FULL PAPER

Highly Regio-Selective Organocatalytic formation of Carbamates from Substituted Cyclic Carbonates

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Abstract: A highly regio-selective catalytic approach has been developed towards carbamates derived from cyclic organic carbonates by reaction of the latter with amine reagents under organo-catalytic control. For various combinations of carbonate and amine substrates, an organocatalyst (TBD: triazabicyclodecene) was used to increase the reaction kinetics while exerting excellent regio-selective control. The current method is the first general approach towards the control over the regio-selectivity of this reaction using a wide variety of easily accessed substituted organic carbonates.

Introduction

The use of carbon dioxide, a renewable carbon feed stock, in synthetic chemistry has witnessed a tremendous development in the last decade.[1] Common awareness has driven the scientific communities to develop new technologies for CO_2 storage and conversion, and undoubtedly catalysis has now become one of the key enabling strategies to access chemicals from this cheap and readily available carbon resource addressing the kinetic inertness of this small molecule.[2] There exist also challenges associated with its high thermodynamic stability, and two important strategies for efficient conversion of CO_2 have become available: (1) the direct use of high-energy co-reactants to counter-balance the unfavorable thermodynamic stability of CO_2, and (2) the use of renewable wind, solar and thermal energy that can accommodate the formation of suitable reducing agents such as H_2 useful for sustainable CO_2 conversion.[3]

The use of small strained heterocycles, including epoxides and oxetanes, as co-reactants for CO_2 conversion has been exploited in the synthesis of cyclic[4] and poly-carbonates,[5] and this field has been developed to a high level of sophistication. In particular, cyclic carbonates are among the most popular class of compounds being readily derived from CO_2 as they have commercial potential.[6] These cyclic carbonates may have various substitutions represented by simple mono-[7] up to more complex 4,5-di[8] and 4,4´,5-tri-functionalized[9] scaffolds (Figure 1 for numbering). The latter two categories are considered to be challenging to prepare using (catalytic) CO_2/epoxide coupling chemistry.

We have become interested in the post-modification of these cyclic carbonates as they represent interesting and modular building blocks in organic synthesis.[10] Cyclic organic carbonates are amenable towards ring-opening by suitable nucleophiles, and their reaction with amines (aminolysis) has been used to prepare their corresponding carbamates,[11] which are interesting pharmaceutical scaffolds.[12] A recent and rational catalytic screening study by Andrioletti[13] provided valuable insight into the type of catalyst and reaction conditions needed for high conversion in the aminolysis reaction of mono-substituted cyclic carbonates. Although this organocatalysis approach proved to be highly efficient, a general noted drawback was the lack of regio-control in the aminolysis step, *i.e.* mixtures of two regio-isomeric carbamates were formed (Figure 1).

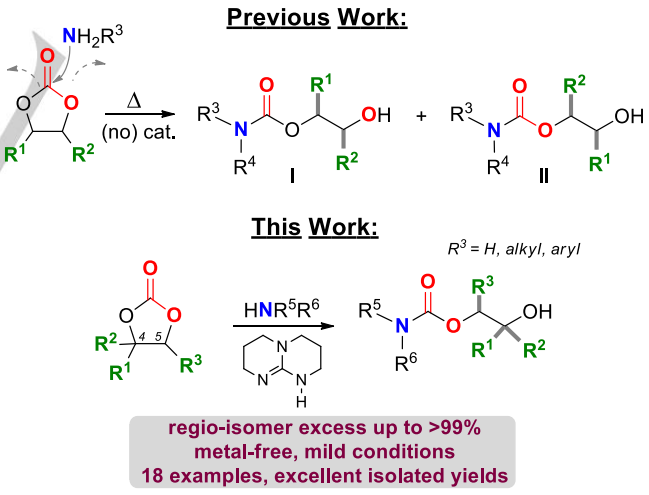

Figure 1. Regio-isomer formation in the aminolysis of cyclic carbonates (Previous Work; upper part, cf. **I** and **II**) and the current organocatalytic, regio-selective formation (This Work; lower part).

As far as we know, there is only one report that shows complete regio-control in the (non-catalyzed) aminolysis of an α-trifluoromethyl-substituted carbonate[14a] but examples of such exquisite selectivity remain extremely limited. The regio-selective ring-opening of cyclic carbonates is indeed an important feature; recently the interest in the formation of more sustainable, non-

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isocyanate based polyurethanes (NIPUs) using bis-cyclic carbonates as intermediates and diamines as nucleophilic reagents has grown significantly.[15] In order to be able to control the polyurethane properties through the formation of a regio-regular polymer backbone, new synthetic methodology addressing the regio-selectivity in the aminolysis step is warranted. Thus, we set out to investigate this aspect in more detail in order to unravel the key features that help to increase regio-control. Inspired by the use of **TBD** (triazabicyclodecene) as an efficient proton-relay catalyst in organic transformations,[10b,13,16] we found that the combination of substituted organic carbonates and amine reagents in the presence of **TBD** as catalyst promotes the regio-selective cleavage of one of the C–O bonds. The presence of this organocatalyst also significantly enhances the overall kinetics, and gives access to a series of regio-pure carbamate structures in high isolated yields. This newly developed procedure towards these attractive scaffolds may hence provide a useful entry into regio-regular urethane based polymers.

Results and Discussion

We recently described the first effective route towards N-aryl carbamates by treatment of mono-substituted cyclic carbonates with aromatic amines in the presence of **TBD** as organocatalyst.[10b] Computational studies revealed a ternary complex as intermediate involving the catalyst, cyclic carbonate and amine reagent interacting via H-bonding. Further, a subtle proton-shuttling mechanism between the three components allowed to deliver the carbamate target under mild reaction conditions. We envisioned that an appropriate substitution of the cyclic carbonate substrate could enforce the **TBD** to direct the amine nucleophile to attack from the least hindered face resulting in site-selective C–O bond cleavage, *i.e.* regio-selective formation of the carbamate product (Figure 2).

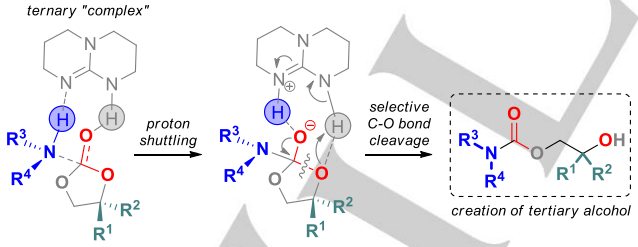
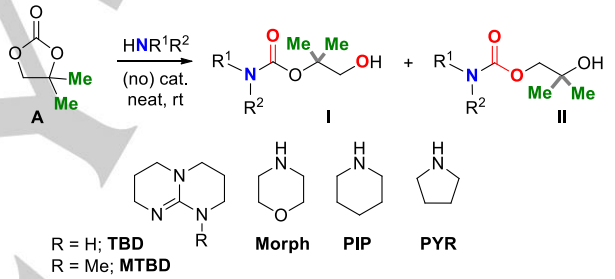


Figure 2. Proposed regio-selective C–O bond breaking in *gem*-disubstituted cyclic carbonates by TBD using amine reagents.

With this idea in mind we selected a gem-disubstituted cyclic carbonate (Table 1, **A**) as substrate to challenge this hypothesis and treated **A** with three different amines (morpholine, piperidine and pyrrolidine) in the presence/absence of **TBD** (entries 1–6). These aminolysis reactions, in the absence of **TBD**, typically lead to mixtures of carbamates **I** (major one) and **II** having a primary and tertiary alcohol fragment, respectively (entries 1, 3 and 5). Remarkably, when **TBD** is added as a catalyst, exclusive formation of carbamate type **II** is observed (regio-selectivity >99:1) in all three cases (entries 2, 3, 5 and 7). Whereas the catalyst-free reactions require longer time and larger excess of the amine reagent, the **TBD**-mediated processes are significantly faster in the presence of only two equivalents of the amine reagent; the reaction carried out with morpholine as amine was already finished in 0.5 h (entry 3). The catalytic performance of an N-methyl protected version of **TBD** (**MTBD**, entry 8) was significantly inferior (*cf.*, entry 3) suggesting that both unprotected N-atoms of the TBD structure are relevant to maintain high reactivity and regio-selectivity. We also tested a tertiary amine (entry 9; no conversion) and an aromatic amine (entry 10) as reaction partners, giving in both cases poorer results in terms of reactivity and regio-control. Therefore, we restricted our further studies to the use of primary and secondary alkyl-amines.

Table 1. Screening study towards the carbamate regio-isomer formation **I** and **II** using the geminal dimethyl-substituted cyclic carbonate **A** andvarious amines as substrates, and TBD as catalyst.[a]



Entry	Cat.	Amine/eq.	t [h]	Conv. [%][b]	I [%][b]	II [%][b]
1	–	Morph, 6.0	18	>99	63	37
2	**TBD**	Morph, 2.0	6	>99	<1	>99
3	**TBD**	Morph, 2.0	0.5	>99	<1	>99
4	–	PIP, 6.0	18	>99	60	40
5	**TBD**	PIP, 2.0	6	>99	<1	>99
6	–	PYR, 6.0	18	>99	46	54
7	**TBD**	PYR, 2.0	6	>99	<1	>99
8	**MTBD**	Morph, 2.0	6	85	17	83
9	**TBD**	NEt_3, 2.0	6	<1	–	–
10	**TBD**	Aniline, 2.0	6	40	84	16

[a] General conditions: 1.0 mmol **A**, 20 mol% TBD, neat, amine quantity indicated. [b] Conversion and percentage of isomers **I** and **II** determined by ^{1}H NMR ($CDCl_3$).

The kinetic profiles of the catalyst-free process and the **TBD**-mediated aminolysis of carbonate **A** by morpholine were then studied in more detail (see Figure 3). From the conversion profiles

it is clear that the TBD mediated aminolysis reaction (5 mol%, neat conditions) is much faster and exclusively delivers the carbamate **II** whereas in the absence of **TBD** the other regio-siomer **I** is formed in excess (**I**:**II** = 63:37). We also checked the regio-selectivities by ^{1}H NMR throughout the entire time span of these studies (0–24 h), and found that for both the non-catalyzed and **TBD**-catalyzed processes these do not change with time.

Inspired by these results we decided to investigate the scope of reaction partners in more detail focusing on the use of various *gem*-disubstituted cyclic carbonates and various amines (Figure 4) using **TBD** as catalyst. The morpholine based carbamate **1** was isolated in high yield (95%, isomer **II**), whereas the other isomer (**I**, carbamate **2**) was conveniently separated by column chromatography (after 18 h; in the absence of **TBD**) and isolated in an appreciable yield of 63%. These examples provided a reference for the synthesis and analysis of other carbamates (**3–10**) derived from different *gem*-disubstituted cyclic carbonates and amine reagents.

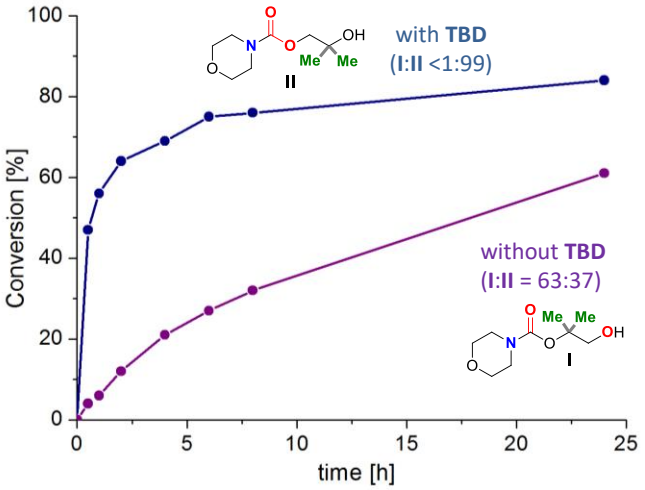


Figure 3. Kinetic profiles for the aminolysis of cyclic carbonate **A** by morpholine in the absence/presence of **TBD**. Conditions: carbonate **A** (1.0 mmol), morpholine (1.0 mmol), **TBD** (5.0 mol%), neat, rt.

The TBD-mediated aminolysis of carbonate **A** and piperidine and pyrrolidine provided the carbamate products **3** (90%) and **4** (97%) in excellent yields and with high regio-selectivity. Other *gem*-disubstituted carbonates were also probed to examine the generality of the approach. The combination of a vinyl and phenyl group at the 4–position of the cyclic carbonate precursor also provided smooth access to various carbamate products of type **II** in high yield (**5–7**; 85-92%) incorporating useful olefin groups with post-modification potential. The carbamates **8–10** obtained from a *gem*-methyl-vinyl-substituted carbonate were also isolated in high yields and under excellent regio-control.

In order to test whether the *gem*-disubstitution in the carbonate precursor plays an important role, we probed the aminolysis of a *syn*-methyl-phenyl based cyclic carbonate by piperidine in the presence of **TBD** (*cf.*, synthesis of **11**). Interestingly, a much lower regio-selectivity was noted (**II**:**I** = 66:34). Thus, it seems that under these conditions no exclusive formation of a single ternary complex comprising TBD, the carbonate and the amine reagent is possible. The *syn*-disubstitution here does not provide enough steric differentiation between both sides of the carbonate scaffold to induce H-bonding with the TBD/amine scaffolds on the least hindered face.

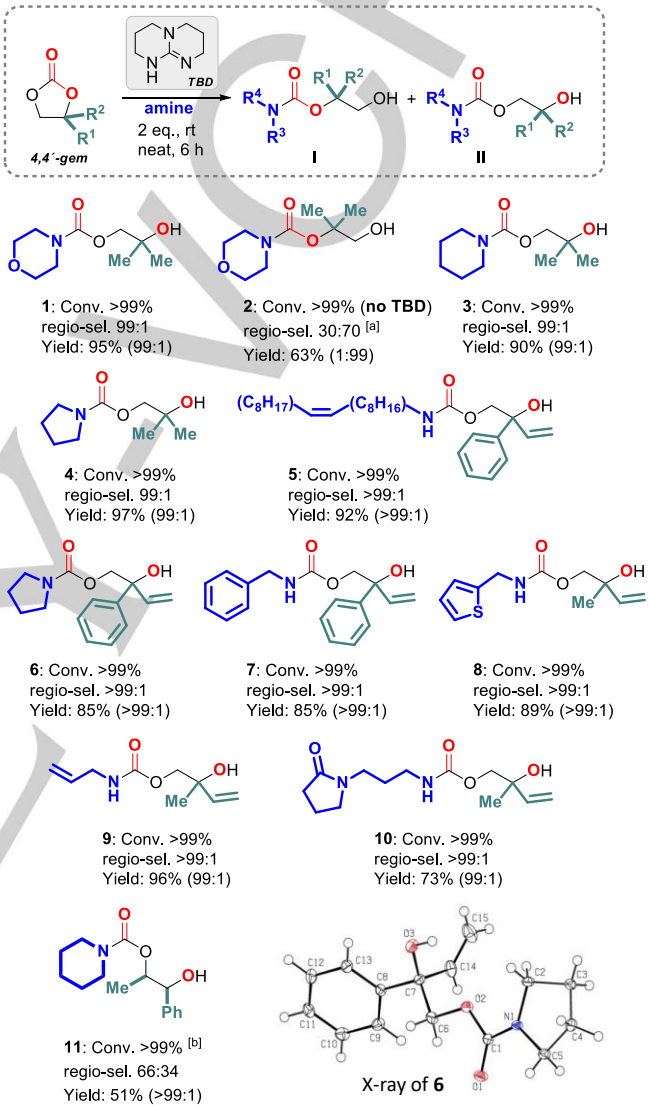


Figure 4. Regio-selective carbamate formation from *gem*-disubstituted cyclic carbonates using **TBD** (20 mol%) as catalyst. Conditions: carbonate (1.0 mmol), amine (2.0 mmol), neat, rt. In brackets the regio-isomeric excess (**II:I**) of the isolated product (in all cases isomer **II**; except for **2**; isomer **I**) measured by ^{1}H NMR spectroscopy and supported by 1D/2D NMR experiments. [a] The reaction time was 18 h, 6 equiv. of morpholine used. [b] The reaction time was 14 h.

Fortunately, we were able to get unambiguous confirmation for the formation of the carbamate type **II** by single crystal X-ray diffraction studies carried out for compound **6** (Figure 4, below). The molecular structure has the proposed connectivity pattern

with a diagnostic tertiary alcohol group as anticipated from the 1D/2D NMR spectroscopic analyses carried out for all the isolated carbamate species **1–10** (see the Supporting Information for more details).

Motivated by the results obtained for the **TBD**-catalysed aminolysis of *gem*-disusbtituted cyclic carbonates, we then examined the use of more complex carbonate substitutions including 4,4´,5-*tri* (see Figure 5) and 4,4´,5,5´-*tetra*-substituted substrates (Figure 6). We first probed 1-methyl-cyclohexene carbonate (*cf.*, syntheses of carbamates **12** and **13**) as substrate and performing the aminolysis using 2-aminomethyl-pyridine and propargylic amine, respectively, in the presence of **TBD**. We were pleased to find that installation of a third substitution on the carbonate precursor also provides clean access to one regio-isomeric carbamate of type **II** in good yields and excellent regio-selectivities. The use of other trisubstituted cyclic carbonates

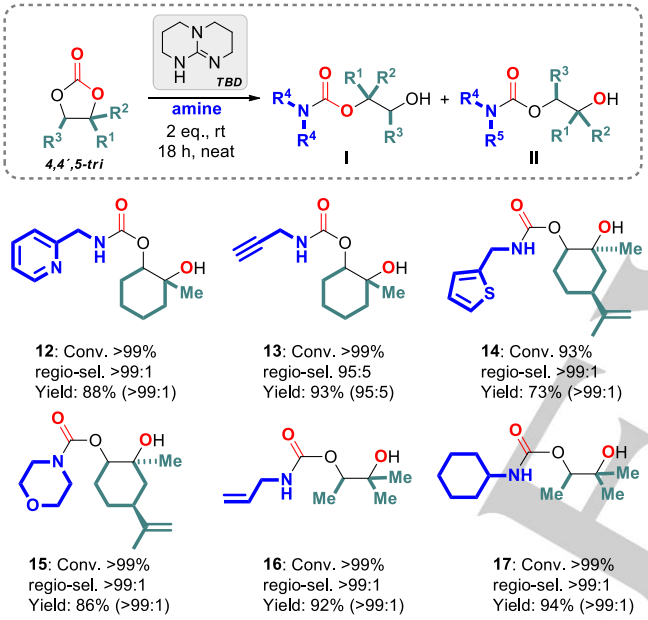


Figure 5. Regio-selective formation of carbamate **12–17** derived from 4,4´,5-trisubstituted cyclic carbonates using **TBD** as catalyst. Conditions: carbonate (0.5 mmol), amine (1.0 mmol), **TBD** (20 mol%), neat, rt. In brackets the regio-isomeric excess (**II:I**) of the isolated product measured by ^{1}H NMR spectroscopy and supported by 1D/2D NMR experiments.

(*i.e.*, limonene carbonate[17] and a trimethyl-substituted one; *cf.*, syntheses of carbamates **14–17**) gave similar results producing the targeted molecules in high isolated yields and regio-selectivity. Apparently, also here the catalytic system is able to direct the C–O bond cleavage process with high accuracy despite a smaller difference in steric impediment of both faces compared to the *gem*-disubstituted carbonate substrates.

Finally, tetra-substituted carbonate precursors were studied as potential reaction partners and treated with allyl amine under TBD catalysis with the aim to produce carbamates **18** and **19b** (Figure 6). Although superb regio-control towards the formation of the carbamate type **II** product was again noted, the isolation turned out to be difficult by chromatographic methods resulting in low isolated yields. In these reactions we observed about 10% diol formation (attributed to hydrolysis of the carbonate precursor by adventitious water),[18] and both the diol as well as the carbonate precursor have very similar R_f values compared to the carbamate product. Longer reaction times indeed gave higher conversion of the carbonate precursor but unfortunately an increasing amount of diol side-product was noted. To our delight, the molecular structure of carbamate **18** could also be confirmed by X-ray analysis, showing unambiguously the preference of formation of carbamate type **II**.

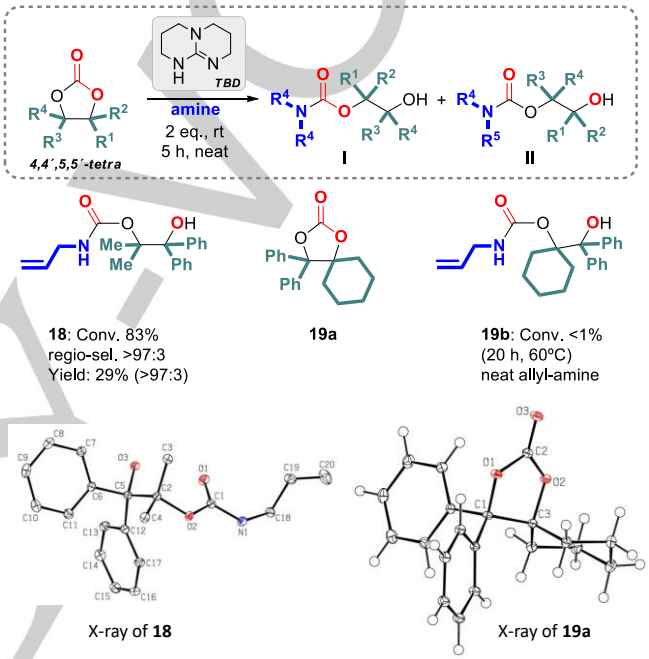
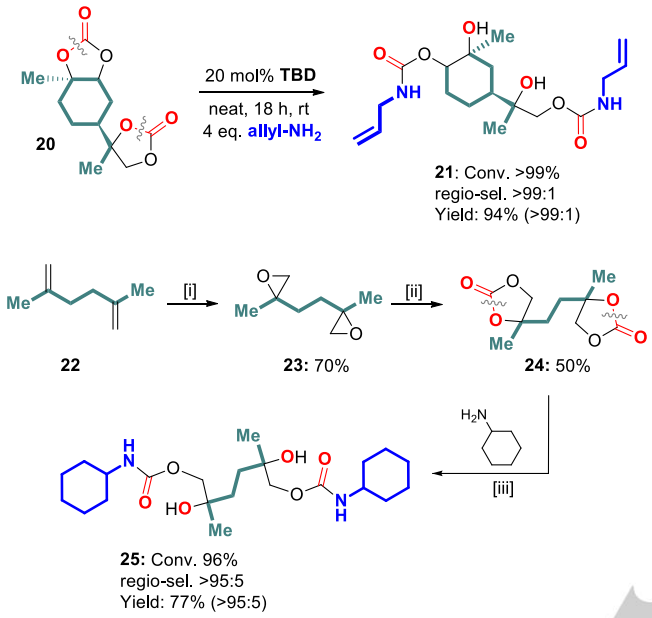


Figure 6. Regio-selective formation of carbamate **18** and **19b** derived from 4,4´,5,5´-tetrasubstituted cyclic carbonates using **TBD** as catalyst. Conditions: carbonate (1.0 mmol), amine (2.0 mmol), **TBD** (20 mol%), neat, rt. In brackets the regio-isomeric excess (**II:I**) of **18** measured by ^{1}H NMR spectroscopy and supported by 1D/2D NMR experiments.

The use of tetrasubstituted cyclic carbonate **19a** (Figure 6) did not result in any observable conversion into carbamate **19b** not even at elevated temperature and in the presence of a large excess of allyl amine. Inspection of the molecular structure determined by X-ray analysis shows the steric impediment around the carbonate fragement to be a likely cause for this sluggish reactivity as the formation of the necessary ternary complex (see Figure 2) is not feasible.

In order to further assess the applicability of this regio-selective carbamate formation in oligourethane formation, the bis-cyclic carbonate of limonene **20** (*trans*-isomer)[9a,19] was treated with allyl amine under similar conditions as reported for the *gem*-disubstituted and trisubstituted cyclic carbonates, and this gave the regio-isomerically pure bis-carbamate **21** in high yield (94%, Scheme 1). The dicarbamate **25** was prepared in 77% yield under

high regio-control (**II**: **I** >95:5) using cyclohexyl amine and the bis-carbonate **24**: the latter was simply prepared from bis-olefin **22** in two steps. The regio-controlled formation of both these di-carbamates **21** and **25** may hold promise for the development of regio-regular polyurethanes.



Scheme 1. Synthesis of bis-carbamate **21** and **25** derived from bis-carbonates **20** and **24**, respectively. Conditions/reagents used: [i] 2.5 eq. m-CPBA, CH_2Cl_2, 0ºC, 3 h. [ii] 0.5 mol% tannic acid, 10 mol% TBAB, 80ºC, 2.5 MPa, 18 h. [iii] 4 eq $CyNH_2$, 36 h, neat. In brackets the regio-isomeric excess (**II:I**) of **21** and **25** measured by ^{1}H NMR spectroscopy and supported by 1D/2D NMR experiments.

Conclusions

In summary, we here describe the first general, catalytic approach towards the regio-selective aminolysis of cyclic carbonates yielding synthetically valuable carbamate scaffolds. The procedure leading to these latter compounds combines high regio-control, high isolated yields and operational simplicity using readily available starting materials. Also, additional experiments have disclosed potential towards the regio-selective formation of oligourethanes, a feature that can be of use in the preparation of regio-regular polymers and fine-tuning the materials properties.

Experimental Section

Typical catalytic experiment

A mixture of cyclic carbonate **A** (116.12 mg, 1.0 mmol),**TBD** (22.84 mg, 20 mol%) and morpholine (174.24 mg, 2.0 mmol) was stirred for 6 h at room temperature. Then the reaction mixture was purified by flash chromatography column using a mixture of EtOAc:hexane (2:1; v/v) affording the desired compound **1** (193 mg, 0.95 mmol) in 95% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.02 (s, 2H, OCH_2C), 3.64-3.73 (m, 4H, CH_2CH_2N), 3.47-3.54 (m, 4H, $-OCH_2CH_2$), 2.23 (s, 1H, OH), 1.25 (s, 6H, CH_3); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 155.82, 73.50, 70.31, 66.64, 44.36, 26.38; IR (neat): 3437 cm^{-1} (OH), 1679 cm^{-1} (C=O); HRMS (ESI+; MeOH): *m/z* calcd. $(C_9H_{17}NO_4Na)$ 226.1050 $(M+Na)^+$; found: 226.1052.

The data for all the other prepared carbamates (and cyclic carbonate precursors) can be found in the Supporting Information.

Crystallographic Studies

The measured crystal was stable under atmospheric conditions; nevertheless it was treated under inert conditions immersed in perfluoro-polyether as protecting oil for manipulation. Data Collection: measurements were made on a Bruker-Nonius diffractometer equipped with an APPEX II 4K CCD area detector, a FR591 rotating anode with Mo Kα radiation, Montel mirrors and a Kryoflex low temperature device (T = −173 °C). Full-sphere data collection was used with ω and φ scans. Programs used: Data collection Apex2 V2011.3 (Bruker-Nonius 2008), data reduction Saint+Version 7.60A (Bruker AXS 2008) and absorption correction SADABS V. 2008−1 (2008). Structure Solution: SHELXTL Version 6.10 (Sheldrick, 2000) was used.[20] Structure Refinement: SHELXTL-97-UNIX VERSION.

Crystal data for carbamate **6**: $C_{15}H_{19}NO_3$, M_r = 261.31, monoclinic, *C*2/c, *a* = 29.6567(12) Å, *b* = 5.7377(2) Å, *c* = 17.2274(7) Å, α = 90º, β = 114.1204(10)º, γ = 90º, *V* = 2675.49(18) Å^3, *Z* = 8, ρ = 1.297 mg·M^{-3}, μ = 0.090 mm^{-1}, λ = 0.71073 Å, *T* = 100(2) K, *F*(000) = 1120, crystal size = 0.40 × 0.20 × 0.20 mm, θ(min) = 1.505°, θ(max) = 32.06°, 18631 reflections collected, 4466 reflections unique (R_{int} = 0.0273), GoF = 1.080, R_1 = 0.0490 and wR_2 = 0.1327 [$I > 2\sigma(I)$], R_1 = 0.0531 and wR_2 = 0.1363 (all indices), min/max residual density = −0.309/0.625 [e·Å^{-3}]. Completeness to θ(32.06°) = 95.4%. CCDC number 1458049.

Crystal data for carbamate **18**: $C_{20}H_{23}NO_3$, M_r = 325.39, orthorhombic, *P*bca, *a* = 13.1420(3) Å, *b* = 10.8641(3) Å, *c* = 23.6246(5) Å, α = 90º, β = 90º, γ = 90º, *V* = 3373.03(14) Å^3, *Z* = 8, ρ = 1.282 mg·M^{-3}, μ = 0.086 mm^{-1}, λ = 0.71073 Å, *T* = 100(2) K, *F*(000) = 1392, crystal size = 0.40 × 0.20 × 0.20 mm, θ(min) = 1.72°, θ(max) = 30.53°, 24833 reflections collected, 4983 reflections unique (R_{int} = 0.0336), GoF = 1.045, R_1 = 0.0407 and wR_2 = 0.1010 [$I > 2\sigma(I)$], R_1 = 0.0525 and wR_2 = 0.1083 (all indices), min/max residual density = −0.221/0.381 [e·Å^{-3}]. Completeness to θ(30.53°) = 96.4%. CCDC number 1458050.

Crystal data for cyclic carbonate **19a**: $C_{20}H_{20}O_3$, M_r = 308.36, monoclinic, *P*2(1)/n, *a* = 9.0867(9) Å, *b* = 16.4872(11) Å, *c* = 10.9948(9) Å, α = 90º, β = 109.094(10)º, γ = 90º, *V* = 1556.5(2) Å^3, *Z* = 4, ρ = 1.316 mg·M^{-3}, μ = 0.087 mm^{-1}, λ = 0.71073 Å, *T* = 100(2) K, *F*(000) = 656, crystal size = 0.45 × 0.40 × 0.40 mm, θ(min) = 2.32°, θ(max) = 36.97°, 27836 reflections collected, 7473 reflections unique (R_{int} = 0.0185), GoF = 1.029, R_1 = 0.0322 and wR_2 = 0.0999 [$I > 2\sigma(I)$], R_1 = 0.0352 and wR_2 = 0.1018 (all indices), min/max residual density = −0.237/0.555 [e·Å^{-3}]. Completeness to θ(36.97°) = 94.6%. CCDC number 1458051.

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Keywords: carbon dioxide • carbamates • cyclic carbonates • organocatalysis • regio-selectivity

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[17] The cyclic limonene carbonate was produced by catalytic coupling of limonene oxide and CO_2 in the presence of an Al(III) aminotriphenolate complex and a chloride based nucleophile at 85ºC and 40 bar. Full details are provided in the Supporting Information.

[18] Reactions were carried out under anhydrous conditions, but despite these precautions the formation of the diol product could not be fully avoided.

[19] The bis-carbonate was prepared from the bis-epoxide of limonene, see ref. 9a for details. The pure *trans* isomer has both ring substituents on the same face of the cyclohexyl ring, and was obtained after recrystallization of the isolated compound.

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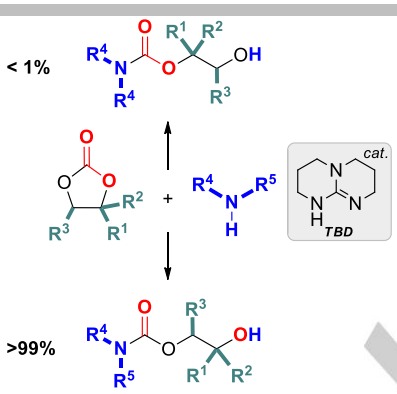
Entry for the Table of Contents:

FULL PAPER

A highly regio-selective and efficient methodology towards the formation of functional carbamate scaffolds is reported. The procedure makes use of the preferential formation of a key ternary intermediate comprising of a substituted cyclic carbonate, an amine and TBD as the organocatalytic mediator. The formation of oligo-carbamates, *en route* to urethane polymers, is also reported with high degree of regio-control over the aminolysis step of the process.



18 examples, isolated yields up to 96%

*Sergio Sopeña, Victor Laserna, Wusheng Guo, Eddy Martin, Eduardo C. Escudero-Adán and Arjan W. Kleij**

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Highly Regio-Selective Organocatalytic formation of Carbamates from Substituted Cyclic Carbonates