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Exploitation of Mechanistic Product Selectivity for the Two-step Synthesis of Optically Active Bio-derived Cyclic Carbonates Incorporating Amino Acids

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Abstract. The synthesis of bio-derived cyclic carbonates is attracting a lot of attention as the incorporation of bio-derived functionality into these compounds provides the opportunity to prepare previously unknown structures, whilst also improving their sustainability profiles. This study presents a facile preparation of diastereomerically pure bio-derived cyclic carbonates displaying a range of optical rotation values. These compounds are obtained from glycidol, amino acids and CO2 in a facile two-step approach. Initially, the diastereomerically pure amino acid functionalised epoxides are prepared through a robust Steglich esterification of enantiopure glycidol (R or S) and an amino acid (D or L). Thereafter, in a second step, cycloaddition of the epoxide with CO2 results in the retention of the initial stereochemistry of the epoxide, furnishing novel diastereomerically pure and optically active cyclic carbonate products. A DFT study has explained the basis of this observed retention of configuration for these compounds. Further, results from this DFT study also provide new mechanistic information concerning a co-catalyst-free cycloaddition reaction starting from glycidol when using the gallium-catalyst, which is found to operate through metal-ligand cooperativity.

Keywords: Cyclic carbonates; Amino acids; Optical activity; Steglich esterification; Carbon dioxide

Introduction

The synthesis of 1,3-dioxolan-2-ones, more commonly referred to as (five-membered) cyclic carbonates, is drawing a significant amount of attention. This is mainly due to the opportunity to use carbon dioxide (CO2) in a non-reductive approach for their synthesis; they can be readily prepared through the attractive atom-efficient cycloaddition of epoxides/CO2. (Scheme 1a).[1] Beyond their appealing synthesis, they are versatile compounds having been applied in a wide range of applications; e.g. electrolytes in Li-ion batteries, use as sustainable and polar aprotic solvents,[2] application as intermediate synths for the preparation of more complex molecules,[3] and as monomers in sustainable polymer synthesis.[4]

To date, efforts in the field have largely been directed towards the development of new catalysts for the cycloaddition of epoxides and CO2 with a range of metal-based[5] and organocatalysts[6] reported. Indeed, in our own recent research we have developed several methods for the cycloaddition of CO2 with epoxides.[7] Synthesis of cyclic carbonates from the cycloaddition of epoxides with CO2 has been further explored with a range of reaction conditions, including the use of diastereomerically pure cycloaddition of epoxides, which has been shown to yield products with a range of diastereomeric purity.[8]

Scheme 1. (a) General synthesis of cyclic carbonates from the cycloaddition of epoxides with CO2. (b) Approaches for the incorporation of epoxides into bio-derived molecules. (c) The two-step synthesis of amino acid functionalised cyclic carbonates in this work.
Lewis acid-based catalyst systems based on the heavier group 13 elements for this conversion.\textsuperscript{[7]} Beyond this, with highly active catalyst systems available, many researchers have begun to develop protocols for the preparation of bio-derived cyclic carbonates.\textsuperscript{[8]} These studies have been predominantly based on the cycloaddition of CO$_2$ to epoxides which are prepared through the stoichiometric oxidation of naturally occurring olefins, such as those found in unsaturated fatty acid esters (Scheme 1b).\textsuperscript{[9]} Beyond this, we have reported how epoxides can also be incorporated into fatty acids through reaction between the carboxylic acid functionality and epichlorohydrin under basic conditions (Scheme 1bii). Epichlorohydrin can be prepared from abundant and cheap glycerol and can therefore be considered as a bio-derived compound.\textsuperscript{[10]} These terminal epoxides can then be readily converted to the corresponding cyclic carbonates. Overall, these examples serve to provide cyclic carbonates that are more sustainably derived than previous examples which are obtained from commercially available fossil-derived epoxides.

In our current research we are seeking to broaden the landscape and availability of bio-derived cyclic carbonates. Beyond this, we are also interested in evaluating any properties displayed by these compounds which differentiate them from the typical cyclic carbonate structures already reported. In this context we became interested in the potential to convert epoxides which have amino acid functionality with a gallium catalyst system previously developed in our laboratory.\textsuperscript{[7b]} This would provide the opportunity to further diversify the already wide substrate scope displayed by this catalyst system, whilst generating compounds which may have properties and applications beyond those of a basic cyclic carbonate. Herein, we describe how cyclic carbonates bearing amino acid functionality can be readily prepared in a two-step approach and highlight the optical activities of these compounds, thus advancing the field of bio-derived cyclic carbonates (Scheme 1c). This is a novel approach, and to the best of our knowledge there has not been a focus on preparing enantio-pure cyclic carbonates, apart from a report by Casto-Osma/Lara-Sánchez and co-workers, who prepared diastereomerically pure bio-derived cyclic carbonates through the crystallization of racemic mixtures.\textsuperscript{[11]}

**Results and Discussion**

Initially we proposed that glycidol\textsuperscript{[12]} could be readily coupled to the carboxylic acid fragment of a Boc-protected amino acid through a robust Steglich esterification, forming the desired amino acid functionalised epoxide substrates. In a first attempt racemic alanine ($D$/$L$ mixture) was coupled to racemic glycidol ($R$/$S$ mixture) (Scheme 2a). This approach furnished excellent yields of the amino acid functionalised epoxide product. However, in the $^{13}$C\{H\} NMR spectra of this coupling product it was clear that there were two distinct species present (Scheme 2b). These two species are the ($L$,$S$)/($D$,$R$) and ($L$,$R$)/($D$,$S$) diastereoisomer pairs and this was confirmed by the individual synthesis of each of these compounds through Steglich esterification of the enantiopure amino acids (1a(L) and 1b(D)) with enantiopure glycidol (a(R) and b(S)) (Scheme 2c). The diastereomeric amino acid functionalised epoxide products present optical properties, as was confirmed through optical rotation measurements (ranging from $+26.5^\circ$ to $-27.2^\circ$ for 2ba($D$,$S$) and 2ab($L$,$R$), respectively).

With the stereochemistry now incorporated into the epoxide substrates it was then necessary to study the second step of our proposed approach; the conversion of the epoxide to a cyclic carbonate. The mechanism of the cycloaddition should be stereo-retentive as attack at the least hindered carbon of the epoxide is generally favoured with most substrates, thus the starting stereochemistry of the epoxide remains in the final cyclic carbonate product.\textsuperscript{[13,14]}

Initially, to demonstrate the possibility of maintaining enantiopurity from the epoxide to cyclic carbonate, reactions using ($R$)-glycidol (a(R)) and (S)-glycidol (b(S)) as substrates were carried out using a previously developed gallium-based catalyst system (Ga-catalyst).\textsuperscript{[18]} The outcome of the reaction was complete conversion of the epoxide to the desired.

![Scheme 2](image-url)
cyclic carbonate product in qualitative conversion and yield (>99 %). However, both substrates suffered from loss of enantiopurity, which was confirmed by measurement of the optical rotation value of the cyclic carbonate products, which gave values of 0 °. This result indicates formation of racemic product mixtures (Scheme 3a). The same reaction was then performed using the corresponding (R)- and (S)-glycidyl methyl ethers (Scheme 3b), whereby in both cases no racemic product mixture was obtained, and the optical rotation values demonstrated that the original stereochemistry remains. The results obtained for these experiments were compared to commercially available compounds with >99% ee and the values were found to be relatively close, thus experimentally confirming the high retention of stereochemistry during the reaction. It should be noted that due to nomenclature reasons, the (R)-glycidyl methyl ether forms the (S)-glycidyl methyl ether cyclic carbonate and likewise, the (S)-glycidyl methyl ether forms the (R)-glycidyl methyl ether cyclic carbonate.

These results can be rationalised by consideration of the mechanisms involved (Scheme 3c). Starting with the simplest mechanistic scenario with glycidyl methyl ether or glycidol (Scheme 3ci), the epoxide coordinates to the catalyst, at which point the halide nucleophile preferentially attacks the least hindered carbon atom (see the later DFT study for details of this with glycidyl methyl ether) and then after CO₂ insertion, final ring-closure results in a cyclic carbonate product which has the same stereochemistry as the starting epoxide. In contrast, the glycidol can follow another distinct pathway (Scheme 3cii). In this scenario, the alcohol of the glycidol reacts with the CO₂ to form a carbonate which then attacks the stereocentre of the epoxide and results in an inversion of the original stereochemistry. This second approach does not actually require a co-catalyst and indeed, upon performing the same reaction with the gallium catalyst in the absence of co-catalyst, the reaction still proceeds (Scheme 3d), although interestingly only providing an 80 % yield over the same reaction time. Taken together, these two distinct mechanisms can result in the formation of a racemic product mixture, as has been experimentally observed. Bo/Urakawa/Kleij and co-workers have previously studied these mechanisms using an aluminium congener of the catalyst applied in this work.

As a result of these initial observations, it would be expected that the stereochemistry of the amino acid functionalised epoxides would then be retained during the cycloaddition with CO₂ using the gallium catalyst system. The next step was therefore to study the conversion of the diastereomerically pure alanine functionalised epoxides to the cyclic carbonate products. Under the standard conditions employed in our laboratory for the conversion of terminal cyclic carbonates, it was possible to provide the
Scheme 4. Results obtained from the cycloaddition of CO₂ to the four enantiopure alanine bearing epoxides using the gallium-based binary catalyst system; cycloadditions performed on a 0.7 mmol scale. X-ray crystal structure of the cyclic carbonate 3ab(L,S) with the Boc-protecting group shown faded and hydrogen atoms omitted for clarity (CCDC number: 2320602)

corresponding amino acid functionalised cyclic carbonate products in excellent yields (Scheme 4), which could be readily purified by column chromatography. Furthermore, the cyclic carbonates were optically active, as was ascertained from optical rotation measurements, providing optical rotation values of +16.3 ⁰, +11.1 ⁰, -10.2 ⁰ and -15.6 ⁰ for 3ba(D,R), 3aa(L,R), 3bb(D,S) and 3ab(L,S), respectively. This is to the best of our knowledge the first time that a bio-derived cyclic carbonate of this type has been prepared. It is notable that the compounds display optical activity in addition to their well-documented aprotic polar nature.

With the two-step methodology successfully applied for the synthesis of these optically active cyclic carbonates derived from alanine, glycidol and CO₂, a wider substrate scope was then studied. There are a large number of amino acids available, and these are generally of the naturally occurring (L) form. As such, a selected range of Boc-protected (L)-amino acids (1c-II) were subjected to the Steglich esterification reaction with either (R)- or (S)-glycidol providing the desired enantiopure epoxides (Scheme 5). In addition to amino acids which contain a single carboxylic acid functionality, both (L)-aspartic (1k) and (L)-glutamic (1l) acids were also studied. These latter examples resulted in amino acids which are coupled to two epoxide moieties and are even more complex, containing three chiral centers. All the

Scheme 5. Substrate scope for the Steglich coupling of (L)-amino acids with either (R)- or (S)-glycidol. For general procedure of the Steglich reaction, see the experimental section at the end of this manuscript. Isolated yields reported.
reactions proceeded smoothly and furnished analytically pure compounds without the need for column chromatography and were suitable for direct use in the proceeding cycloaddition reaction.

Again, as with the initial alanine study, under the standard conditions employed in our laboratory for the conversion of terminal cyclic carbonates,\textsuperscript{[70]} it was possible to provide the corresponding amino acid functionalised cyclic carbonate products in good to excellent yields (Scheme 6). In all cases, it is proposed that the resulting compounds have high diastereopurity, although we cannot fully exclude the possibility of a small fraction of partial racemisation. In experimental support of this purity, it can be seen that the compound derived from glycin, which only has one chiral center, provides very similar optical rotation values for both enantiomers (3ca(R) and 3cb(S), respectively). The other pairs of compounds do not present this mirroring as the optical rotation values are a result of the combination of two (or three) distinct chiral centers from the amino acid and cyclic carbonate moiety.

Figure 1 shows the distribution of optical rotation values exhibited by the amino acid functionalised cyclic carbonates prepared in this study. From the plot it is clear to see there is a well distributed range and thus it is possible to select a specific optical rotation value between -45 and +25° by correct combination of the amino acid and glycidol.

At this point we turned our attention to Density Functional Theory (DFT) calculations in an attempt to understand the observed selectivity expressed by both glycidyl methyl ether and glycidol substrates. Based on our previous studies with the gallium catalyst in this work\textsuperscript{[70]} we expected an initial complexation of the catalyst and epoxide substrate, leading to an intermediate (IC). Thereafter, subsequent halide attack at the least hindered carbon position (TS_R/S), forming the primary alkyl halide complex, with retention of the initial epoxide (R)/(S) stereochemistry as is observed experimentally in this work could be proposed. Alternatively, halide attack could occur at the most hindered position (TS_R/S), leading to a secondary alkyl halide is also possible. These different positions of attack have been studied previously for other catalyst systems using a range of substrates.\textsuperscript{[14]} More specifically, this report demonstrated that for alkyl-substituted terminal epoxides, the reaction is predominantly controlled by steric factors.

**Scheme 6.** Substrate scope for the cycloaddition of the amino acid functionalised cyclic carbonates and CO₂. Reaction conditions: Substrate (0.7 mmol epoxide), Gallium catalyst (0.5 mol%), TBAI (2.0 mol%), 8.0 bar CO₂, rt, overnight. Isolated yields reported.

**Figure 1.** Plot of the optical rotation values available from the amino acid functionalised cyclic carbonates prepared in this work.
of the gallium catalyst system described in this current study, barriers for attack at both positions, for both (R)-
and (S)-glycidyl methyl ether are shown in Figure 2. For both (R)- and (S)-glycidyl methyl ether, attack at the α-position is energetically favourable (by around 3.0 and 5.0 kcal mol\(^{-1}\), respectively), corroborating the experimental stereochemical observations for retention of configuration due to almost exclusive attack at the β-position. To further probe the calculated energy differences between the halide attack at the α- and β-positions, we employed Non-Covalent Interaction (NCI) analysis within the Quantum Theory of Atoms In Molecules (QTAIM) framework. As can be observed in Figure 2b, for attack at the α-position, the incoming halide experiences significantly greater repulsive interactions (green/yellow regions) from the methyl ether chain compared to attack at the β-position. The blue region, clearly visible in the β-attack transition states, highlights attractive non-covalent interactions.

With an explanation for stereochemical retention of the glycidyl methyl ether substrates provided, we turned our attention to the related (R)- and (S)-glycidol substrates and their loss of enantiopurity upon reaction with CO\(_2\) during the cycloaddition reaction. A related aluminium congener of the gallium catalyst used in this study for the cycloaddition of CO\(_2\) and glycidol has previously been reported and shown to convert glycidol in the absence of a co-catalyst.\(^{[15]}\) This previous work presents the involvement of an epoxide–alcohol–water cluster forming a hydrogen bonding network reducing the energy of the cycloaddition transition state and leading to the loss of enantiopurity in the resulting glycidol carbonate product. This mechanism is initiated through the alcohol group binding to the aluminium centre instead of the conventional epoxide oxygen atom of the molecule. With this mechanism in mind, we explored the
equivalent gallium catalysed pathway using the catalyst in this study to explain our experimental findings (Figure 3) that the gallium catalyst system also functions in the absence of halide nucleophile. Initially, binding of the glycidol to the gallium catalyst through the alcohol functionality leads to IC_{OH}. The OH bound glycidol can then undergo a proton transfer to the oxygen atom of the phenoxide moiety of the catalyst structure, leading to the overall neutral alkoxide species and the protonated ligand, IC_{lig-H}. For the gallium congener we have found that this cluster can be stabilised by an additional glycidol molecule. This intermediate is slightly distinct from that previously found for the aluminium catalyst which was observed to involve a water molecule. Thereafter, from IC_{lig-H} the final cyclic carbonate product is formed, FC, through a concerted CO₂ addition-epoxide ring opening-proton shuttle pathway, with an energy span barrier of 35.7 kcal mol⁻¹ from IC_{OH/gly}. The pathway involving H₂O and the gallium catalyst, the same as was reported for the aluminium congener was also studied. This pathway is 8.8 kcal mol⁻¹ higher in energy and is thus less favourable, highlighting important differences between the two related catalysts. It should be noted that the concentration of glycidol, acting as the solvent, will favour the formation of the key glycidol cluster. The experimental reaction in the absence of co-catalyst using the gallium catalyst in this work presented a yield of only 80% after 24 h, and thereafter, a rather slow increase in further conversion. This can be explained through this glycidol hydrogen bonding cluster pathway; at later stages of the reaction where the availability of glycidol is significantly reduced. As a result, access to this mechanistic pathway is limited, thus slowing the reaction down and hindering the overall yield of the reaction. Importantly, these results further exemplify the non-innocent character of these ligands and adds to the literature and understanding of this phenomenon.

**Conclusion**

A range of enantiopure amino acid functionalised cyclic carbonates have been prepared. This has been possible by initial coupling of amino acids with glycidol through a Steglich esterification and thereafter, cyclodeaddition of the epoxide/CO₂ to form the cyclic carbonate using a previously reported gallium-based catalyst system. Importantly, the mechanism of the cycloaddition proceeds with retention of configuration, and this is key to the presented synthetic approach. The cyclic carbonates display a wide range of optical rotation values and therefore make these new compounds potentially useful in future applications where the properties of cyclic carbonates (polar aprotic compounds) are required and where optical properties would be of interest. Meanwhile, they also present potentially useful synthetic intermediates with a high-level of diastereo-purity. The DFT study has confirmed the selectivity during the cycloaddition reaction, which results in the overall retention of configuration from that of the starting epoxide. Meanwhile, the co-catalyst-free mechanism for the conversion of glycidol to glycidol carbonate has also been studied in detail. These results show that the intermediates are slightly distinct from those when the related aluminium congener is applied as catalyst. Furthermore, the reason why longer times are needed to complete the reaction in the absence of the co-catalyst for the gallium catalyst is also explained. This latter result exemplifies the non-innocent character of these ligands through involvement in metal-ligand cooperativity.

**Experimental Section**

**General procedure for the Steglich coupling of a Boc-protected amino acid and glycidol:** Boc-protected amino acid (1.5 equiv., 3.0 mmol), EDC·HCl (0.58 g, 1.5 equiv., 3.0 mmol) and DMAP (24.0 mg, 0.1 equiv., 0.2 mmol) were dissolved in 70 mL of DCM in a round-bottom flask at room temperature. Thereafter, glycidol (0.13 mL, 1.0 equiv., 2.0 mmol) was added to the reaction mixture, which was then left stirring overnight. After this time, the mixture was extracted with aqueous solution of HCl 1.0 M (3 x 50 mL), saturated NaHCO₃ (3 x 50 mL) and brine (2 x 50 mL). The organic phase was dried over MgSO₄ and then concentrated under vacuum to afford the product. This compound was found to be analytically pure and immediately used in the cycloaddition reactions without further need for purification. Yield was based on consumption of the glycidol.

**Typical procedure for the cycloaddition reactions with CO₂:** A high-pressure reactor, equipped with a stirrer bar, was charged with the gallium catalyst (1.7 mg, 0.5 mol%), TBAI co-catalyst (5.2 mg, 2.0 mol%), amino acid functionalised epoxide (0.7 mmol of epoxide) and 1.0 mL MEK. The reactor was then filled with CO₂ to 2.0 bar and partially vented, a procedure that was repeated 3 times, before being finally filled with CO₂ to a pressure of 8.0 bar. The reactor was left stirring overnight at room temperature. At the end of the reaction the reactor was cooled and slowly vented. The crude reaction mixture was purified by column chromatography using DCM as the eluent.

**Computational Study Information:** All DFT calculations undertaken using the ORCA 4.2.1 computational software. Solvation optimizations and analytical frequency calculations were performed at the RI-B97-D3/def2-TZVP level of theory. Final single-point energies and solvation corrections were calculated at RJCOSX-ωB97M-V/def2-TZVPP level of theory. All solvation corrections were calculated using the SMD model with a parameters for hexan-1-ol which has previously been shown to be a good solvation environment for amino acid epoxide solvents. Analytical frequencies were calculated for inclusion of the Zero Point Energy (ZPE) correction and entropic contributions to the free energy term as well as confirming all intermediate were true without any imaginary modes and all transition states had the correct critical frequency of decomposition. Numerical precision integration grids were increased beyond the default settings, to Grid4 for the SCF step and Grid5 for the final energy evaluation. Concentration correction, to account for the low catalyst loading and substrate/solvent environment was applied as a free energy correction based on the Van’t Hoff reaction quotient equation RT ln(Q) where Q accounts for the concentration gradient between the substrate and the catalyst. Graphical visualization and structural analysis performed from the DFT calculations using Avogadro 1.2.0 NCI analysis performed with the...
multiwfn software package,[27] with visualisation in VMD 1.9.4.[28]

X-Ray Diffraction Study Information: Diffraction data were collected using an Oxford Diffraction Supernova diffractometer, equipped with an Atlas CCD area detector and a four-circle kappa goniometer. For the data collection, Mo source with multilayer optics was used. Data integration, scaling, and empirical absorption correction were carried out using the CrysqAlis Program package.[29] The structures were solved using direct methods and refined by Full-Matrix-Least-Squares against F² with SHELXL[30] under OLEX2.[31] The non-hydrogen atoms were refined anisotropically, and hydrogen atoms were placed at idealized positions and refined using the riding model. Full-matrix least-squares refinements were carried out by minimizing Σ[Σ(Fo² − Fc²)]² with the SHELXL weighting scheme and stopped at shift/err < 0.001. The final residual electron density maps showed no remarkable features. Graphics were made with OLEX2 and Mercury.[32] Crystal data, particular details are given in Table S1. Crystallographic data (excluding structure factors) for the structure reported in this paper has been deposited with the Cambridge Crystallographic Data Centre (CCDC) as supplementary publication number: 2320602.[33]

Supporting Information

Additional references cited within the Supporting Information[18-33]

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[28] Deposition Number 3ab(L,5) <url>https://www.ccdc.cam.ac.uk/services/structures/?id=doi:10.1002/ejoc.202400219</url> contains the supplementary crystallographic data for this paper. This data is provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe <url>http://www.ccdc.cam.ac.uk/structures/Access Structures service</url>.
Synthesis of cyclic carbonates bearing amino acid functionality is described. The use of enantiopure amino acids and glycidol, in the initial formation of the substrate, combined with the stereo-retentive mechanism of the cycloaddition with CO\textsubscript{2} furnishes bio-derived cyclic carbonates which display a range of optical activities. A DFT study provides important insights into the operative mechanism.

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