Stereodivergent Carbamate Synthesis by Selective In Situ Trapping of Organic Carbonate Intermediates

Wusheng Guo,[a][b] Victor Laserna,[a][b] Eddy Martin,[a] Eduardo C. Escudero-Adán[a] and Arjan W. Kleij*[a][c]

Abstract: Trans-carbamate structures can be prepared in a diastereoselective approach by a judicious one-pot combination of in situ prepared organic carbonates and suitable amine reagents under appropriate reaction conditions. This unprecedented approach allows for stereo-divergence from a single oxirane substrate with easy access to both cis and trans carbamate isomers with high stereo-selectivity (dr > 19:1). Key to control the diastereo-selective nature of the conversions leading to the trans carbamates is the in situ formation of trans-configured oligo/polycarbonates through Al-catalysis providing the targeted products after aminolysis. The present results demonstrate the valorization of a renewable carbon-based reagent (CO₂) into new valuable scaffolds and an unusual stereo-control exerted through carbonate intermediates. A series of control experiments support the proposed mechanistic rationale towards the trans-carbamate products which is based on the trapping of an in situ formed trans-configured oligo/polycarbonate.

Introduction

Carbamates are ubiquitous scaffolds found in a range of synthetic products of general use in agrochemical and pharmaceutical applications,[1] and in polymer science.[2] Their seemingly privileged incorporation into a wide range of chemical structures has been enabled by methodologies that are conventionally based on the use of toxic reagents including phosgene and its derivatives.[3] Driven by the need for more sustainable approaches towards carbamates, both linear[4] and cyclic organic carbonates[5] have become common reaction partners for amines to afford these widely targeted molecules. The latter category of carbonate structures can be easily obtained through epoxide/CO₂ coupling reactions[6] thus providing a way towards the valorization of a waste combustion product being safe, cheap and readily accessible.

The aminolysis reaction of cyclic organic carbonates (COCs) is well-documented and typically proceeds under mild reaction conditions when using simple alkylamines and mono-substituted COCs. The efficient aminolysis of di- and tri-substituted COCs has been seldom reported and should proceed with retention of configuration (Scheme 1). Cis-carbamates are produced straightforwardly from their respective cis-COCs derived from cyclic oxiranes and CO₂ for which the synthetic methodology has advanced significantly over the years.[6] However, the trans-carbamates cannot be easily accessed as there exists no general method for the formation of trans-COCs from cyclic oxirane precursors and CO₂.[7]

![Scheme 1. Divergent approach towards carbamate synthesis using carbonate intermediates via a sequential \(1 \rightarrow 2; \text{cis} \) or one-pot \(1+2; \text{trans} \) approach. C represents a cycloalkyl skeleton with \(n\) representing the number of C-atoms.]

In order to chase this synthetic challenge, we envisioned that in situ formation of a trans oligo/polycarbonate from cyclic oxiranes and CO₂ could trigger the formation of a trans-carbamate by aminolysis. The use of appropriate catalytic copolymerization conditions would selectively lead to a growing trans-configured oligo-carbonate chain with subsequent aminolysis of the metal-bound oligomer giving rise to trans-carbamates in a one-pot approach (Scheme 1). Here we report on a general, stereo-divergent method for a wide range of functionalized carbonate structures derived from organic carbonate intermediates. Both the cis and trans diastereoisomers of these carbonate scaffolds can be formed with excellent stereo-control, with the family of unusual trans-configured products being generated through a conceptually new approach.

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Supporting information for this article is given via a link at the end of the document.
Results and Discussion

As part of a screening study we first considered the one-pot conversion of cyclopentene oxides (cyclopentene oxide, CPO, 3,4-epoxyfururan, three different primary amines R’-NH₂ (R’ = Cy, Bu, Oc) and CO₂ using Al-catalysis (Table 1).

Suitable nucleophilic additives, including NBu₃Br (Br) and PPNCl (Cl; PPN = bis(triphenylphosphine)iminium) were used as these were previously shown to have the best potential in the formation of polymeric carbonates using aminotriphenolate complexes. It should be noted that cyclohexene oxide (CHO) generally has excellent copolymerization potential, whereas cyclopentene oxides (Y = C or O; Scheme to Table 1) are known to be more challenging substrates. Thus, we envisioned that successful in situ formation of oligomeric carbonates derived from cyclopentene oxides would serve better to validate a more general approach towards trans carbonates.

First, 3,4-epoxyfururan was investigated using both Al-catalysts A and B varying the co-catalyst nature and amount, and the amount of solvent (MEK; methyl ethyl ketone), see entries 1–11 of Table 1. In the absence of Al-catalyst and nucleophile no conversion was noted (entry 1), while the use of complex A or nucleophile (TBAB) alone gave poor carbamate yields of 15% and 9%, respectively (entries 2 and 3). Combination of both catalyst components gave more productive catalysis and afforded the desired carbamate product in much higher yields of up to 76% with excellent stereo-control (dr > 99:1, entry 4). Additional variation of the amount of solvent, changing TBAB for PPNCl or using Al-complex B (entries 5–11) did not further improve these results, and at higher tem-peratures (90°C, entry 10 versus 4) loss of stereo-selectivity was noted.

In the case of cyclopentene oxide as substrate (entries 12–21), similar observations were done although in these reactions Al-complex B combined with PPNCl provided the best compromise in terms of yield and diastereo-selectivity: the results reported in Table 1 show that the use of typical copolymerization conditions (i.e., using Cl as nucleophile, Al-catalyst B, 60°C)[10,11] leads to the preferred formation of the targeted trans-carbamate product with high dr’s of up to 96:4 (entry 14) when n-octylamine is used, and 89:11 in the case of n-butylamine (entry 19). Again, in the absence of nucleophilic additive (as noted with 3,4-epoxyfururan), much lower yields of carbamate are noted (entries 16, 17 and 20) likely to be the result of a relatively slow background reaction based on a carbamate nucleophile derived from the amine and CO₂ (Figure 1).[12] Longer reaction times do not seem to significantly affect the yield of carbamate (cf. entries 16 versus 17) under low-pressure conditions (10 bar).

We therefore tried the carbamate synthesis also under more severe pressure conditions (40 bar, entry 20 Table 1; cf. entry 21) and found only a small increase in the yield of the carbamate derived from CPO. This further confirms that for efficient formation of the trans-carbamate product under these relatively mild reaction conditions the presence of an external nucleophile is required, and offers the major pathway leading to trans-carbamate product through in situ trans-carbonate formation.

Table 1: Screening of suitable catalytic conditions to form the trans-carbamate products from cyclopentene oxides (Y = C, O), Amines R’-NH₂ and CO₂. Nu

<table>
<thead>
<tr>
<th>Entry</th>
<th>Y/R’</th>
<th>Cat [mol%]</th>
<th>Nu [mol%]</th>
<th>T/t [ºC][h]</th>
<th>Yield [%][b]</th>
<th>dr[c]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>O/Cy</td>
<td>–</td>
<td>–</td>
<td>70, 70</td>
<td>&lt;1</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>O/Cy</td>
<td>A, 0.5</td>
<td>–</td>
<td>70, 70</td>
<td>15</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>3</td>
<td>O/Cy</td>
<td>–</td>
<td>Br, 2.0</td>
<td>70, 70</td>
<td>36:64</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>O/Cy</td>
<td>A, 0.5</td>
<td>Br, 2.0</td>
<td>70, 70</td>
<td>76:9</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>5</td>
<td>O/Cy</td>
<td>A, 0.5</td>
<td>Cl, 2.0</td>
<td>70, 70</td>
<td>79:21</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>O/Cy</td>
<td>A, 0.5</td>
<td>Cl, 2.0</td>
<td>70, 70</td>
<td>63:37</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>O/Cy</td>
<td>A, 0.5</td>
<td>Cl, 1.0</td>
<td>70, 70</td>
<td>91:9</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>O/Cy</td>
<td>B, 2.0</td>
<td>Cl, 1.0</td>
<td>70, 70</td>
<td>73:27</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>O/Cy</td>
<td>A, 0.5</td>
<td>Br, 2.0</td>
<td>70, 70</td>
<td>70:30</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>O/Cy</td>
<td>A, 0.5</td>
<td>Br, 2.0</td>
<td>70, 70</td>
<td>27:73</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>O/Cy</td>
<td>A, 0.5</td>
<td>Br, 2.0</td>
<td>70, 70</td>
<td>&gt;99:1</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>O/Cy</td>
<td>A, 0.5</td>
<td>Br, 2.0</td>
<td>70, 70</td>
<td>72:28</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>O/Cy</td>
<td>B, 0.5</td>
<td>Cl, 1.0</td>
<td>60, 24</td>
<td>85:15</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>O/Cy</td>
<td>B, 2.0</td>
<td>Cl, 2.0</td>
<td>60, 60</td>
<td>96:4</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>O/Cy</td>
<td>B, 2.0</td>
<td>Cl, 2.0</td>
<td>70, 60</td>
<td>83:17</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>O/Cy</td>
<td>–</td>
<td>–</td>
<td>60, 24</td>
<td>&gt;99:1</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>O/Cy</td>
<td>–</td>
<td>–</td>
<td>60, 60</td>
<td>&gt;99:1</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>C/Bu</td>
<td>A, 0.5</td>
<td>Br, 2.0</td>
<td>70, 70</td>
<td>57:43</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>C/Bu</td>
<td>B, 2.0</td>
<td>Cl, 2.0</td>
<td>60, 24</td>
<td>89:11</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>C/Bu</td>
<td>–</td>
<td>–</td>
<td>60, 24</td>
<td>&gt;99:1</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>C/Bu</td>
<td>B, 2.0</td>
<td>–</td>
<td>60, 24</td>
<td>11:89:1</td>
<td></td>
</tr>
</tbody>
</table>

[a] Conditions: epoxide (4 mmol), R’-NH₂ (1.2 equiv; R = Oc, Cy; 4 equiv.; R = Bu) using 0.5 mL MEK (methyl ethyl ketone), pCO₂ (10 bar). b] NMR yields using mesitylene as internal standard. c] Determined by ¹H NMR. d] Using 1.0 mL of MEK. e] Isolated yields. f] Using 2.0 mL of MEK. g] Neat conditions. h] Reaction carried out at 40 bar.
Similar behavior in carbamate formation was also noted for one other cyclic and one acyclic epoxide when they were probed under similar temperature/pressure conditions (see Tables S1 and S2). In these latter cases good to excellent selectivity for the trans-carbamates ($dr > 99:1$) was noted validating further the current approach using an external nucleophilic additive.

Figure 1. Potential background reaction to form a trans carbamate through the formation of a carbamate nucleophile from an amine and CO₂.

Having established a set of suitable reaction conditions leading selectively to trans-configured carbamates, we then investigated the scope in more detail (1–15, see Figure 2). As reference materials for the assignment of the trans-products 1b–15b, the cis-carbamates 1a–15a were separately prepared by prior formation of their cis cyclic carbonates derived from the respective epoxides under appropriate conditions.[6d] The aminolysis reaction was then carried out by addition of the appropriate amine and details are reported in the Supporting Information. In general, the stereo-control towards the trans-carbamates 1b–15b is excellent providing the compounds with $dr$'s of $\geq 93:7$ (apart from 4b and 13b; $dr = 89:11$ and 77:23, respectively). The approach is applicable towards various five- and six-membered cyclic and also acyclic epoxides (cis-2-butenol oxide, cf. formation of 12b and 13b) without compromising significantly the diastereo-selectivity of the reaction. Various functionalized amines are tolerated bearing allyl (2b and 15b), cyclopropyl (8b), thiophenelyl (9b), and pyridyl (11b) groups whereas the use of more functional epoxides allows for the incorporation of potentially useful furan (3b, 5b, 7b and 8b) or cyclohexenyl (2b and 14b) fragments.

The molecular structures for carbamates 1–15 (both diastereoisomers) were fully supported by 1D/2D NMR and IR spectroscopic techniques, and HRMS; for 5a and 5b the X-ray molecular structures (see Figure 3 and Supporting Information)[13] were determined and further supported their cis and trans assignment in line with the spectroscopic data. The isolated yields for the cis-carbamates 1a–15a are generally higher than those obtained for the trans diastereoisomers 1b–15; this suggest that the one-pot approach with the amine present at the early stage of the reaction may, as expected, slow down overall kinetics as the amine may compete with epoxide coordination to the Al-center in complexes A or B.

Figure 2. Scope for the formation of the trans-carbamates 1b–15b. All reactions were carried out on a 4 mmol scale using 0.5 mL MEK, $p(CO₂) = 10$ bar, cat/co-cat amounts are in mol%, and AlCl₃ = complex A; AlMe₃ = complex B. All $dr$ values were determined by $^1$H NMR.

Figure 3. X-ray molecular structures determined for cis-5a (top) and trans-5b (below) together with part of the numbering scheme.
The isolated yields for the cis-carbamates 1a–15a are generally higher than those obtained for the trans diastereoisomers 1b–15b; this suggest that the one-pot approach with the amine present at the early stage of the reaction may, as expected, slow down overall kinetics as the amine may compete with epoxide coordination to the Al-center in complexes A or B. In order to investigate the mechanism of trans-carbamate formation, several additional experiments were conducted (see Scheme 2).

First, an isolated sample of a copolymer based on CHO/CO₂ (cf., path 3, Scheme 2) was subjected to the general reaction conditions of the one-pot carbamate formation (i.e., in the presence of [Al] complex A, TBAB, MEK, 70°C, 18 h) but the presence of the n-butyl amine did not provoke any observable aminolysis between 25-80°C as evidenced by ¹H NMR comparative studies (Supporting Information). Then we decided to freshly prepare the CHO/CO₂ copolymer in the absence of the amine using [Al] catalyst A (0.5 mol%) and TBAB (2.5 mol%) at 70°C for 24 h; at this stage ¹H NMR analysis showed virtually full conversion into a fully alternating poly(cyclohexene)carbone (PCHC, 99% polymer selectivity) with trace amount (1%) of trans-cyclohexene carbonate (trans-CHC). This copolymer (without applying the usual work up and with the metal likely still bound to the polymer)[15] was treated with 3 equiv of n-butyl amine for 10 h at 70°C and then again analysed by ¹H NMR. Fortunately, conversion (65%) to the carbamate 1b (dr > 99:1) was noted with the remaining 35% consisting of a mixture of 85% PCHC and 15% of trans-CHC (i.e., a clear increase in the cyclic carbonate/polymer ratio is noted). The relative increase in trans-CHC can be explained by a depolymerisation of the metal-free copolymer[16] when adding the amine which may compete for coordination to the Al-center (Scheme 2, pathway 1). The decordinated polymer then leads to trans-CHC by a relatively fast alkoxide back-biting process towards the trans-carbonate and in situ aminolysis to give trans-configured 1b as product.

A similar polymer degradation/aminolysis sequence (Scheme 2, pathway 1) seems plausible for the acyclic cis-2-butene oxide case. Control experiments were performed in the absence of amine reagent following the reaction conditions reported for 12b-trans and 13b-trans (Figure 2). The ¹H NMR analysis showed the mixture to contain only the cyclic carbonate product with a trans selectivity of up to 83% which is in reasonable agreement with the reported dr values for the two carbamate products derived from cis-2-butene oxide. Copolymers derived from cis-2-butene oxide have been reported recently by Darensbourg et al.[9c] showing that polymer-selective bifunctional M(salen) catalysts (M = Co, Cr) give virtually only trans-carbonate upon alkoxide backbiting; this suggests that the trans-carbamates derived from cis-2-butene oxide also originate from pre-polymer formation.

However, the diastereoselective formation of trans-carbamates using substrates such as CPO and 3,4-epoxyfuran cannot be explained via pathway 1 (Scheme 2). The group of Darensbourg has demonstrated that such a pathway is thermodynamically not feasible due to a high ring strain present in this trans cyclic carbonate, and therefore preferably results in degradation towards the starting epoxide and CO₂. Under high pressure conditions, carbonate rather than alkoxide backbiting is facilitated resulting in exclusive cis-carbonate formation[10] excluding trans-carbamate formation through a trans cyclic carbonate intermediate.

We have recently shown by a combined experimental/computational approach that the coupling between limonene oxide (LO; Scheme 3) and CO₂ gives exclusive...
formation of a fully alternating copolymer with a relative high barrier for (trans) cyclic carbonate formation.\cite{10} In this Al-mediated polymerization process the CO₂ insertion step was shown to be rate-limiting, suggesting that possible polymer degradation would have to proceed through alkoxide back-biting; both metal-bound and metal-free oligo/polycarbonates based on LO, however, are kinetically incompetent to give a trans cyclic carbonate via depolymerisation. This behaviour is reminiscent of copolymers derived from CPO which also cannot produce trans-COC through alkoxide back-biting. Therefore, another degradation process (i.e., pathway 2 in Scheme 2) leading to formal trans-carbamate formation was considered.

In order to investigate this in more detail, we envisioned that carbamate formation from tri-substituted cyclic oxiranes such as LO (Scheme 3) could serve to mimic the reactivity of CPO and related cyclic oxiranes. When we subjected both 16 (methyl-cyclohexene oxide) and 17 (cis-LO) to reaction conditions typically used for the formation of carbamates 1b–15b, we only observed the formation of trans-carbamates 18–20. The origin of the trans-selectivity is ascribed to an attack of the amine on the oligo/polycarbonate itself being either metal-bound (pathway 2a) or metal-devoid (pathway 2b) through aminolysis at a carbonate linkage retaining thus the carbamate product.\cite{16}

![Scheme 3. Carbamate formation reactions using tri-substituted epoxides as reagents. Conditions: 4 mmol scale, 0.5 mL MEK, p(CO₂) = 10 bar, cat/co-cat amounts in mol%. All δr values were determined by ¹H NMR.](image)

Conclusions

In summary, we here present an unprecedented catalytic approach towards trans-configured carbamates by selectively trapping of trans-carbonate intermediates with amine reagents. Supporting experiments have revealed that either in situ aminolysis of trans cyclic carbonates obtained through polycarbonate back-biting or aminolysis of in situ prepared trans-configured (metal-bound) oligo/polycarbonates is a new approach to exert a high degree of diastereo-selective control. Such a control is a new tool in the synthesis of CO₂-derived fine chemicals showing potential in other types of synthetic transformations focusing on this renewable C₁ building block.

**Experimental Section**

**Typical procedure for the formation of the cis-carbamates**

The cyclic carbonates were first synthesized from carbon dioxide according to reported literature procedures\cite{6,d,17} using Al(III) amino-triphenol complex (AlCl₃) as catalyst. After that, the respective carbonate (1 mmol, 1 eq.) and the corresponding amine (1.2 eq. for non-volatile amines; 4 eq. for volatile amines) were charged into a 5 mL round bottom flask and the reaction mixture was stirred at 50-70 °C for an appropriate time frame. After the reaction, the analytically pure carbamate product was isolated by flash chromatography. The Supporting Information contains all details regarding these cis-carbamates.

**Typical procedure for the formation of the trans-carbamates**

The respective epoxide (4 mmol, 1 eq.), Al-complex (AlCl₃, 0.5–2.0%; R = Cl or Me), amine (1.2 eq. for non-volatile amines; 3 eq. for volatile amines), TBAB/PPNCl and MEK (1 mL) were charged into a 30 mL stainless steel autoclave. The autoclave was then subjected to three cycles of pressurization and depressurization with carbon dioxide (0.5 MPa, 5 bar), before final stabilization to a pressure of 1 MPa (10 bar). The autoclave was sealed and heated to 60–90 °C and left stirring for an appropriate time frame. Then, the autoclave was cooled to rt and carefully depressurized. The analytically pure carbamate product was then isolated by flash chromatography. The Supporting Information contains all details regarding these trans-carbamates.

**Acknowledgements**

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**Keywords:** aluminium • carbamates • carbon dioxide • diastereoselective synthesis • organic carbones


Under the reaction conditions, the amine may react with CO₂ to form a carbamate species which can ring-open the epoxide to form the trans-cyclopropane alkene in very low yield. Thus, this is a much slower reaction than the ones studied here with added nucleophiles. This background reaction proceeds somewhat better under much harsher pressure conditions (i.e., 50 bar) with concomitant formation of substantial aminoalcohol side-product; see: F. Kojima, T. Aida, S. Inoue, J. Am. Chem. Soc. 1986, 108, 391-395. Apparently, under the mild conditions reported here the formation of a carbamate nucleophile derived from the amine and CO₂ is either catalytically incompetent or only formed in very low concentration. The use of secondary amine reagents leads only to amino alcohol formation, i.e. aminolysis of the oxirane substrate occurs.

For more details: CCDC-1039441 and CCDC-1432217.


Note that the regio-selectivity for the formation of 18b is different from the ones observed for trans 19 and 20. This is likely a function of the amine reagent as the formation of other carbamates from methylcyclohexene oxides using p-methoxy-benzylamine under similar reaction conditions was shown to give a regio-isomeric mixture (combined yield 32%; regio-selectivity 56:42). See for full details the Supporting Information.

cuts both ways: stereodivergence in carbamate synthesis has been achieved through a selective trapping of carbonate intermediates under Al-catalysis using cyclic oxiranes, amines and CO$_2$ as reaction partners. Both trans and cis carbamates were produced with dr values >19:1. Mechanistic investigations support the view of a key trans-configured oligo/polycarbonate intermediate controlling the stereo-selectivity in this conceptually new catalytic CO$_2$ conversion approach.

- operationally simple, under mild Al-catalysis
- dr > 19:1, isolated yield up to 82%
- 18 examples based on (a)cyclic oxiranes
- in situ trapping of trans-carbonate intermediate

stereodivergent carbamate synthesis by selective in situ trapping of organic carbonate intermediates

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