted Organic Carbonates

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ABSTRACT: Trisubstituted cyclic organic carbonates with multiple though well-defined stereochemical configurations are difficult to prepare. Here we present a conceptual design towards these CO_2 based synthons using hydroxyl-substituted cyclic epoxide precursors and their catalytic conversion, to afford these challenging target compounds with fused ring sizes up to eight under excellent stereo-control. The observed stereochemistry of the organic carbonates combined with various control experiments revealed that these compounds are formed through a mechanistic manifold that involves a depolymerization reaction within an oligomeric carbonate induced by a pendent hydroxyl nucleophile. This manifold therefore provides an alternative approach towards CO_2 valorization into functional, cyclic carbonate scaffolds of use in synthetic chemistry.

Keywords: *carbon dioxide, cyclic organic carbonates, depolymerization*, *homogenous catalysis, stereoselectivity*

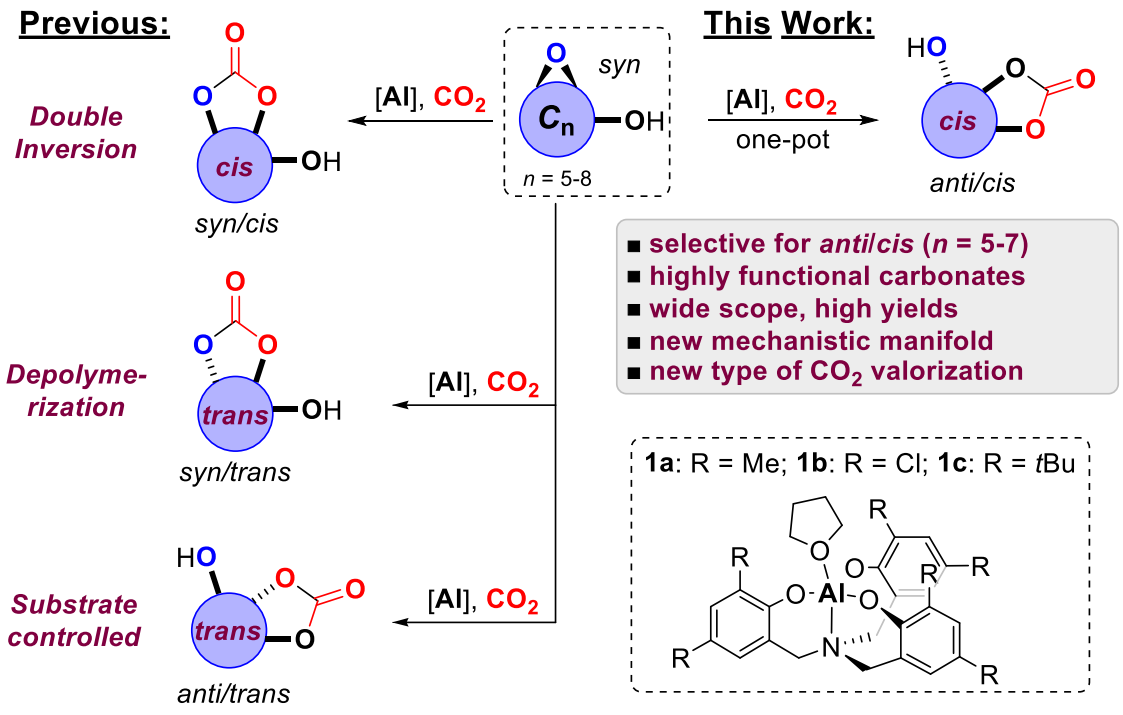
■ INTRODUCTION

Carbon dioxide offers a cheap and renewable carbon feedstock for fine-chemical synthesis[1] and recent progress clearly testifies the imminent role of homogeneous catalysis to turn this waste into more complex molecules.[2] In this respect, cyclic organic carbonates are increasingly used as useful synthetic intermediates if appropriate substituted with functional groups that, after activation, furnish reactive intermediates for a wide variety of transformations.[3] Whereas mono-substituted organic carbonates are fairly easily prepared and methodologies for di-substituted versions[4] have recently become available, it remains a huge challenge to prepare more densely substituted/functionalized organic carbonate scaffolds[5] which ultimately may limit further exploration of the synthetic potential of these structures.

We recently reported the synthesis of bicylic organic carbonates which have carbon dioxide incorporated as a temporary protecting group and deliver *cis*-diols upon hydrolysis.[6] In addition, we communicated the use of acyclic epoxy alcohols that can be converted into organic carbonates through a substrate-controlled CO_2 activation process.[7] Inspired by these results and the need to develop efficient procedures for highly substituted and functional organic carbonates prompted us to consider an unexplored approach towards the coupling of CO_2 and cyclic *syn*-configured epoxyalcohols. Stereoselective conversions in cyclic carbonate synthesis have been subject of various recent investigations[8] but represent a relatively new area in CO_2 valorization catalysis. We envisioned that various cyclic carbonate scaffolds with different stereochemistry (Scheme 1) could be produced from a common *syn*-configured cyclic epoxy alcohol precursor (*i.e*, stereodivergence) through previously reported reaction manifolds (Scheme 1). A double inversion pathway (Scheme 1) retains the original stereochemistry of the substrate would afford a *syn*/*cis* configured product,[9] whereas under appropriate reaction conditions a metal-alkoxide driven depolymerization of an *in*

situ prepared polycarbonate species takes place with inversion of configuration at one of the epoxide-carbons giving a *syn*/*trans* isomer. An alcohol mediated activation of carbon dioxide and intra-molecular ring-opening leads to yet another diastereo-isomer (*anti*/*trans*). Whereas these known manifolds thus lead to diastereoisomeric *syn*/*cis*, *syn*/*trans* and *anti*/*trans* configured organic carbonate products, these approaches are not able to provide the corresponding *anti*/*cis* isomer (Scheme 1, at the right).

Scheme 1. The Conversion of Different Ring-Size Cyclic Epoxy-alcohols into Functionalized Organic Carbonate Scaffolds with various Stereochemical Configurations.



Therefore, we set out to design a new conceptual approach towards such *anti*/*cis* configured carbonate scaffolds to further widen the synthetic potential of these epoxy-alcohol substrates while controlling the stereoselectivity, functionality and scope of these transformations. Here we report

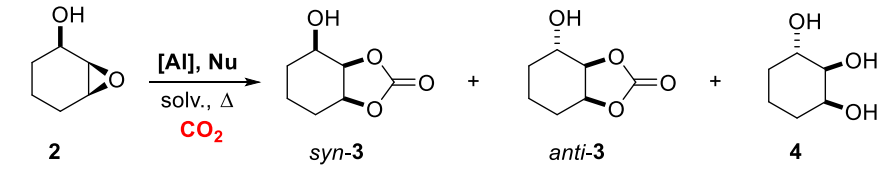
a general, catalytic and stereoselective approach towards the formation of functional *anti*/*cis* bicyclic carbonates through a new and substrate-triggered mechanism. The latter conveniently allows the preparation of challenging trisubstituted organic carbonates, and their post-synthetic potential is also reported.

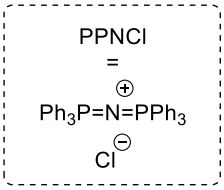
■ RESULTS AND DISCUSSION

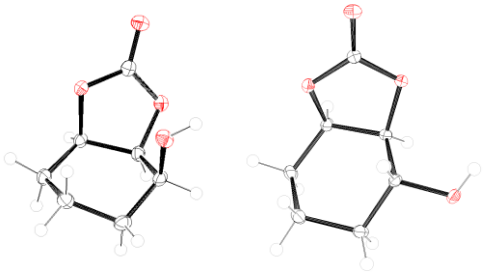
First, we examined the use of a simple and synthetically accessible epoxy-alcohol substrate based on a cyclohexyl skeleton (Table 1, **2**; see Supporting Information (SI) for details on this type of substrate synthesis). Various reaction conditions including nucleophilic additive, Al-catalyst, temperature and pressure were varied to examine the influence on the compositions of the reaction mixture (see also Table S1). In general, we found that three principal products were formed in these experiments (*syn*/*cis*-**3**, *anti*/*cis*-**3** and triol **4**) which were unambiguously identified by 1D and 2D NMR spectroscopy, and for *syn*/*cis* **3** and *anti*/*cis* **3** also by X-ray diffraction (see inserts in the Figure to Table 1).[10]

The *syn/cis* isomer of **3** (82% yield) was formed as the major reaction component by using only the nucleophilic additive (Table 1, entries 1–6; NBu_4Br), and its synthesis is the result of a double inversion mechanism.[8b] However, in the presence of Al-complexes **1a–1c** (see Scheme 1; Table 1, entries 7–11, see also Table S1) the diastereoselectivity could be tuned towards the formation of *anti/cis* **3** (entry 8; 88% yield) whose stereochemistry cannot be explained by the known manifolds detailed in Scheme 1.

Table 1. Screening of Reaction Conditions towards the Stereoselective Formation of Carbonates 3. MEK is Methylethyl Ketone, see for Al-complexes 1a-1c Scheme 1, Nu Stands for Nucleophile.[a]





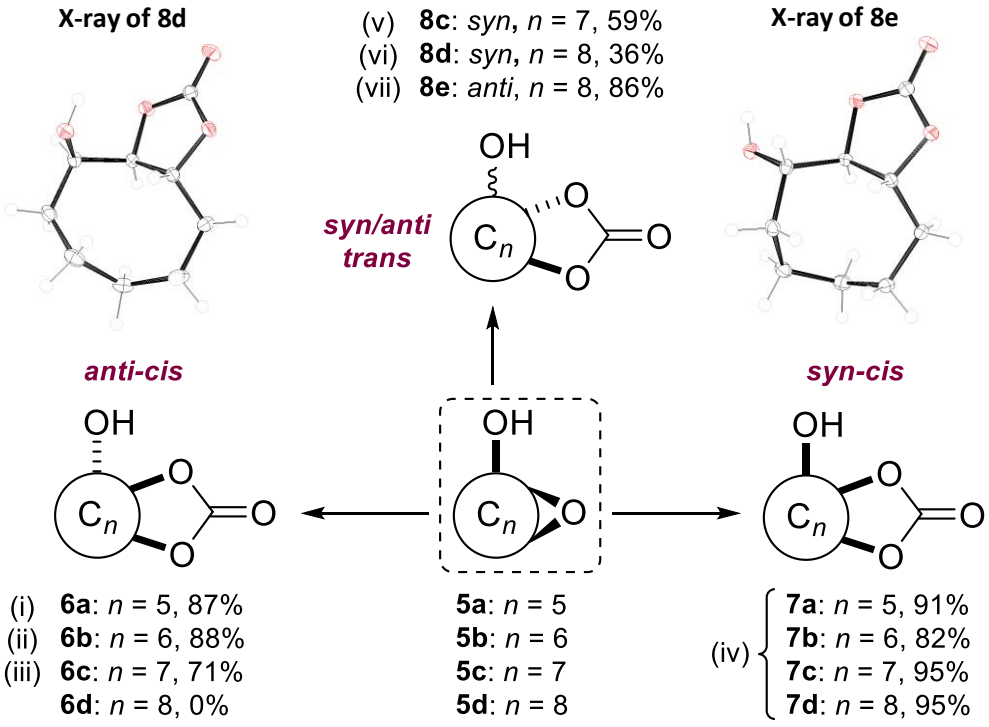


Entry	[Al, (mol %)	Nu (mol %)	Solvent	Conv. (%)[b]	Sel. *syn*/*anti*/4 (%)[b]
1	–	**Br**, 2.5	MEK	51	38 : 54 : 6
2	–	**Br**, 5.0	MEK	73	50 : 41 : 9
3	–	**Br**, 10	MEK	>99	68 : 23 : 9
4[c]	–	**Br**, 25	MEK	>99	82 : 13 : 5[d]
5	–	**Br**, 10	MeOH	>99	2 : 13 : 85
6	–	**Br**, 10	Tol	>99	35 : 35 :30
7	**1a**, 0.5	**Br**, 1.0	MEK	>99	0 : 71 : 29
8	**1a**, 1.0	**Br**, 2.5	MEK	>99	0 : 89 : 11[e]
9[f]	**1a**, 0.5	**Cl**, 0.5	Tol	>99	0 : 91 : 9
10	**1b**, 0.5	**Br**, 1.0	MEK	>99	0 : 83 : 17
11	**1c**, 1.0	**Br**, 2.5	MEK	>99	11 : 64 : 25

[a]General conditions: 0.50 mmol of **2**, $p(CO_2)^o$ = 10 bar, 70ºC, solvent (200 μL), amounts of [**Al**] and **Nu** indicated. **Br** is NBu_4Br and **Cl** stands for PPNCl, see Figure. [b]Determined by ^1H NMR ($CDCl_3$). [c]At 50ºC. [d]Isolated yield of *syn*/*cis* **3** was 82%. [e]Isolated yield of *anti*/*cis* **3** was 88%. [f]At 40 bar of CO_2.

Therefore, in order to gain more insight into the operating mechanism leading to these *anti*/*cis* configured bicyclic carbonates, we decided to consider various hydroxyl-substituted cyclic epoxides (Scheme 2, **5a–d;** for their synthesis see the SI). The conversion of five-, six- and seven-membered hydroxyl-substituted cyclic epoxides **5a–5c** and the conditions leading to the *anti/cis* bicyclic carbonates **6a–6c** (yield: 71–87%) had to be optimized individually (details on the screening conditions in Tables S2–S4), whereas the synthesis towards *anti*/*cis* **6d** was not feasible.

Scheme 2. Preparation of Different Diastereoisomeric Bicyclic Carbonates 6–8.

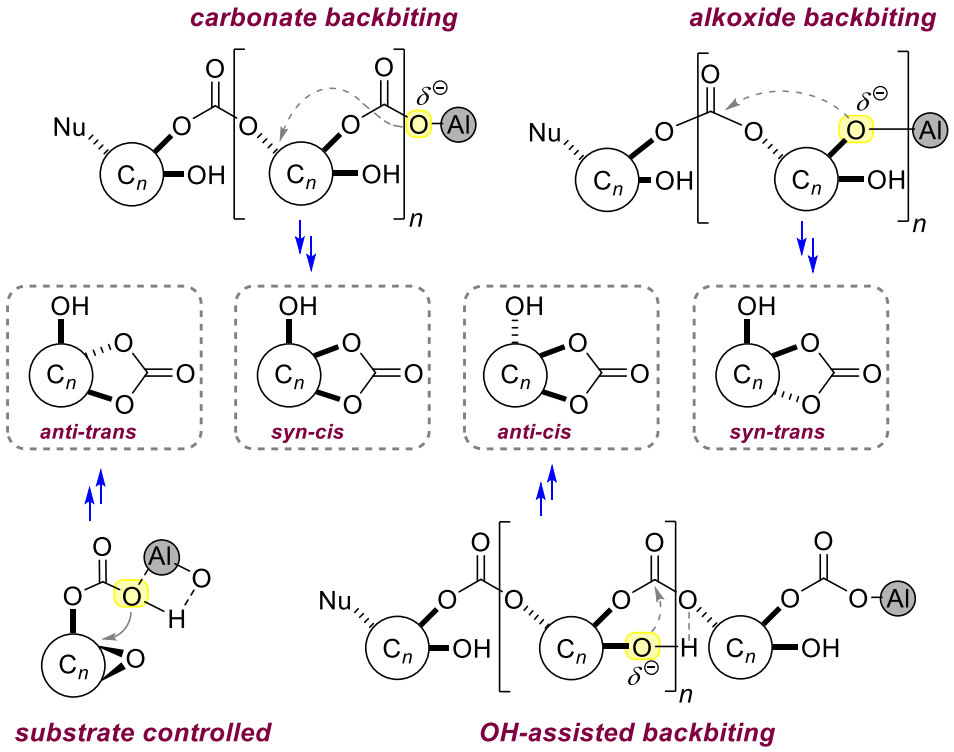


[a]General conditions: 0.50 mmol substrate, 40 bar CO_2, 70ºC, 18 h, solvent (200 μL), reported yields are of the isolated compound after chromatographic purification. Specific conditions: (i) **1a** (1.0 mol%), PPNCl (1.0 mol%), MEK; (ii) **1b** (0.50 mol%), NBu_4Br (1.0 mol%), MEK; (iii) **1a** (5.0 mol%), DMAP (5.0 mol%), Tol; (iv) NBu_4Br (25 mol%), MEK; (v) **1a** (1.0 mol%), PPNCl (5.0 mol%), Tol; (vi) **1a** (2.5 mol%), PPNCl (2.5 mol%), MEK; (vii) **1a** (5.0 mol%), DMAP (5.0 mol%), Tol.

The synthesis of the isomeric *syn*/*cis* carbonates **7a–7d** was simply mediated by using high loadings of the nucleophilic additive NBu_4Br, and is pertinent to the aforementioned double inversion pathway.[8b] In contrast, the manifold leading to **6a–6c** is distinct, and the applied experimental conditions favor a backbiting process of an oligocarbonate intermediate produced *in situ* from cyclic epoxides as previously reported.[8] Standard depolymerization[11] of oligo/polycarbonates would produce a *trans* configured cyclic carbonate product through a metal-alkoxide terminus (alkoxide backbiting, see Scheme 3), and consequently a *syn*/*trans* configured product. Alternatively, carbonate backbiting (Scheme 3) in a polymer with a metal-carbonate end-group would furnish a *syn*/*cis* carbonate product. Therefore the mechanism accountable towards the formation of the *anti*/*cis* configured carbonates **6a–6c** is distinct from these previous reported depolymerization pathways. We propose that the hydroxyl-unit is actively involved in the depolymerization process as outlined in Scheme 3 (OH-assisted backbiting). The OH may be readily activated towards nucleophilic attack onto the adjacent carbonate unit through H–bonding and likely this process is favored over the standard depolymerization process for substrates of type **5a–b** (with n = 5 or 6). An OH-assisted depolymerization nicely fits the experimentally observed formation of *anti*/*cis* carbonate products **3** and **6a–6c**.

This latter mechanistic hypothesis was further challenged by consideration of seven- and eight-membered cyclic epoxide substrates as these are generally less prone towards copolymerization with CO_2.[12] The experimental conditions were therefore varied such that copolymerization would be favored.[8,11] The larger ring-size, bicyclic carbonate products **8c** and **8d** (assumed to be generated *via* a standard alkoxide backbiting process) could be isolated though their yields were modest/low due to competitive pathways leading to other stereoisomers as shown in Scheme 3; (optimized conditions from Tables S3 and S4, SI).

Scheme 3. Mechanistic Pathways to the Differently Configured Bicyclic Carbonate Products Observed Experimentally. Al Stands for an Aluminum Catalyst such as Complexes 1a-c.



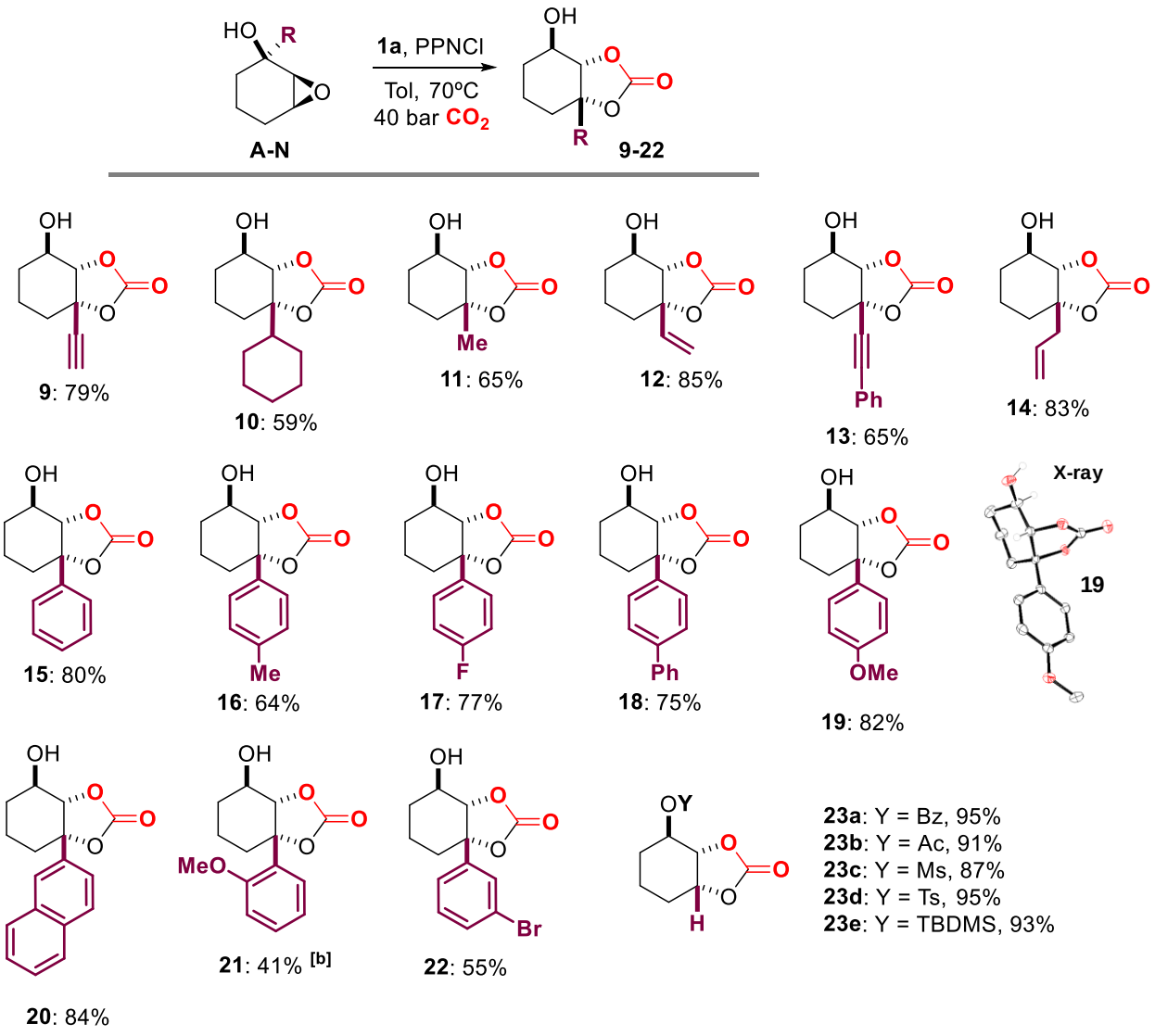
Such *trans* configured carbonates are typically not formed from smaller bicyclic epoxides (n = 5 or 6) as the intrinsic ring strain in the bicylic carbonate product would lead to decarboxylation and/or decomposition.[13]

The *anti*/*trans* carbonate **8e** (86%) was obtained in high yield in the presence of **1a**/DMAP and its configuration suggests the occurrence of substrate-assisted (and *not* an OH-mediated depolymerization) activation of CO_2 (Scheme 3) facilitated by the Al-complex **1a** as previously described by us for acyclic epoxy-alcohols.[7,14] Thus, it seems that for larger ring-size hydroxy-substituted cycloalkanes the formation of an *anti*/*cis* configured bicyclic carbonate is less likely to

occur due to competitive pathways that lead to other diastereoisomers. As far as we know, the formation of **8d** and **8e** represent rare examples of bicyclic carbonates with fused eight-membered rings, and their structures were unambiguously confirmed by X-ray analyses (inserts to Scheme 3; optimized reaction conditions from Table S4, SI).

In order to examine whether the formation of the unusual *anti*/*cis* configured bicyclic carbonates could be extended to more functional derivatives, we then turned our focus (Scheme 4) on the conversion of substituted versions of hydroxy-cyclohexene oxides **A–N** (Scheme 4) under similar conditions as reported in Table 1, entry 9. Gratifyingly, the carbonate products **9–22** could be generally prepared in good isolated yields of up to 85% and with wide functional group diversity allowing for the introduction of synthetically useful alkyne (**9** and **13**), vinyl/olefin (**12** and **14**) and *para*- and/or *meta*-substituted aromatic fragments (**17** and **22**). Cyclohexene oxide substrates with *ortho*-substituted aryl groups display more sluggish reactivity, and only a moderate yield for **21** (41%) was obtained after 66 h indicating some degree of steric impediment in this transformation. Intriguingly, the straightforward and high yield synthesis of a series of *tri*-substituted functional bicyclic carbonates could be easily achieved which is known to be extremely challenging in the area of CO_2/epoxide couplings.[5] The presence of a vinyl group in the cyclic carbonate structure (such as in **12**) conveniently allows for post-modification chemistry as recently demonstrated.[15] Beside the formation of tri-substituted, functional carbonates **9–22**, *anti/cis* configured **3** could be easily converted in high yield and selectivity into bicyclic carbonate scaffolds **23a–e**: these latter compounds incorporate rather common and synthetically useful protecting groups including benzoyl, mesyl and a bulky silyl. It should be noted that the R fragments from the cyclohexene oxide substrates are not attached to

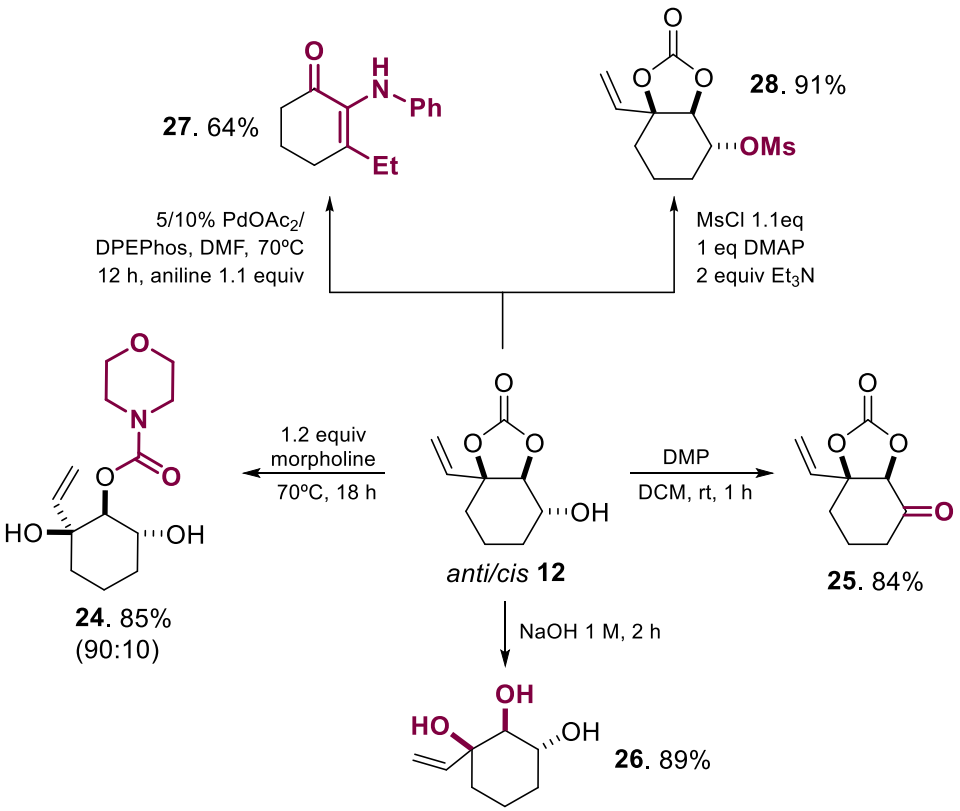
Scheme 4. Substrate Scope for the Conversion of Various Hydroxy-Substituted Cyclohexene Oxides into *Anti*/*Cis* Configured Bicyclic Carbonates 9–22 and Protected Derivatives 23a–e.[a]



[a]Conditions: 0.50 mmol epoxide substrate, Al-complex **1a** (1.0 mol%), PPNCl (5.0 mol%), toluene (200 μL), 70°C, 40 bar CO_2. Reported yields are isolated ones after chromatographic purification. [b]Reaction time was 66 h; Bz = benzoyl, Ac = acetyl, Ms = mesyl, Ts = tosyl, TBDMS = *tert*-butyldimethylsilyl.

the same carbon center as the (unprotected) alcohol group in the carbonate products *anti*/*cis* **3** and **9–22**, and the X-ray structure determined for **19** (Scheme 4) further confirming the general spectroscopic assignments. These results further support that the original alcohol unit of the epoxide substrate is incorporated into the cyclic carbonate ring of the product and thus implies, as suggested, that this OH unit is actively involved towards the formation of the bicyclic carbonate product.

Scheme 5. Synthetic Potential of Carbonate 12 and conversion into its derivatives 24–28.



Finally, we used vinyl-substituted bicyclic carbonate **12** as a starting point to demonstrate the potential of these functionalized carbonates in organic synthesis and to access other useful precursors (Scheme 5). Treatment of **12** with morpholine gave access to carbamate **24** in good yield (85%) and with high regio-selectivity (90:10).[3e] A Dess-Martin oxidation of **12** furnished

the ketone derivative **25** in 84% yield. Simple hydrolysis under basic conditions converted **8** into vinyl substituted triol product **26** (89%) of potential use in natural product synthesis.[16] A decarboxylative amination[17] gave access to stereoselective formation of tetrasubstituted olefin **27** (64%) while the alcohol group in **12** could be protected by a mesyl group to afford **28** in 91% yield. It should be noted that these transformations are rather general and should be applicable to the other bicyclic carbonates reported in Scheme 4.

■ CONCLUSION

In summary, we here present a unique manifold to access stereoselectively *anti*/*cis* configured bicyclic carbonates that are the result of a hydroxy-mediated depolymerization process of *in situ* prepared oligocarbonate precursor. This new manifold affords a wide range of challenging trisubstituted bicyclic carbonates that cannot be accessed through any previously reported methodology. Thus, this new depolymerization manifold provides a new valorization approach for carbon dioxide and its conversion into useful precursors for synthetic chemistry as demonstrated herein. Currently we are examining the use of other, related epoxy alcohol scaffolds in various coupling reactions with a focus on synthetic applications.

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Notes

The authors declare no competing financial interest.

ASSOCIATED CONTENT

Supporting Information. Copies of analytical data/spectra, and full characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Note that *anti*/*cis* and *syn*/*cis* notations refers to the relative position of the OH group with respect to a *cis*-configured cyclic carbonate unit.

(10) Further details can be found in the Supporting Information.

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(12) Kruper and Dellar reported the formation of a *trans*-configured carbonate product in high yield derived from cycloheptene oxide, and this may the result of an *in situ* depolymerization process. See: Kruper, W. J.; Dellar, D. V. *J. Org. Chem*. **1995**, *60*, 725–727.

(13) For decarboxylation/decomposition of *trans* configured (oligo)carbonates derived from cyclopentene/cyclohexene oxides at elevated temperatures: (a) Darensbourg, D. J.; Wei, S.-H.; Yeung, A. D.; Ellis, W. C. *Macromolecules* **2013**, *46*, 5850−5855. (b) Darensbourg, D. J.; Wei, S.-H.; Wilson, S. J. *Macromolecules* **2013**, *46*, 3228−3233. (c) Darensbourg, D. J.; Bottarelli, P.; Andreatta, J. R. *Macromolecules* **2007**, *40*, 7727−7729.

(14) Note that acyclic epoxy alcohols have distinct reactivity compared to cyclic analogues, and much lower tendencies towards *in situ* copolymerization with CO_2, and therefore favor the alcohol-assisted CO_2 activation pathway.

(15) Vinyl cyclic carbonates have recently shown to be useful in fine-chemical targeted synthesis: (a) Cai, A.; Guo, W.; Martínez-Rodríguez, L.; Kleij, A. W. *J. Am. Chem. Soc*. **2016**, *138*, 14194−14197. (b) Khan, A.; Zheng, R.; Kan, Y.; Ye, J.; Xing, J.; Zhang, Y. J. *Angew. Chem. Int. Ed.* **2014**, *53*, 6439−6442.

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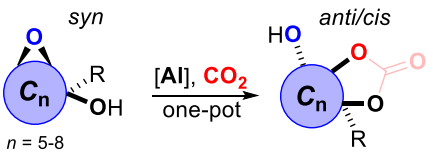
SYNOPSIS/TOC:



- diastereoselective for *anti*/*cis*
- polysubstituted functional carbonates
- wide scope, yield up to 88%
- new mechanistic manifold