Organocatalysis

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A Metal-Free Synthesis of N-Aryl Carbamates under Ambient Conditions

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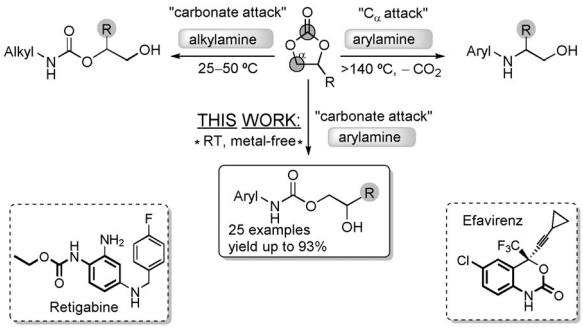
Abstract: *The first chemo- and site-selective process for the formation of N-aryl-carbamates from cyclic organic carbonates and aromatic amines is reported. The reactions proceed smoothly under extremely mild reaction conditions using TBD (triazabicyclodecene) as an effective and cheap organocatalyst, thus providing a sustainable and new methodology for the formation of a wide variety of useful N-aryl carbamate synthons in good to excellent yields. Computational investigations have been performed and show the underlying reason for the observed unique reactivity as related to an effective proton-relay mechanism mediated by the bicyclic guanidine base.*

The conversion of carbon dioxide into value-added organic compounds continues to be a vivid area of research in academic and industrial settings.[1] The valorization of CO_2 is important to create value from a waste material, and currently efforts have already shown great potential towards the use of CO_2 to store energy,[2] and as a synthon for the creation of new polymers[3] and fine-chemicals.[4] Another area of widespread interest and importance concerns the preparation of organic carbonates. More recently, focus has been shifted towards the use of these carbonates as intermediates in organic synthesis.[5] An attractive route towards the conversion of cyclic carbonates into useful products concerns their aminolysis by aliphatic amines, thus affording N-alkyl carbamate structures (Scheme 1).[6] However, the corresponding site-selective aminolysis induced by aromatic amines to yield N-aryl carbamates (NARCs) is surprisingly unknown.

The low nucleophilic character of aromatic versus aliphatic amines poses a huge challenge to prepare NARCs. Recent work[7] concerning the catalytic reaction between cyclic carbonates and aromatic amines has revealed that high reaction temperatures (>140 °C) are needed to achieve appreciable conversion rates. However, these temperature requirements significantly compromise the chemoselectivity of the process with no observable formation of the NARC. At high reaction temperatures aromatic amines prefer the attack on the α-carbon atom (Scheme 1) of the cyclic carbonate, hence yielding a plethora of decarboxylated side-products including N-alkylated amines and their derivatives.[7] Relevant studies[8] concerning the reaction of noncyclic dialkylcarbonates with aromatic amines were reported, albeit with a limited scope at temperatures greater than 80 °C. Thus, it still remains highly challenging and attractive to selectively prepare NARCs through a site-specific aminolysis reaction using aromatic amines (Scheme 1, below) from cyclic carbonates under mild reaction conditions. Such a new and sustainable process would represent a valuable alternative to reported (metal-based) processes[9] which require either harsh reaction conditions or more expensive reagents/metal precursors, and conventional routes to NARCs based on isocyanates.[10]



Scheme 1. Reaction manifold of cyclic organic carbonates with amine nucleophiles and new reactivity towards NARC formation under mild reaction conditions.

Furthermore, the NARC compounds may offer synthetically attractive scaffolds as they partially mimic fragments of pharmaceutical compounds such as Efavirenz and Retigabine (Scheme 1).[11] Also, thermolysis of NARCs offers a useful, phosgene-free route towards aryl isocyanates which are key reagents in the synthesis of polyurethane polymers.[12] Inspired by this unresolved challenge, we set out to explore a new preparative method towards NARCs and envisioned that the use of hydrogen-bond activation of cyclic carbonates could offer a viable substrate conversion strategy as recently demonstrated for aminolysis reactions involving alkylamines.[6a] Herein we report on the unprecedented chemoselective formation of (functionalized) NARCs from cyclic carbonates under extremely mild reaction conditions using arylamines as reagents, thus providing a highly sustainable method for these important scaffolds.

Our initial screening phase (Table 1 and Table S1 in the Supporting Information) focused on the use of aniline (**A**) and propylene carbonate (PC; **B**) as substrates, and various

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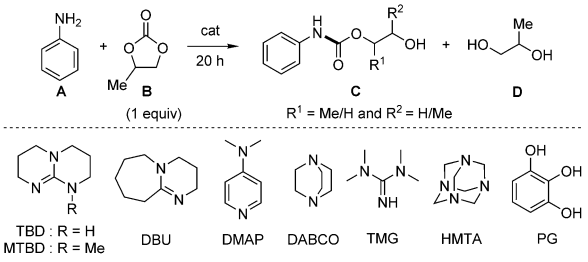
Table 1: Selected entries from the optimization of reaction conditions for the organocatalyzed N-aryl carbamate formation from aniline and PC.[a]



Entry	A (equiv)	Cat. (mol%)	T [°C]	B Conv. [%][b]	C Yield [%][b]	D Yield [%][b]
1	1.5	–	100	0	0	0
2[c]	1.2	TBD (5)	100	60	25	31
3[d]	1.2	TBD (10)	100	69	14	47
4	3	TBD (5)	70	60	40	19
5	3	TBD (10)	70	82	48	34
6	1.5	TBD (10)	70	75	38	30
7	1.5	MTBD (10)	70	26	10	15
8	1.5	DBU (10)	70	46	26	19
9	1.5	PG (10)	70	0	0	0
10	1.5	DMAP (10)	70	12	4	7
11	1.5	TMG (10)	70	35	19	16
12	1.5	DABCO (10	70	<2	0	<2
13	1.5	HMTA (10)	70	0	0	0
14	1.5	TBD (10)	55	72	48	22
15[d]	1.5	TBD (10)	45	65	40	25
16	1.5	TBD (30)	20	98	76[e]	21
17	3	TBD (30)	20	99	70	20
18	1.5	TBD (40)	20	98	75	20
19[f]	1.5	TBD (30)	140	94	0	trace
20[g]	1.5	TBD (30)	20	95	77	14

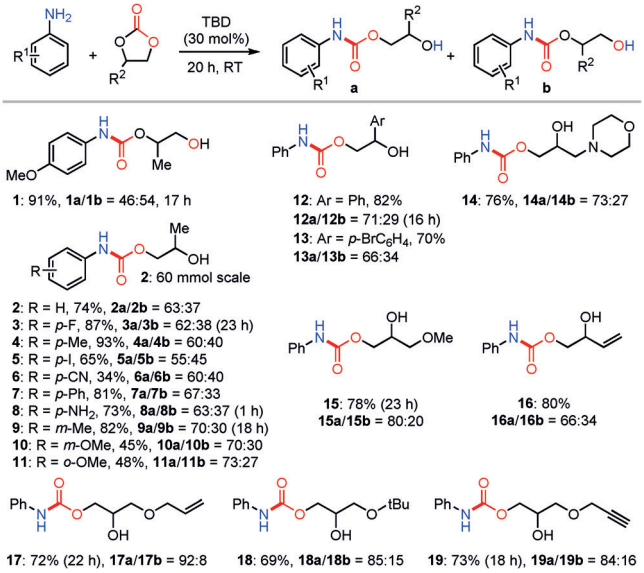
[a] Reaction conditions: 2 mmol of **B**, the indicated number of equivalents of **A**, and the catalyst were combined and reacted for 20 h (no solvent was used); see Table S1 for more entries for the optimization process. [b] Conversion determined by ^{1}H NMR spectroscopy. Yield determined by relative integration of the signals of the methyl groups. [c] 16 h. [d] 40 h. [e] Yield of isolated product is 74%. [f] 16 h, complex mixture noted by ^{1}H NMR spectroscopy. [g] Performed under anhydrous conditions. See the Supporting Information for details. DABCO = 1,4-diazabicyclo[2.2.2]octane, DBU = 1,8-diazabicyclo[5.4.0]-undec-7-ene, DMAP = 4-dimethylaminopyridine, HMTA = hexamethylenetetramine, MTBD = 1-methyl-1,5,7-triazabicyclo[4.4.0]-dec-5-ene, PG = pyrogallol, TBD = triazabicyclodecene, TMG = 1,1,3,3-tetramethylguanidine.

N-heterocyclic structures as potential organocatalytic activators. It is important to emphasize that the reaction run at 100 °C for 20 hours in the absence of a catalyst (entry 1) did not show any observable conversion of the substrates and was in line with the challenging nature of this conversion. We were pleased to note that at 100 °C (entry 2) the use of TBD (5 mol%) gave an appreciable PC conversion of 60% with a 25% yield of the targeted NARC product **C**. However, under these reaction conditions, substantial formation of the diol **D** was also observed. Performing the reaction for a longer period of time gave only a slightly higher conversion at higher TBD loading (entry 3, 69%) with significantly higher amounts of undesired diol being formed. The reaction at 70 °C (entry 4) showed a promising result when using a higher amount of aniline: while maintaining virtually the same conversion level as noted at 100 °C (60%), the chemoselectivity for **C** was markedly improved.[13]

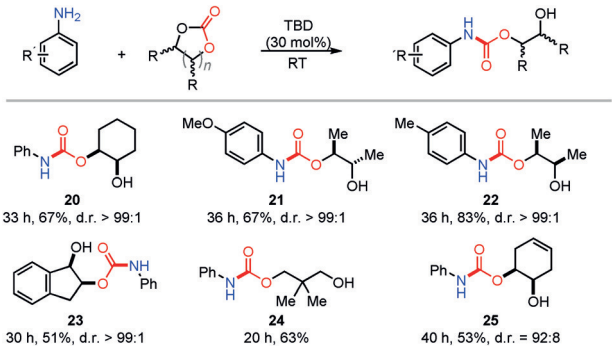
An increase in TBD loading (Table 1, entries 5 and 6) showed higher conversion levels but still with substantial diol formation, therefore we decided to first screen other nitrogen bases as potential catalysts (entries 7–13) and a previously reported hydrogen-bond activator (PG).[14] In all cases studied the conversion levels were (much) lower than those observed for TBD under similar reaction conditions (see entry 6). The addition of a solvent gave poorer results and generally we performed the substrate scope reactions under neat conditions. However, in some cases a very small amount of CH_3CN (typically 20 μL) was necessary to maintain a liquid phase (see the Supporting Information).

Finally, the reaction temperature and amount of aniline were further optimized (Table 1, entries 14–18), and satisfying results were finally achieved using 30 mol% of TBD at 20 °C and 1.5 equivalents of aniline, thus providing 98% PC conversion and good selectivity for **C** (yield of isolated product: 74%). When the reaction was performed at 140 °C with TBD as the catalyst (entry 19), a highly complex mixture of components was formed with only trace amounts of diol present; **C** could not be detected in the crude reaction mixture. This result strongly suggests that for high chemoselectivity towards **C** and site-selective attack of the aromatic amine onto PC (Scheme 1), a low temperature combined with a sufficiently high loading of TBD are required.

Encouraged by the results from the screening phase, the substrate scope was then investigated using various anilines and monosubstituted, functional cyclic carbonates[15] as reaction partners (Scheme 2) under mild reaction conditions. In general, good to excellent yields (up to 93%) of the isolated NARCs **1**–**19** were obtained. A variety of functional groups are tolerated using this procedure, including electron-donating and, remarkably, even electron-withdrawing groups (F, I,



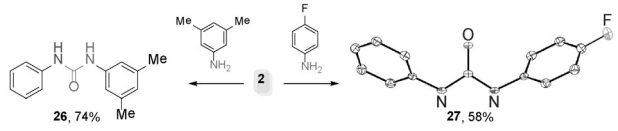
Scheme 2. TBD-catalyzed formation of NARCs from monosubstituted cyclic carbonates (only the major isomer is shown).



Scheme 3. TBD-catalyzed formation of the NARCs **20–25** from five- and six-membered disubstituted cyclic carbonates.

CN, and Ph). Substituents on the various positions on the aniline scaffold (*ortho*, *meta*, or *para*) were also tolerated. Of further note is that the synthesis of **2** could be easily scaled up (60 mmol, 9.2 g) with a slightly improved yield of 79% upon isolation. The use of carbonates other than PC as a reagent allows the introduction of various groups (e.g., **12–19**) including useful bromoaryl (**13**), morpholine (**14**), alkene (**16–17**), and alkyne (**19**) groups.[16] The molecular structure of **13a** was also further supported by X-ray analysis (Supporting Information).[17] Apart from monosubstituted carbonates, disubstituted five/six-membered carbonates[5d,15a–b] also showed good potential as substrates in the formation of NARCs (Scheme 3; **20–25**). The formation of all products (except **24**) proceeded with high levels of stereoretention. The proposed atom connectivity in **23** (only one regioisomer was isolated) was fully supported by two-dimensional NMR analysis. Secondary aromatic amines exhibited much lower reactivity under the present reaction conditions (see Table S2 in the Supporting Information).

Given the screening studies[13] we hypothesized that formation of nonsymmetrical ureas would be feasible by treatment of pure NARCs with aniline derivatives under appropriate reaction temperatures. Indeed, such ureas (Scheme 4; **26** and **27**) are the major products noted (other



Scheme 4. TBD-catalyzed formation of the nonsymmetrical ureas **26** and **27** from NARC **2** (concomitant formation of diol byproduct observed). Reaction conditions: 100 °C, 20 h, TBD (30 mol%).

than the formation of **D**) when **2** is treated with 3 equivalents of the respective aniline. These results reinforce the idea that NARCs are indeed intermediates towards urea formation under high-temperature conditions, and this corroborates the observation of rather chemoselective formation of the NARC product under ambient conditions.

To get better insight into the operative mechanism of the NARC formation, quantum chemical studies were performed using aniline and butylamine as representative amine nucleophiles, and PC as a carbonate substrate. This data demonstrates that the reaction of aniline with PC is not feasible because of an activation barrier of 40.9 kcal mol^{-1} (solid red line in Figure S1 in the Supporting Information). Moreover, the calculations also point out that a direct butylamine attack (dashed red line) is not kinetically favored at room temperature, with a free energy barrier of 33.3 kcal mol^{-1}. Therefore, the presence of water acting as a proton-relay catalyst was considered (blue traces) as the reactions in general are not performed under anhydrous conditions. This new mechanism indeed decreases significantly the barrier for the aniline pathway from 40.9 to 33.9 kcal mol^{-1}, though this value still remains considerably high for the reaction to occur under ambient conditions. For the butylamine case, the barrier was also effectively lowered to 24.2 kcal mol^{-1}, thus confirming the experimental observation that the reaction proceeds smoothly at room temperature.[6a] To reinforce the accuracy of the computational method, the obtained structures of the butylamine pathway underwent single-point CCSD(T) calculations (Figure S1). The obtained absolute barrier was determined at 41.5 kcal mol^{-1} (orange line), thereby unequivocally demonstrating that the presence of water is crucial for the process to occur and also revealing that the B97-D3 functional, at most, only slightly underestimates the barriers. The calculated energy barrier for the butylamine attack under water catalysis using CCSD(T) is 33.2 kcal mol^{-1} and thus 9.8 kcal mol^{-1} higher than observed from B97-D3/6-311G** (see the Supporting Information).

The results for the TBD-mediated reactions (Figure 1) show that the mechanism for the transformation of butylamine and aniline involves several steps. Both reactions have remarkably similar barriers, that is, 18.1 and 17.5 kcal mol^{-1} for aniline and butylamine, respectively. These values are consistent with the reactions taking place at room temperature (see Table 1 and Table S1). The mechanistic pathways are slightly different for each substrate. The first intermediate (INT-0) could only be optimized for the butylamine pathway.

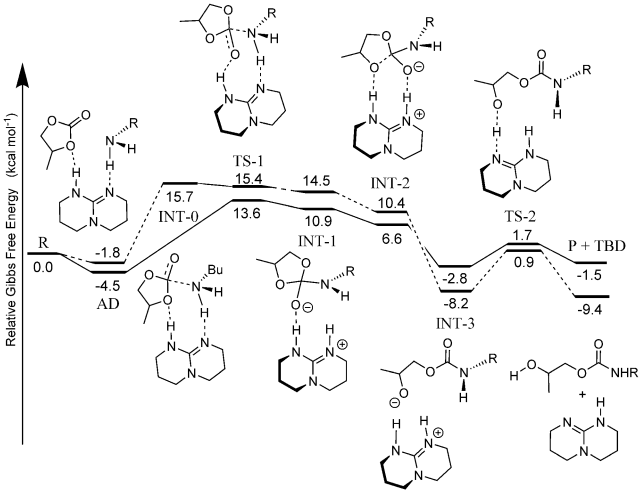


Figure 1. Gibbs free energy profile for the TBD-catalyzed reaction mechanism of PC with aniline (solid line) and butylamine (dashed line).

In this step, the amine approaches the carbonate group, with the carbon center adopting a tetrahedral geometry. Next, TS-1 is a mutual step and rate-determining for both pathways. This transition state constitutes an ion pair comprising a protonated $TBDH^+$ and an alkoxide (INT-1). Formation of INT-2 is characterized by an elongated C–O bond (1.66 Å) in the cyclic species and is stabilized by two hydrogen bonds with the $TBDH^+$. In the subsequent step, INT-3 is produced and the substrate is now linear, thus retaining still an alkoxide character. The final step is the proton transfer from $TBDH^+$ to the substrate through the transition-state TS-2. Compared with the reaction assisted by water, the TBD is a much more effective proton-relay catalyst,[18] thus providing significantly lower kinetic barriers. Also, when MTBD (methylated TBD) is used, much poorer catalysis behavior was noted (Table 1, entries 6 and 7), thus clearly indicating that hydrogen-bonding stabilization is also crucial in this reaction.

In summary, we have presented a new and highly attractive route towards the challenging formation of N-aryl carbamates derived from readily available cyclic carbonates and aromatic amines under virtually solvent-free and metal-free conditions. TBD is shown to be an effective organocatalyst for the site-selective and chemoselective formation of the N-aryl carbamate products and DFT studies have revealed an interesting proton-relay mechanism. The present methodology is operationally simple, easily scalable, and has great potential in synthetic chemistry.

Experimental Section

Typical NARC formation: the respective carbonate (2 mmol, 1 equiv), amine (1.5 equiv) and TBD (30 mol%) were charged into a 5 mL round-bottom flask and the reaction mixture was stirred at RT for the required time. The analytically pure N-aryl carbamate product was then isolated by flash chromatography. The NARCs were fully characterized by $^1H/^{13}C$ NMR and two-dimensional NMR spectroscopy (COSY, HSQC, HMBC and DEPTQ135 when necessary), as well as IR and HRMS. Full details are provided in the Supporting Information.

Computational results are available in full format under https://iochem-bd.iciq.es:8443/browse/handle/100/137.

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Keywords: anilines · cyclic carbonates · hydrogen bonds · N-aryl carbamates · organocatalysis

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