A New and Metal-free Synthesis of N–Aryl Carbamates under Ambient Conditions

Wusheng Guo,[a] Joan Gónzalez-Fabra,[a] Nuno A. G. Bandeira,[a] Carles Bo[a][b] and Arjan W. Kleij*[a][c]

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/attractive reaction conditions using TBD (triazabicyclodecene) as an effective and cheap organocatalyst 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 showing the underlying reason for the observed unique reactivity which is 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 affording N-alkyl carbamate structures (Scheme 1).[6] However, the corresponding site-selective aminolysis induced by aromatic amines yielding 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 (>140ºC) are needed to achieve appreciable conversion rates. However, these temperature requirements significantly compromise the chemo-selectivity of the process with no observable formation of the NARC. At high reaction temperatures aromatic amines prefer the attack on the *a*-carbon (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 non-cyclic dialkyl-carbonates with aromatic amines were reported although with quite limited scope at temperatures >80^{o}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 carbonate under mild reaction conditions. Such a new and sustainable process would represent a valuable alternative to reported (metal-based) processes[9] that require either harsh reaction conditions and/or more expensive reagents/metal precursors, and conventional routes to NARCs based on isocyanates.[10]

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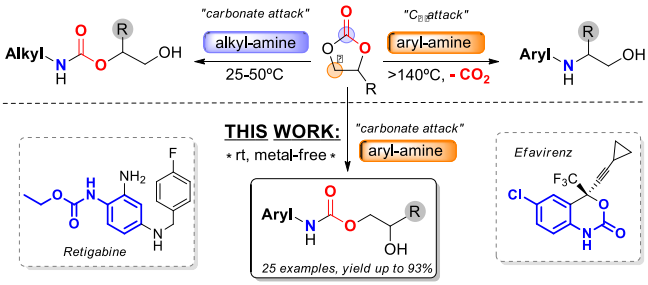
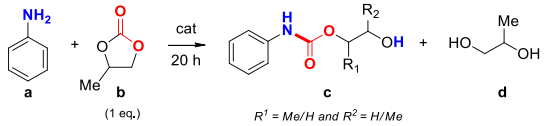
Furthermore, the NARC compounds may offer synthetically attractive scaffolds as they partially mimic fragments of pharmaceutical compounds such as Efavirenz and Retigabine (Scheme 1).[11] Also, thermolysis of NARCs offers a useful, phosgene-free route towards aryl isocyanates which are key reagents in 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 *alkyl*-amines.[6a] Here we report on the unprecedented chemo-selective formation of (functionalized) NARCs from cyclic carbonates under extremely mild reaction conditions using aryl-amines as reagents providing a highly sustainable method for these important scaffolds.



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

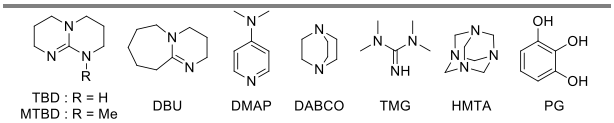
Our initial screening phase (see Table 1 and Supporting Information, Table S1) focused on the use of aniline (**a**) and propylene carbonate (PC, **b**) as substrates and various *N*-heterocyclic structures as potential organocatalytic activators. It is important to emphasize that the reaction performed at 100ºC for 20 h in the absence of any catalyst (entry 1) did not show any observable conversion of the substrates in line with the challenging nature of this conversion. We were pleased to note that at 100ºC (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 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 70ºC (entry 4) showed a promising result using a higher amount of aniline: while maintaining virtually the same conversion level as noted at 100ºC (60%), the chemo-selectivity for the NARC **c** was markedly improved.[13]

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



entry	**a** [eq.]	Cat. [mol %]	T [°C]	Conv.[b] **b** [%]	Yield[b] **c** [%]	Yield[b] **d** [%]
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	70	26	10	15

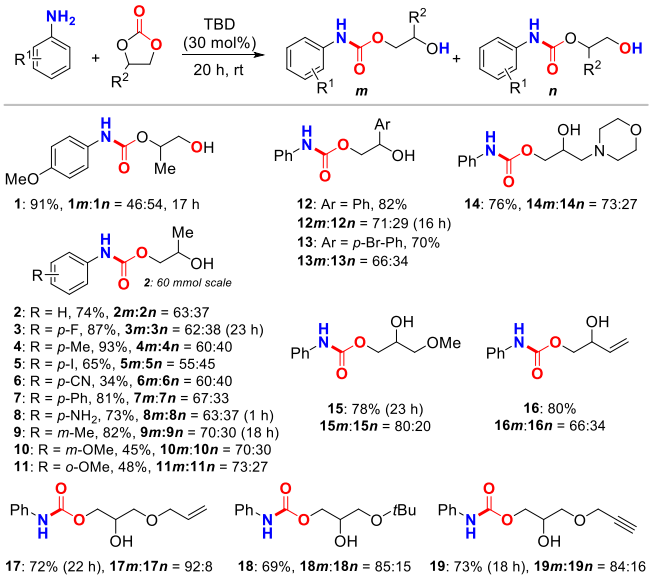
		10				
8	1.5	DBU 10	70	46	26	19
9	1.5	PG 10	70	0	0	0
10	1.5	DMAP 10	70	12	4	7
11	1.5	TMG 10	70	35	19	16
12	1.5	DABCO 10	70	<2	0	<2
13	1.5	HMTA 10	70	0	0	0
14	1.5	TBD 10	55	72	48	22
15[d]	1.5	TBD 10	45	65	40	25
16	**1.5**	**TBD 30**	**20**	**98**	**76**[e]	**21**
17	3	TBD 30	20	99	70	20
18	1.5	TBD 40	20	98	75	20
19[f]	1.5	TBD 30	140	94	0	trace
20[g]	1.5	TBD 30	20	95	77	14



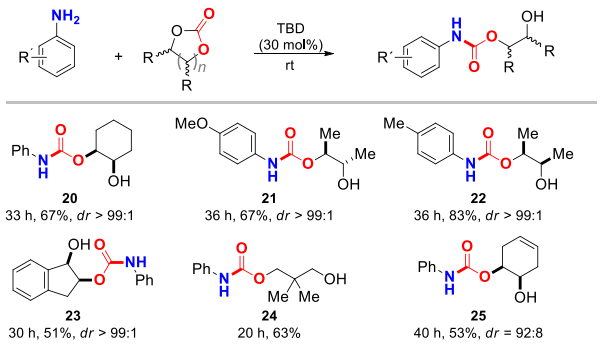
[a] Reaction conditions: 2 mmol of **b**, indicated equiv of **a** and catalyst, solvent free, 20 h; see ESI for more entries for the optimization process (Table S1). [b] Based on ^{1}H NMR conversion and yield determined by relative integration of the methyl signals. [c] 16 h. [d] 40 h. [e] Isolated yield is 74%. [f] 16 h, complex mixture noted by ^{1}H NMR. [g] Performed under anhydrous conditions, see SI for details. Abbreviations: DABCO = 1,4-diazabicyclo[2.2.2]octane, DBU = 1,8-diazabicyclo[5.4.0]-undec-7-ene, DMAP = 4-dimethylamino-pyridine, MTBD = 1-methyl-1,5,7-triazabicyclo[4.4.0]-dec-5-ene, TBD = triazabicyclodecene, TMG = 1,1,3,3-tetramethyl-guanidine, PG = pyrogallol. HMTA = hexamethyl-enetetramine.

An increase in TBD loading (entries 5 and 6) showed higher conversion levels but still with substantial diol formation and 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 (*cf*., entry 6). The addition of a solvent gave poorer results and generally we performed the substrate scope reactions under neat conditions; in some cases though a very small amount of CH_3CN (typically 20 *m*L) was necessary to maintain a liquid phase (Supporting Information).

Finally, the reaction temperature and amount of aniline were further optimized (entries 14–18), and satisfying results were finally achieved using 30 mol% of TBD at 20ºC and 1.5 equiv of aniline providing 98% PC conversion and good selectivity for the NARC **c** (isolated yield: 74%). When the reaction was performed at 140ºC with TBD as catalyst (entry 19), a highly complex mixture of components was formed with only trace amounts of diol being present; the NARC **c** could not be detected in the crude mixture. This strongly suggests that for high chemo-selectivity towards the NARC product **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.

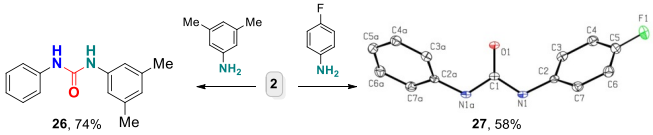


Scheme 2. TBD catalysed formation of NARCs from mono-substituted cyclic carbonates (only the major isomer is shown).



Scheme 3. TBD catalysed formation of NARCs **20–25** from five- and six-membered di-substituted cyclic carbonates.

Encouraged by the results from the screening phase, the substrate scope was then investigated using various anilines and mono-substituted, functional cyclic carbonates[15] as reaction partners (Scheme 2) under mild reaction conditions. In general, good to excellent isolated yields of the NARCs **1–19** up to 93% were obtained. A variety of functional groups are tolerated using this procedure including electron-donating and remarkably also electron-withdrawing groups [F (**3**), I (**5**), CN (**6**) and Ph (**7**)] on the aniline scaffold with reasonable scope in the position (*ortho*, *meta* or *para*) of the substituent. Of further note is that the synthesis of NARC **2** could be easily scaled up (60 mmol, 9.2 g) with a slightly improved isolated yield of 79%. The use of carbonates other than PC as reagent allows for introduction of various groups (*cf.*, **12**–**19**) including useful bromo-aryl (**13**), morpholine (**14**), alkene (**16–17**) and alkyne (**19**) groups.[16] The molecular structure of **13*m*** was also further supported by X-ray analysis (Supporting Information).[17] Apart from mono-substituted carbonates also di-substituted five/six-membered carbonates[5d,15a-b] 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 stereo-retention. The proposed atom connectivity in **23** (only one regio-isomer was isolated) was fully supported by 2D NMR techniques. Secondary aromatic amines exhibited much lower reactivity under the present conditions (see Table S2).



Scheme 4. TBD catalysed formation of non-symmetrical ureas **26** and **27** from NARC **2** (concomitant formation of diol byproduct observed). Conditions: 100ºC, 20 h, TBD (30 mol%).

Hinted by the screening studies[13] we hypothesized that formation of non-symmetrical ureas would be

feasible by treatment of pure NARCs with aniline derivatives under appropriate reaction temperatures. Indeed, such ureas (*cf*., **26** and **27**) are the major product noted (Scheme 4; beside the formation of diol **d**, Table 1) when **2** is treated with 3 equiv of the respective aniline. These results reinforce the idea that NARCs are indeed intermediates towards urea formation under high temperature conditions, and this corroborates well with the observation of rather chemo-selective formation of the NARC product under ambient conditions.

In order to get a better insight in the operative mechanism of the NARC formation, quantum chemical studies were performed using aniline and butylamine as representative amine nucleophiles and PC as carbonate substrate. This demonstrates that the reaction of aniline with PC is not feasible due to an activation barrier of 40.9 kcal·mol^{-1} (solid red line in Figure S1). Moreover, the calculations also point out that a direct butylamine attack (dashed red line) is not kinetically favoured 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} 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 (details in the Supporting Information; 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** (*cf.* Supporting Information).

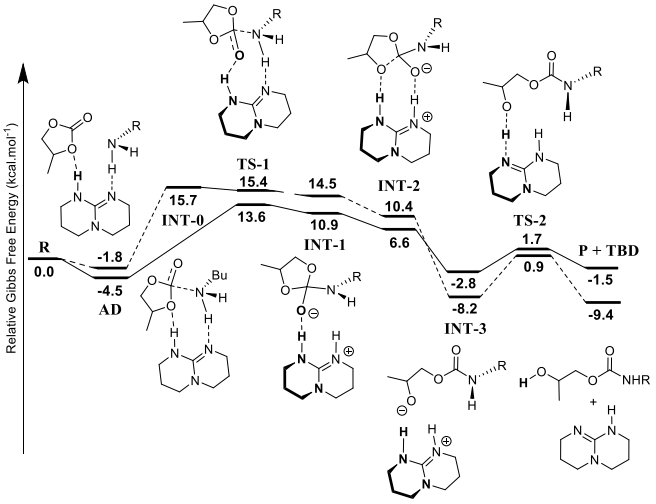


Figure 1. Gibbs free energy profile for the TBD-catalyzed reaction mechanism of PC with aniline (solid line) and butylamine (dashed line).

The results for the TBD-mediated reactions (depicted in Figure 1) show that the mechanism for the transformation of butylamine and aniline involves several steps. Both reactions have remarkably similar barriers, *viz*. 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 (*cf*., Table 1 and S1). The mechanistic pathways are slightly different for each substrate. The first intermediate (**INT-0**) could only be optimized for the butylamine pathway. In this step, the amine approaches the carbonate group, with the carbon centre 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 of a protonated TBDH$^+$ and an alkoxide (**INT-1**). Formation of **INT-2** is characterised by an elongated C–O bond (1.66 Å) in the cyclic species and

is stabilised by two hydrogen bonds with the $TBDH^+$. In the subsequent step, **INT-3** is produced and the substrate is now linear retaining still an alkoxide character. The final step is the proton transfer from $TBDH^+$ to the substrate through transition state **TS-2**. Compared with the reaction assisted by water, the TBD is a much more effective proton-relay catalyst[18] providing significantly lower kinetic barriers. Also, when MTBD (methylated TBD) is used, much poorer catalysis behaviour was noted (Table 1, *cf*. entries 6 and 7) clearly indicating that H-bonding stabilization is also crucial in this reaction.

In summary, we here present 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 chemo-selective 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 large 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 $^{1}H/^{13}C$ NMR, 2D NMR (COSY, HSQC, HMBC and DEPTQ135 when necessary), IR and HRMS. Full details are provided in the Supporting Information.

Acknowledgements

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Keywords: Carbon dioxide • N-aryl carbamates • organic carbonates • organocatalysis • site-specificity

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[16] The different regio-isomers of NARC products **12**, **13** and **16** can be easily separated by flash chromatography; see the Supporting Information for details.

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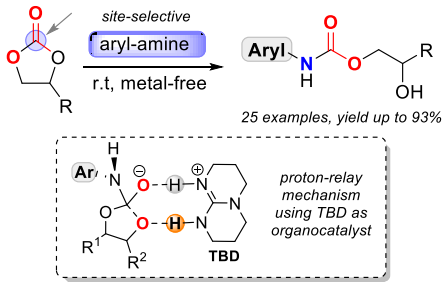
Entry for the Table of Contents:

COMMUNICATION

The previously unknown site-selective attack of arylamine on cyclic carbonates to deliver N-aryl carbamates as the principal product is reported. The organocatalyst TBD guides an effective proton-relay process mediating a chemo-selective formation of the carbamate target under extremely mild conditions.



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