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A Metal-Free Synthesis of *N*-Aryl Oxazolidin-2-ones by the One-Pot Reaction of Carbon Dioxide with *N*-Aryl Aziridines

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Abstract. The cost-effective $TPPH_2$/TBACl-catalyzed ($TPPH_2$ = dianion of tetraphenyl porphyrin; TBACl = tetrabutyl ammonium chloride) carbon dioxide cycloaddition to *N*-aryl aziridines was successful in synthesizing *N*-aryl oxazolidin-2-ones. A catalytic tandem reaction was also developed, in which *N*-aryl aziridines were initially synthesized and then reacted with carbon dioxide without being purified. The procedure occurred with a very high atom economy, molecular nitrogen being the only by-product of the entire tandem process.
In addition, the mechanism of catalytic cycle was investigated by DFT calculations.

Keywords: *N*-aryl oxazolidin-2-one; Carbon dioxide; Aziridine; Porphyrin; DFT study

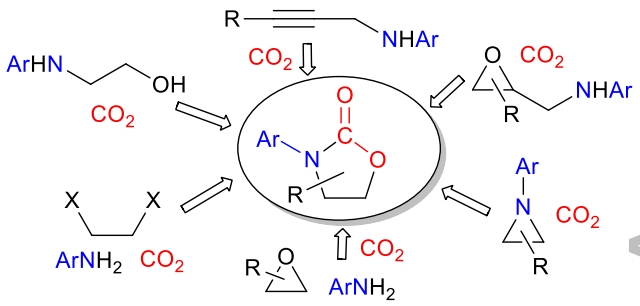
Introduction

Oxazolidinones are largely used as intermediates as well as chiral auxiliaries in organic synthesis[1] and constitute a class of active pharmaceutical molecules,[2] whose activity depends on the chemical nature of oxazolidinone's substituents. Excellent pharmaceutical properties are usually observed when a *N*-aryl moiety is present in the heterocycle structure; in fact, some *N*-aryl oxazolidin-2-ones (NAOs), such as Linezolid,[3] Tedizolid[4] and Toloxatone,[5] are FDA-approved drugs for treating bacterial and microbial infections. Consequently, a great scientific interest has been devoted to developing efficient procedures for synthesizing *N*-aryl substituted oxazolidinones.

Among the available methodologies that are specifically designed for synthesizing NAOs, those involving CO_2 (CO_2 = carbon dioxide) as one of the reagents is of particular interest. This is due to the importance of using this greenhouse gas as a renewable C1 synthetic building block.

Several catalytic systems have been developed and, besides the reaction of CO_2 with amino alcohols,[6] unsaturated amines[7] and epoxy amines,[8] three-component reactions involving CO_2/epoxide/aniline[9] or CO_2/haloalkane/aniline[10] CO_2/alkene/aniline[11] combinations, have also emerged as efficient catalytic systems for producing *N*-aryl oxazolidin-2-ones (Scheme 1).

Surprisingly, the synthesis of NAOs by the direct cycloaddition of CO_2 to *N*-aryl aziridines was less developed with respect to the analogous reaction involving *N*-alkyl and *N*-benzyl aziridines.[12] The lack of a general method for producing differently substituted NAOs from *N*-aryl aziridines has been ascribed to the lower basicity and nucleophilicity of *N*-aryl with respect to *N*-alkyl aziridines, which implies their limited reactivity towards CO_2.[13]



Scheme 1. Selected examples of the CO_2-based synthesis of NAOs

To the best of our knowledge, only the (salen)chromium(III)/DMAP-catalyzed (DMAP = *N*,*N*-dimethyl-4-aminopyridine) synthesis of *N*-phenyl oxazolidin-2-ones[12a] and the last step of the Toloxatone synthesis, promoted by a dimeric

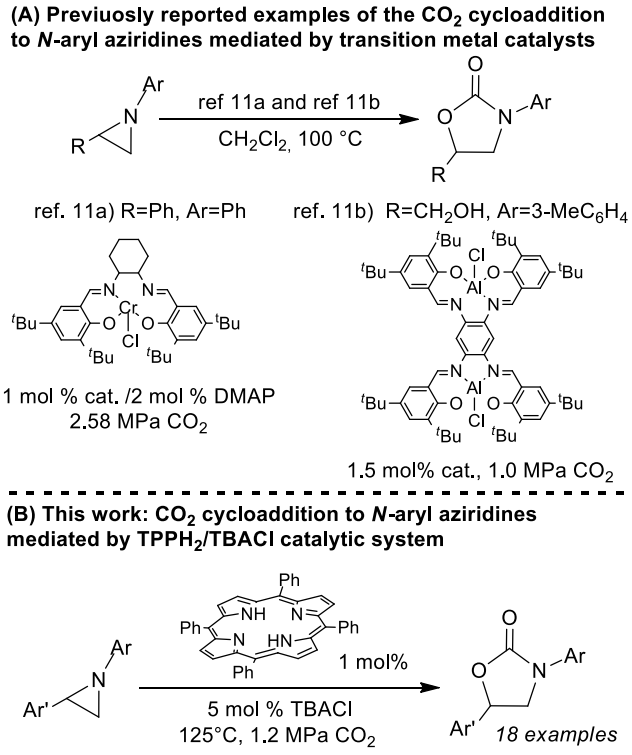
aluminium (III) Schiff base complex,[12b] occurred by the direct CO_2 cycloaddition to a *N*-aryl aziridine compound (Scheme 2).

Recently, we reported a ruthenium porphyrin-based catalytic procedure for synthesizing *N*-alkyl oxazolidin-2-ones[14] and, during our efforts to apply the same procedure for synthesizing NAOs, we discovered that the reaction was efficiently promoted by the low-cost $TPPH_2$/TBACl catalytic system ($TPPH_2$ = tetraphenyl porphyrin; TBACl = tetrabutyl ammonium chloride). The presence of a transition metal complex was not required.

Results and Discussion

Synthetic study

We report here the optimization and study scope of the synthesis of *N*-aryl oxazolidin-2-ones, which were obtained either by reacting CO_2 with purified *N*-aryl aziridines or by applying a cost-effective, tandem procedure. The latter methodology consists in the Ru(TPP)CO-catalyzed synthesis of *N*-aryl aziridines that were converted, without being purified, into corresponding NAOs by the $TPPH_2$/TBACl-catalyzed cycloaddition of CO_2.



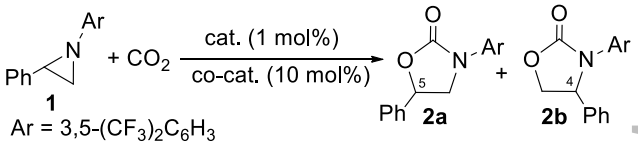
Scheme 2. (A) Transition metal- and (B) metal free-mediated CO_2 cycloaddition to *N*-aryl aziridines

The reaction of 1-(3,5-*bis*(trifluoromethyl)phenyl)-2-phenylaziridine (**1**) with CO_2 (Table 1) was first run in the presence of Ru(TPP)$(NAr)_2$/TBACl catalytic system (Ar = 3,5-$(CF_3)_2C_6H_3$), by using the experimental conditions already employed for synthesizing *N*-alkyl oxazolidin-2-ones.[14a] Even if a very good **2a**/**2b** regioisomeric ratio was obtained, the modest values of the aziridine conversion and oxazolidinone selectivity indicated a limited catalytic efficiency of the ruthenium *bis*-imido catalyst (Table 1, entry 1). The reaction produced, alongside the desired *N*-aryl-oxazolidin-2-ones **2a**/**2b** in a low yield, other side-products which were not characterized.

Interestingly, when Ru(TPP)$(NAr)_2$ was replaced with $TPPH_2$, the aziridine conversion of 20 % was observed (Table 1, entry 2) and this value increased to 61 % by running the reaction in THF (Table 1, entry 3) where CO_2 is better solubilized. Thus, in order to assess the role of $TPPH_2$ in the catalytic cycle, the reaction was run in the presence of TBACl alone and obtained results indicated that $TPPH_2$ was responsible for a better **2a**/**2b** regioisomeric ratio (compare entries 3 and 4 of Table 1). In addition, $TPPH_2$ had a positive effect on the reaction rate, as proved by the larger aziridine conversion, which was observed after 6 hours of reaction (Table 1, entries 3 and 4, values in parenthesis).

No aziridine conversion was observed by only using $TPPH_2$ underlining the essential role of TBACl. Albeit the catalytic activity of tetrabutylammonium halides was already reported in the synthesis of *N*-alkyl oxazolidin-2-ones,[15] the efficiency of the sole TBACl in promoting the formation of NAOs has never been reported. Lower or no catalytic efficiency was observed when either PPNCl (*bis*(triphenylphosphine)iminium chloride) (Table 1, entry 5) or DMAP (Table 1, entry 6) was employed as the co-catalyst.

Table 1. Synthesis of oxazolidin-2-ones **2a**/**2b**[a]



entry	cat./co-cat.	conv. %[b]	sel. %[b]	**2a**/**2b** ratio
1[c]	Ru(TPP)$(NAr)_2$ /TBACl	60	40	97:3
2[c]	$TPPH_2$/TBACl	20	90	90:10
3	$TPPH_2$/TBACl	61 (20[d])	80	90:10
4	-/TBACl	63 (5[d])	79	74:26
5	$TPPH_2$/PPNCl	49	78	65:35
6	$TPPH_2$/DMAP	-	-	-

[a] Reaction conditions: 0.11 M THF *N*-aryl aziridine solution in a steel autoclave for 15 h at 100°C, 1.2 MPa CO_2 and cat./co-cat./aziridine = 1:10:100. [b] Determined by ^{1}H NMR by using 2,4-dinitrotoluene as the internal standard. [c] Benzene as the reaction solvent. [d] After 6 hours.

Considering the importance of applying such a convenient method for synthesizing NAOs, the $TPPH_2$/TBACl-based methodology was investigated in detail. Reaction parameters of the model

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cycloaddition of CO_2 to **1** were systematically tuned in order to magnify the catalytic performance (Figure 1) (see SI for experimental details). First, a series of catalytic reactions was performed by using the experimental conditions reported in Table 1 and changing the aziridine concentration from 7.5 x 10^{-2} to 2.0 mol/L.

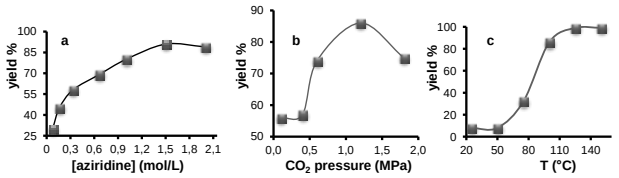

Figure 1. Optimization of reaction's experimental conditions

As shown in Figure 1a, the best yield/regioisomeric ratio combination was observed by using 1.5 mol/L of aziridine **1** in THF (86 % yield, **2a**/**2b** = 86:14). Next, five different reactions were conducted by using experimental conditions of Table 1, except for the aziridine concentration that was fixed at 1.5 mol/L, and applying five different CO_2 pressures (Figure 1b). The oxazolidin-2-one yield increased up to 86 % (**2a**/**2b**=86:14) at 1.2 MPa CO_2 and then the efficiency of the process dropped by further raising the CO_2 pressure. This effect can be due to a small volumetric expansion,[16] which caused an aziridine dilution with a consequent negative effect on the catalytic performance (see catalytic effect of the aziridine molarity in Figure 1a).

Then, reaction parameters optimized up to now (1.5 mol/L of **1** and 1.2 MPa CO_2) were used to study the effect of the temperature on the catalytic efficiency (Figure 1c). By raising the reaction temperature to 125°C, the aziridine was completely converted into oxazolidin-2-one with 99 % yield and a **2a**/**2b** regioisomeric ratio of 86:14 (Table 2, entry 1). A further increment of the reaction temperature did not cause any additional positive effect. This good result was maintained by decreasing the reaction time from 15 to 8 hours and halving the TBACl amount (from 10 % to 5 %). In this last case the positive effect of $TPPH_2$ was evident, as proven by the lower performance observed by using 5 mol % of TBACl alone (conv. = 84 %, sel. = 72 %, **2a**/**2b** = 80:20 *versus* conv. = 99 %, sel. = 99 %, **2a**/**2b** = 86:14 observed in the presence of $TPPH_2$ too). The replacement of THF with the more eco-friendly 2-MeTHF solvent, which derives from natural sources,[17] was responsible for worse catalytic results (conv. = 99 %, sel. = 81 % **2a**/**2b** = 80:20)

Thus, the optimized experimental conditions of $TPPH_2$/TBACl/aziridine = 1:5:100, 1.5 mol/L of aziridine, 1.2 MPa CO_2, 125°C and 8 h were employed for studying the reaction scope (see SI for experimental details). The procedure was effective for synthesizing oxazolidin-2-ones reported in Table 2 with aziridine conversions, product selectivities and regioisomeric ratios up to 99 %, 99 % and 96:4, respectively.

Data reported in Table 2 suggested that the reaction productivity was related to both electronic and steric factors. The presence of EWG as R group had a beneficial effect on the reaction outcome. In fact, the quantitative conversion of aziridine into the corresponding axazolid-2-one was observed when the nitrogen atom was bonded either to the 3,5-$(CF_3)_2C_6H_3$ (Table 2, entry 1) or 4-$(NO_2)_2C_6H_4$ aromatic group (Table 2, entry 2). In these cases, the reaction productivity was not greatly influenced by the electronic characteristics of Ar' group linked to the aziridine carbon atom. In fact, good aziridine conversions and product selectivities were achieved by introducing whether EDG (Table 2, entries 3-5) or a halogen atom (Table 2, entry 6) onto the Ar' moiety. A slight decrease on the reaction performance was observed by inserting into the molecule the very strong electron-deficient C_6F_5 substituent as the Ar' group (Table 2, entry 7). It is interesting to note that the reaction worked well also when EWGs were present on Ar' (Ar' = C_6F_5) and R was an EDG (R = ^{t}Bu); in fact oxazolidin-2-one **16a**/**16b** was obtained from **15** with very good conversion (92 %) and selectivity (86 %) as well as regioselectivity (**16a**/**16b** = 91:9) (Table 2, entry 8). This result suggested that the presence of two groups with opposite electronic features can induce the polarization of the aziridine C-N bond, independently on the position where they are located. We propose that, regardless of how the stretching of the aziridine C-N bond is produced, the bond polarization facilitates the C-N bond cleavage and in turn the CO_2 cycloaddition. This hypothesis could explain the slight decrease of the reaction productivity, which was observed in the synthesis of **14a**/**14b** when both the nitrogen and carbon aziridine atoms linked aryl moieties bearing EWGs (entry 7).

When Ar' = Ph, the bond polarization increased by enhancing the electron-withdrawing nature of the R substituent on the *N*-aryl group. Thus, in accordance to what is stated above, better catalytic efficiencies were observed by moving from OMe to a chlorine substituent, as the R group on the *para* position of the aryl moiety (entries 9-12). The dependence of the reaction productivity on the electronic characteristic of R was more pronounced when R was placed in *ortho* or *meta* position with respect to the nitrogen atom. In fact, while an acceptable yield of oxazolidin-2-ones **26a**/**26b** (60 % yield) was still observed by reacting aziridine **25** with CO_2 (entry 13), only traces of oxazolidin-2-ones deriving from aziridine **27** were formed (entry 14), due to the negative coupling of electronic and steric effects.

Although aziridine **28**, showing 3,5-$(Cl)_2C_6H_3$ substituent on the nitrogen atom (Table 2, entry 15), efficiently reacted with CO_2 forming **29a**/**29b**, oxazolidin-2-ones **31a**/**31b** were obtained only in moderate selectivity (30 %) by using aziridine **30**, which shows 3,5-$(NO_2)_2C_6H_3$ group on the nitrogen atom (Table 2, entry 16). Unexpectedly, **31a**/**31b**

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compounds were obtained together with many other uncharacterized side-products.

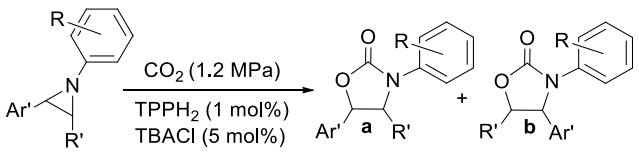
Next, the reactivity of aziridines having Ar' = Ph and R' = Me was investigated and, as reported in entries 17 and 18 of Table 2, the presence of two substituents on both carbon atoms of the aziridine ring had a negative effect on both the conversion and selectivity values. In accordance to the dependence of the reaction productivity on the electronic feature of the *N*-Ar moiety, the negative effect was more pronounced when R was an EDG (compare entries 17, R = 3,5-$(CF_3)_2$ and 18, R = 4-^{t}Bu of Table 2). Finally, 1-(3,5-*bis*(trifluoromethyl)phenyl)-2-methyl-2-phenylaziridine **36**, deriving from the reaction of α-methyl styrene and 3,5-*bis*(trifluoromethyl)phenyl azide, was tested in the reaction with CO_2. The lack of the oxazolidin-2-one formation suggested that the ring-opening reaction involved the more substituted carbon atom which, in this case cannot be attacked by the nucleophilic species due to the high steric hindrance.

Except in one case (Table 2, entry 13), all the reactions reported in Table 2 occurred with a **a**/**b** regioselectivity higher than 77:24 and the convenient **a**/**b** ratio allowed us to easily isolate the desired oxazolidin-2-one isomer **a** by chromatographic purification (see SI).

Considering our expertise in synthesizing *N*-aryl aziridines,[18] we developed a tandem procedure in order to improve the reaction sustainability. The first step of the tandem reaction consisted in the Ru(TPP)CO-catalyzed reaction of aryl azide with a styrene derivative forming the corresponding aziridine and then, after checking the aziridine yield by ^{1}H NMR spectroscopy and evaporating the reaction solvent to dryness, the residue was solubilized in THF and transferred into the autoclave where the $TPPH_2$/TBACl-mediated CO_2 cycloaddition to aziridine yielded the desired oxazolidin-2-one.

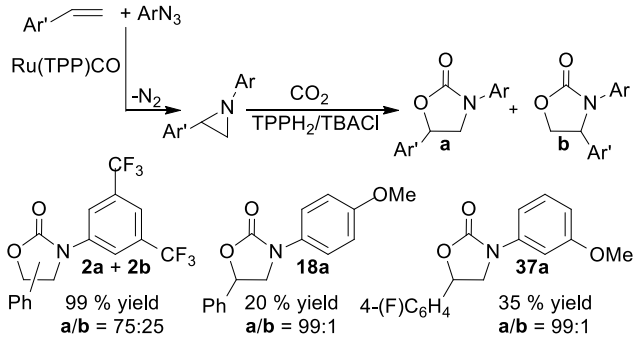
In order to investigate the applicability of the methodology, the tandem protocol was applied for synthesizing oxazolidin-2-ones **2a**/**2b**, **18a** and **37a** (Scheme 3). To evaluate the influence of unreacted reagents on the catalytic performance, we intentionally tested the tandem syntheses of product **2a**/**2b** and **18a** as case studies. The two *N*-aryl azides, forming corresponding aziridines **1** and **17**, show a very different reactivity (while **1** was obtained in 99 % yield, aziridine **17** was only formed in 65 % yield) and also the transformation of **1** and **17** into **2a**/**2b** and **18a**, respectively occurred with a very different efficiency (entries 1 and 9 of Table 2). As reported in Scheme 3, **2a**/**2b** and **18a** compounds were obtained with yields and **a**/**b** regioselectivities very similar to those obtained by using purified aziridines (compare entries 1 and 9 of Table 2 with values reported in Scheme 3) to indicate that the tandem procedure was efficient as well as the two-step process.

Table 2. Study of the reaction scope[a]



entry	*N*-aryl aziridine	conv. %[b]	sel. %[c]	**a**/**b** ratio[b]
1	**1**, Ar' = Ph, R' = H, R = 3,5-$(CF_3)_2$	99	99	**2a**/**2b** = 86:14
2	**3**, Ar' = Ph, R' = H, R = 4-NO_2	99	99	**4a**/**4b** = 78:22
3	**5**, Ar' = 4-tolyl, R' = H, R = 3,5-$(CF_3)_2$	99	90	**6a**/**6b** = 80:20
4	**7**, Ar' = 4-(^{t}Bu)C_6H_4, R' = H, R = 3,5-$(CF_3)_2$	98	86	**8a**/**8b** = 99:1
5	**9**, Ar' = 4-(Me)C_6H_4, R' = H, R = 4-NO_2	99	90	**10a**/**10b** = 85:15
6	**11**, Ar' = 4-(Br)C_6H_4, R' = H, R = 3,5-$(CF_3)_2$	99	99	**12a**/**12b** = 80:20
7	**13**, Ar' =C_6F_5, R' = H, R = 3,5-$(CF_3)_2$	80	80	**14a**/**14b** = 82:18
8	**15**, Ar'= C_6F_5, R = 4-^{t}Bu	92	86	**16a**/**16b** = 91:9
9	**17**, Ar' = Ph, R' = H, R = 4-OMe	85	23	**18a**/**18b** = 99:1
10	**19**, Ar' = Ph, R' = H, R = 4-^{t}Bu	95	57	**20a**/**20b** = 96:4
11	**21**, Ar' = Ph, R' = H, R = 4-Br	99	50	**22a**/**22b** = 90:10
12	**23**, Ar' = Ph, R' = H, R = 4-Cl	97	74	**24a**/**24b** = 89:11
13	**25**, Ar' = Ph, R' = H, R = 2-NO_2	99	60	**26a**/**26b** = 64:36
14	**27**, Ar' = Ph, R' = H, R = 3-OMe	80	<9	-
15	**28**, Ar' = Ph, R' = H, R = 3,5-Cl_2	94	99	**29**/**29b** = 81:19
16	**30**, Ar' = Ph, R' = H, R = 3,5-$(NO_2)_2$	99	30	**31a**/**31b** = 77:24
17	**32**, Ar' = Ph, R' = Me, R = 3,5-$(CF_3)_2$	73	71	**33a**/**33b** = 94:6
18	**34**, Ar' = Ph, R' = Me, R = 4-^{t}Bu	70	40	**35a**/**35b** = 83:17

[a] Reaction conditions: 1.5 M THF *N*-aryl aziridine solution in a steel autoclave for 8 h with $TPPH_2$/TBACl/aziridine = 1:5:100 at 125°C and 1.2 MPa of CO_2. [b] Determined by ^{1}H NMR using 2,4-dinitrotoluene as the internal standard. [c] Isolated by flash chromatography



Scheme 3. Tandem synthesis of oxazolidin-2-ones **2a**/**2b, 18a** and **37a**

It should be underlined that the tandem reaction was effective when the aziridination occurred without a complete azide conversion, as in the case of the less reactive 4-(OMe)$C_6H_4N_3$ azide, whose reaction with styrene formed corresponding aziridine **17** in a non-quantitative yield. In this latter case, the crude of the aziridine formation, containing both Ru(TPP)CO and unconverted *N*-aryl azide, was treated as described above and compound **18a** was obtained with values comparable to those reported in entry 9 of Table 2. This experiment indicated that the outcome of the second step of the tandem procedure was not affected by the presence of any reaction components previously used for the synthesis of *N*-aryl aziridine, including Ru(TPP)CO, which did not have any catalytic influence in the CO_2 cycloaddition.

It is worth noting that the tandem procedure was also effective for synthesizing, as the only regioisomer, oxazolidin-2-one **37a**, which is a potent anti-inflammatory, being a Δ-5 desaturase (D5D) inhibitor[19] (Scheme 3). Although a modest reaction productivity (35 % yield) was observed, this result is noteworthy in view of the in vitro pharmaceutical activity of **37a**, which has previously been obtained from corresponding epoxide in the very low yield of 3-4 %.[19]

We can envisage a general application of the tandem methodology for synthesizing NAOs for the following reasons: i) The presence of Ru(TPP)CO doesn't compromise the CO_2 cycloaddition to N-aryl aziridine; ii) The styrene excess, which is required in the aziridination step, can either be eliminated during the solvent evaporation (when low-boiling liquid styrenes are used) or separated during the chromatographic purification of oxazolidin-2-one; iii) When the ArN_3 consumption is incomplete, the residual azide amount doesn't alter the oxazolidin-2-one formation and it can be easily removed during the chromatographic purification of oxazolidin-2-one.

Theoretical investigation of the N-aryl oxazolidin-2-one formation.

In order to shed some light on the catalytic role of porphyrin $TPPH_2$ in the CO_2 cycloaddition into *N*-aryl aziridines, a DFT study was carried out. Previous theoretical studies on the oxazolidinone formation either investigated the active role of metals in activating aziridine towards the CO_2 nucleophilic attack[20] or modelled uncatalyzed reactions.[21] In these latter cases, very high energy barriers were calculated (*ca.* 50 kcal mol^{-1}) emphasizing the positive effect of a metal catalyst on the reaction efficiency. In all the reported DFT studies, *N*-alkyl aziridines were considered as the starting materials.

Since computational data on the CO_2 cycloaddition to *N*-aryl aziridines promoted by an organocatalyst has not been reported yet, we started our investigation (see Computational Details for more information) by modelling the most plausible arrangements and interactions between all the involved reactants, namely TBACl, $TPPH_2$, *N*-aryl aziridine (**1**) and CO_2. Fixing the porphyrin macrocycle, as the 'ground floor' of these molecular architectures, the formation of different adducts between $TPPH_2$ and alternatively CO_2 (adduct **38a**), TBACl (adduct **38b**) and aziridine (**1**) (adduct **38c**) were evaluated without introducing any structural simplification (Figure 2).

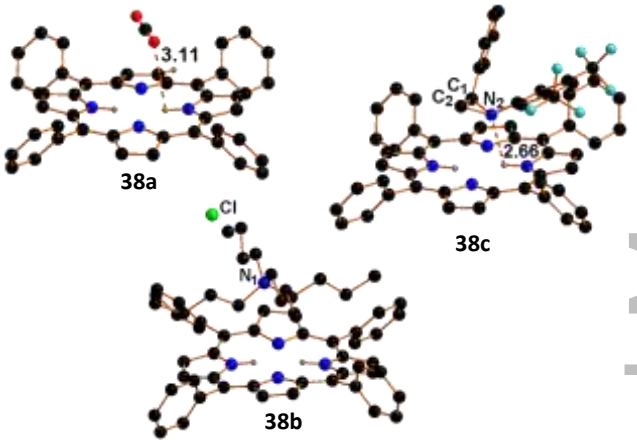


Figure 2. Optimized structures of adducts between $TPPH_2$ and CO_2 (**38a**), TBACl (**38b**) and *N*-aryl aziridine **1** (**38c**). Hydrogen atoms are omitted for clarity.

The formation of the adduct **38a** was discharged in view of its endergonicity (+3.5 kcal mol^{-1}) as well as the long distance between the porphyrin core and CO_2 in the optimized structure (3.11 Å). On the other hand, the formation of **38c**, although feasible from an energy viewpoint (-4.8 kcal mol^{-1}), was also excluded since all the investigations of its further evolution into the final *N*-aryl oxazolidin-2-one **2** failed. It worth noting that an adduct similar to **38c** was optimized by T. Ema *et al.* in the study of the calix[4]pyrrole-catalyzed cyclic carbonate synthesis by the reaction of epoxide with CO_2.[22] In this case, the adduct stability was ascribed to the establishment of hydrogen-bonding interactions between the oxygen atom of epoxide and the pyrrolic protons of the macrocyclic molecule. Conversely, the presence of hydrogen bonds was not detected in **38c** due to the long distance (2.66 Å, Figure 2) between NH

moieties of the tetrapyrrolic core and the aziridine nitrogen atom.

On these bases, the computational analysis was performed by considering **38b** the starting adduct (Figure 2), whose formation was estimated to be exergonic by -7.5 kcal mol^{-1}. The presence of the peripheral *meso*-phenyl substituents was responsible for the establishment of a tridimensional arrangement where the TBACl salt was lodged through weak cooperative electrostatic interactions, which were well considered by using B97D functional.[23]

Next, the adduct **39**, which derived by the reaction of **38b** with aziridine **1**, was optimized with a free energy gain of -0.9 kcal mol^{-1} (Figure 3).

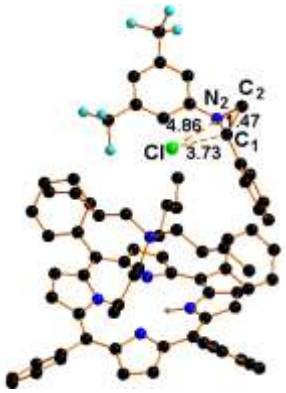


Figure 3. Optimized structure of the adduct **39**. Hydrogen atoms are omitted for clarity.

The comparison between **39** and **40**, which is formed between TBACl and **1** in the absence of $TPPH_2$ (see SI), highlighted the beneficial role of the porphyrin. In fact, while the adduct **39** is exergonically achieved (-8.4 kcal mol^{-1}), the formation of adduct **40** was endergonic by +3.5 kcal mol^{-1}. Next, the reaction proceeded by the ring-opening process due to the nucleophilic attack of the chloride anion to the aziridine C_1 atom, which is 1.13 Å closer than C_2 to Cl^- ion (Figure 3).

The transition state **39$_{TS}$** of the ring-opening step was located and the N_2-C_1 bond distance, which was 1.47 Å in adduct **39**, elongated to 2.23 Å in **39$_{TS}$** (Figure 4). Contemporary, the chloride anion efficiently exerted its nucleophilic action, since the Cl···C_1 distance was significantly shortened by *ca*. 1.29 Å (from 3.73 Å in **39** to 2.44 Å in **39$_{TS}$**). The free energy barrier, associated to the formation of **39$_{TS}$**, was estimated to be +23.5 kcal mol^{-1}.

After the transition state, the reaction evolved through the minimum **41** (Figure 4) with a free energy gain of -6.3 kcal mol^{-1}, compared to **39$_{TS}$**. In adduct **41**, the Cl-C_1 bond of 1.94 Å was formed and the N_2···C_1 distance elongated up to 2.48 Å, allowing the formation of an open $C_1C_2N_2$ chain. While the nitrogen N_2 atom, of the original aziridine cycle, increased its negative charge (the NBO, natural bond orbital, calculated charge[24] was -0.68 in **41** and -0.48 in **39**), an opposite trend was observed for the chloride anion, since its NBO calculated charge of -0.94 in **39** became -0.20 in **41**.

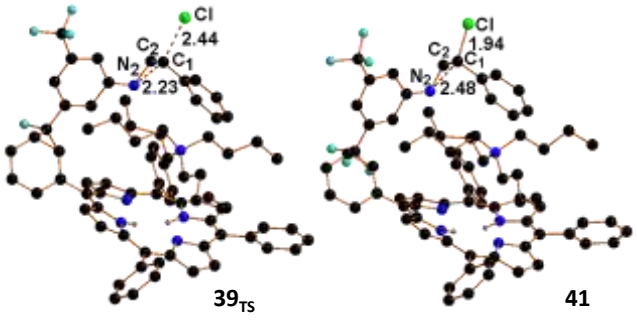


Figure 4. Optimized structure of transition state **39$_{TS}$** and adduct **41**. Hydrogen atoms are omitted for clarity.

Similarly to what observed in the cyclic carbonate formation catalyzed by the calix[4]pyrrole/TBAI binary system,[22] adduct **41** was 17.2 kcal mol^{-1} higher in free energy than the starting **39**. This result suggested that the productive formation of the final oxazolidinone might be due to following more favorable steps, involving the CO_2 activation and the ring-closing process (see below).

The negatively charged nitrogen N_2 atom of **41** was able to activate a CO_2 molecule with the consequent formation of adduct **42** with a N_2-C_3 bond of 1.52 Å and a bent O_1C_3O and O_1C_1Cl arrangements (129.6° and 120.6, respectively). Adduct **42** (Figure 5) was exergonically formed by -1.7 kcal mol^{-1} with the calculated CO_2 IR vibration at 1674 cm^{-1}. At this point, one of the two oxygen atoms of CO_2, namely O_1, was responsible for the ring-closing process with the consequent formation of **2a** and the chloride anion release.

The transition state **42$_{TS}$** of this final step was located and it showed an almost linear O_1-C_1-Cl arrangement (*ca*. 173.2°) and O_1···C_1 and C_1···Cl distances of 2.14 and 2.32 Å, respectively (O_1···C_1 and C_1···Cl distances in **42** were 3.83 and 1.89 Å, respectively). The free energy barrier, associated to the process, was estimated to be + 11.3 kcal mol^{-1}.

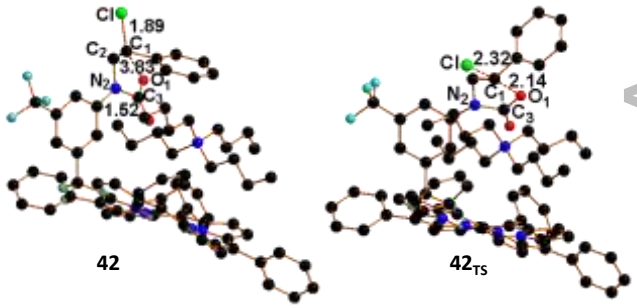


Figure 5. Optimized structure of **42** and transition state **42$_{TS}$**. Hydrogen atoms are omitted for clarity.

The production of the final compound **2a** occurred by the free energy gain of -28.1 kcal mol^{-1} and the restoration of the initial adduct **38b**, able to activate a new aziridine molecule **1** to restart another catalytic cycle. The complete free energy profile of the formation of **2a** is shown in Figure 6.

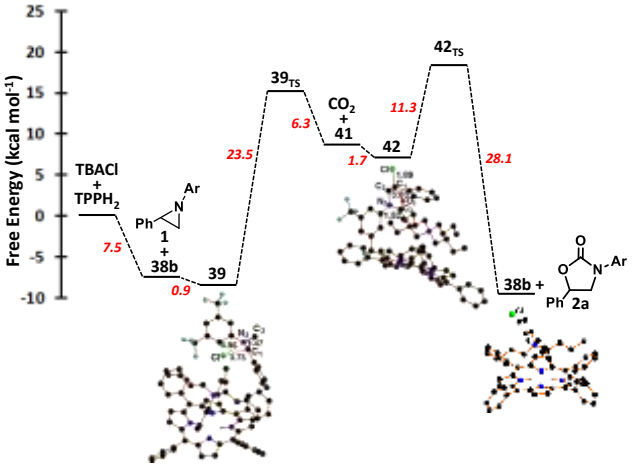


Figure 6. Free energy profile of the catalytic formation of *N*-aryl oxazolidin-2-one **2a.**

As shown in Figure 6, the highest encountered free energy barrier of 23.5 kcal mol^{-1} was much lower than those reported for uncatalyzed processes (*ca*. 50 kcal mol^{-1})[21b] to confirm the role of $TPPH_2$ in facilitating the catalytic cycle.

The reaction between aziridine **1** with CO_2, forming oxazolidin-2-one **2a**, was exergonic by -2.2 kcal mol^{-1}. The achieved value is consistent with others reported in literature for similar processes, such as the (salen)Cr-catalyzed aziridine/CO_2 coupling reaction, where the corresponding *N*-alkyl oxazolidin-2-one was located at -3.9 kcal mol^{-1}, with respect to the starting reagents.[20a]

Conclusion

In conclusion, we here report the cost-effective synthesis of differently substituted NAOs by using the $TPPH_2$/TBACl-based eco-friendly synthetic procedure. The reactivity which was observed in the presence of TBACl alone deserves a particular attention to better evaluate the real efficiency of the employed catalytic systems. In our case, the addition of 1.0 mol % of $TPPH_2$ had a positive effect on the reaction productivity and this result is noteworthy in view of the low cost, commercial availability and no toxicity of the porphyrin catalyst.

The DFT study of the reaction underlined the beneficial effect of $TPPH_2$ on the synthesis of the oxazolidin-2-ones through the formation of stable adducts. In the presence of $TPPH_2$ the free energy barrier of the reaction was halved with respect those reported for the uncatalyzed CO_2 coupling to *N*-alkyl aziridines.

Finally, a tandem reaction, which did not require the purification of *N*-aryl aziridine, was developed. The tandem methodology allowed the synthesis of the pharmaceutically active *N*-aryl oxazolidin-2-one **37a** in a yield higher than that reported in literature.

The very high sustainability and atom-economy of the procedure is assured by merging the virtuous use of CO_2, as a raw material, with the conversion of *N*-aryl azides into NAOs by producing benign molecular nitrogen as the only stoichiometric by-product of the two-step procedure. Note that also the aziridination step of the tandem procedure was efficiently catalyzed by a commercially available compound.

Experimental Section

SI contains experimental details for the synthesis and characterization of all products, copies of NMR spectra and the coordinates and free energies of all the optimized structures.

General synthesis of *N*-aryl oxazolidin-2-ones reported in Table 2: In a 2.0 mL glass liner equipped with a screw cap and glass wool, tetraphenylporphyrin (2.3 mg, 3.75 x 10^{-3} mmol), tetrabutyl ammonium chloride (5.2 mg, 3.75 x 10^{-2} mmol) and aziridine (3.75 x 10^{-1} mmol) were dissolved in THF (0.25 mL). The reaction mixture was cooled to -78°C and the vessel was transferred into a stainless-steel autoclave; three vacuum-nitrogen cycles were performed and 1.2 MPa CO_2 was charged at room temperature. The autoclave was placed in a preheated oil bath at 125°C and stirred for 8 h, then it was cooled at room temperature and slowly vented. The solvent was evaporated to dryness and the crude analyzed by ^{1}H NMR spectroscopy by using 2,4-dinitrotoluene as the internal standard. The product was isolated by flash chromatography (silica gel, *n*-hexane/ethyl acetate = 9:1).

General synthesis of *N*-aryl oxazolidin-2-ones by the tandem procedure: In a Schlenk flask, Ru(TPP)(CO) (0.25 g, 3.37 x 10^{-2} mmol), the desired styrene (8.40 mmol) and *N*-aryl azide (1.68 mmol) were refluxed in benzene (50 mL). After 4.0 h, two mL of the solution were taken, dried *in vacuo* and analyzed by ^{1}H NMR spectroscopy after adding 2,4-dinitrotoluene as the internal standard in order to determine the aziridine yield. When the reaction was complete, the solvent was evaporated to dryness *in vacuo*, the crude dissolved in the opportune THF volume (the aziridine concentration has to be 1.5 M) and transferred a 2.0 mL glass liner equipped with a screw cap and glass wool. Next, tetraphenylporphyrin and tetrabutyl ammonium chloride were added and, after cooling to -78°C, the vessel was transferred into a stainless-steel autoclave. Three vacuum-nitrogen cycles were performed and 1.2 MPa CO_2 was charged at room temperature. The autoclave was placed in a preheated oil bath at 125°C, stirred for 8 h, then cooled to room temperature and slowly vented. The solvent was evaporated to dryness and the crude analyzed by ^{1}H NMR spectroscopy by using 2,4-dinitrotoluene as the internal standard. The product was isolated by flash chromatography (silica gel, *n*-hexane/ethyl acetate = 9:1).

Computational Details. All the minima and transition states along the Potential Energy Surface were isolated and characterized at B97D-DFT level of theory [23] within the Gaussian 16 package.[25] The inclusion of the dispersion forces into the functional was important for taking into account the weak interactions between the different reactants in the formation of adducts. All the optimized structures were validated as minima or transition states by the vibrational frequencies calculations. All the

calculations were based on the CPCM model[26] for the tetrahydrofuran, the solvent that was experimentally used. The 6-31G basis set, with the addition of the polarization functions (d, p) was adopted.

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FULL PAPER

A Metal-Free Synthesis of *N*-Aryl Oxazolidin-2-ones by the One-Pot Reaction of Carbon Dioxide with *N*-Aryl Aziridines

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