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COMMUNICATION

Organocatalyzed Carboxylative Cyclization of Propargylic Amides with Atmospheric CO_2 towards Oxazolidine-2,4-diones

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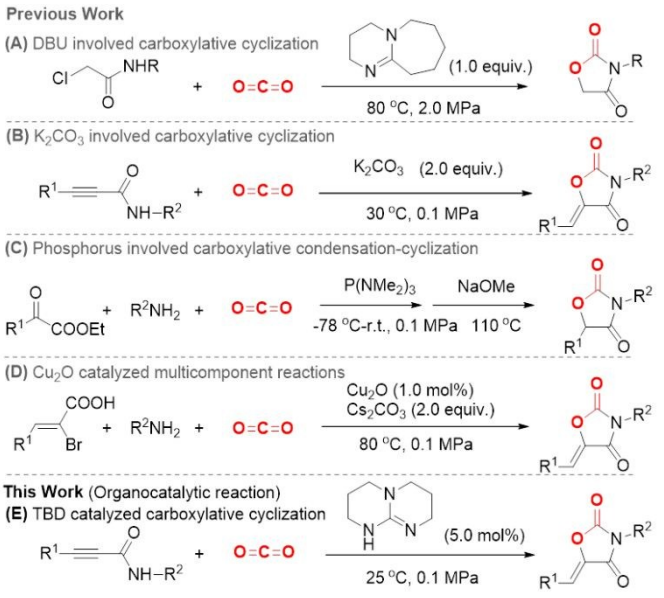
The metal-free carboxylative cyclization of propargylic amides with CO_2 to oxazolidine-2,4-diones was achieved for the first time employing 1,5,7-triaza-bicyclo-[4.4.0]dec-5-ene (TBD) as organocatalyst. The method allows for the efficient and selective synthesis of a variety of (*Z*) 5-alkylidene 1,3-oxazolidine-2,4-diones, and a variety of functional groups are well-tolerated under mild reaction conditions. Theoretical studies reveal that the bifunctional activity (base/H-bond donor) of TBD plays a key role in accelerating this reaction.

Oxazolidine-2,4-diones are important motifs in organic chemistry, due to their widespread presence in natural products and the actual uses in medicine and agriculture as antiepileptic agents, anti-inflammatory agents, and herbicides.[1] Traditional synthetic methods of oxazolidine-2,4-diones mostly require multistep reactions and relatively harsh conditions, in which toxic and hazardous compounds such as phosgene or isocyanates are usually involved.[1a,2] In view of environmental-friendly point, catalytic transformations of CO_2 generating high value-added chemicals and polymers provide a greener alternative to this area.[3] Up to now, several examples have been described in the literature on the construction of oxazolidine-2,4-diones using CO_2 as a feedstock, as shown in Scheme 1. Among them, Saliu and co-workers reported that 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) mediated the carboxylation of *N*-substitued-2-chloroacetamide with CO_2 in one-step procedure (Scheme **1A**).[4] Later on, Ma group reported that K_2CO_3 involved the carboxylation of propargylic amides with CO_2, selectively yielding 5-alkylidene cyclic oxazolidine-2,4-diones under ambient conditions (Scheme **1B**).[5] Recently, Zhang and coworkers presented a tandem phosphorus mediated carboxylative condensation of primary amines and *α*-ketoesters using atmospheric CO_2 as a carboxylative reagent, and one-pot NaOMe-catalyzed cyclization to construct functionalized oxazolidine-2,4-diones (Scheme **1C**).[6]



Scheme 1. CO_2 involved synthesis of oxazolidine-2,4-diones

In contrast to the above processes mediated by stoichiometric organic/inorganic bases, approach to catalytic carboxylation reactions using CO_2 as carboxylative agent is highly desired. Up to now, the only catalytic precedent reported by Kim *et al* is Cu_2O catalyzed three-component reaction of amines, 2-bromo-3-phenylacrylic acid and CO_2 in the presence of two equivalent of $CsCO_3$ (Scheme **1D**)[7]. Herein, we firstly present an effective metal-free catalytic strategy to prepare oxazolidine-2,4-diones by the carboxylative cyclization of propargylic amides with atmospheric CO_2 at room temperature, employing 1,5,7-triaza-bicyclo-[4.4.0]dec-5-ene (TBD) as organocatalyst. Notably, this mild method is a convenient and operationally simple protocol to afford functionalized 5-alkylidene 1,3-oxazolidine-2,4-diones with high chemo- and stereoselectivity (Scheme **1E**).

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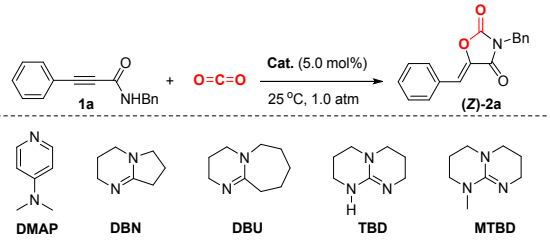
Table 1. Nitrogen Lewis bases catalyzed carboxylative cyclization of *N*-benzyl-3-phenylpropiolamide **1a** with CO_2[a]

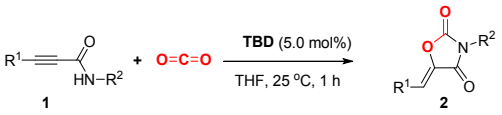


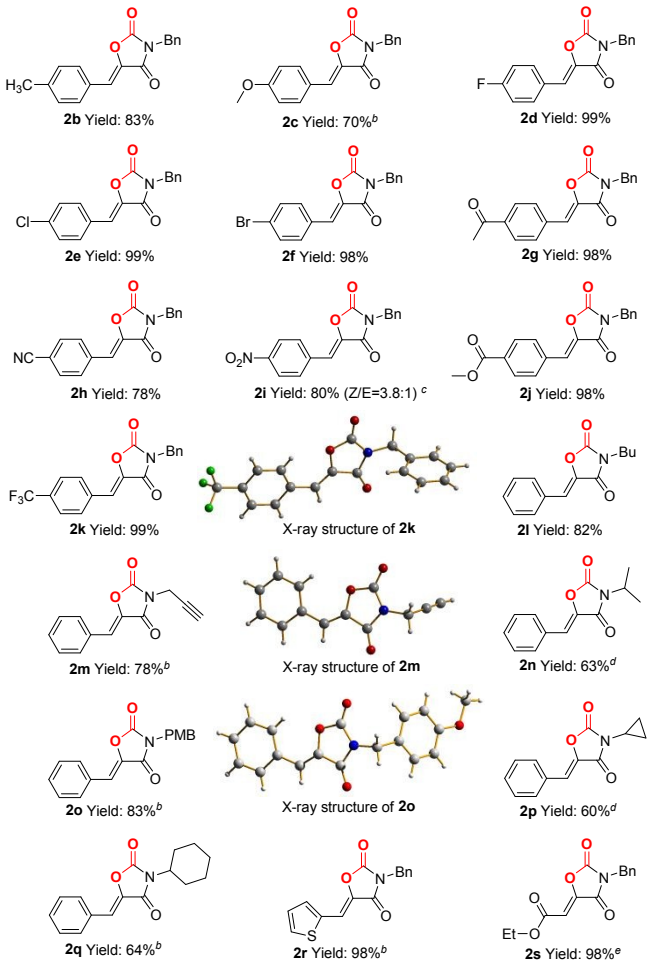
Entry	Cat.	solvent	t (h)	Yield (%)[b]
1	DMAP	DMF	1	NR[c]
2	DBN	DMF	1	16
3	DBU	DMF	1	23
4	TBD	DMF	1	50
5	MTBD	DMF	1	33
6	TBD	DMSO	1	16
7	TBD	DCM	1	44
8	TBD	CH_3CN	1	75
9	TBD	THF	1	98
10[d]	TBD	THF	4	5
11	-	THF	4	NR[c]

[a] General reaction conditions: Propargylic amide **1a** (0.5 mmol), **Cat**. (0.025 mmol, 5 mol%), Solvent (0.2 mL), CO_2 (1.0 atm), 25 °C. [b] Determined by ^{1}H-NMR spectroscopy. [c] No reaction. [d] Hydrous THF used as solvent. DMAP = 4-dimethylaminopyridine, DBN = 1,5-Diazabicyclo[4.3.0]non-5-ene, DBU = 1,8-Diazabicyclo[5.4.0] undec-7-ene, TBD = 1,5,7-triaza-bicyclo-[4.4.0]dec-5-ene, MTBD = 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene.

Initially, we systematically examined the carboxylative cyclization of *N*-benzyl-3-phenylpropiolamide **1a** with CO_2 as a benchmark reaction, employing common and commercially available nitrogen Lewis bases as organocatalysts in a variety of solvents at ambient conditions. The results are summarized in Table 1. When using **DMAP** as organocatalyst, the reaction didn't occur in DMF solution (Table 1, entry 1). To our delight, this carboxylative cyclization took place when changing to **DBN** or **DBU**, and the desired oxazolidine-2,4-dione **2a** as the sole product was obtained in 16% and 23% yield within 1 h, respectively (Table 1, entries 2 and 3). In addition, the absolute stereostructure of (*Z*)-**2a** was clearly confirmed based on the previous literature.[5] By further using **TBD** or **MTBD**, we found that the product **2a** was produced in higher yield (Table 1, entries 4 and 5). The solvent effect has also been examined in the presence of **TBD** (Table 1, entries 6-9). We found that THF was the optimal solvent for this reaction, and up to 98% yield was obtained within only 1 h. It should be pointed out that this process is usually carried out under strictly water-free conditions. When using wet THF as solvent, only 5% yield of **2a** was obtained within 4 h (Table 1, entry 10). Moreover, no reaction was observed in the absence of catalyst (Table1, entry 11).

Table 2. TBD-catalyzed carboxylative cyclization of functionalized propargylic amides with CO_2[a]





[a] General reaction conditions: Propargylic amide **1** (0.5 mmol), TBD (0.025 mmol, 5 mol%), THF (0.2 mL), CO_2 (1.0 atm), 25 °C. Yields were determined by ^{1}H-NMR spectroscopy of the crude mixture. [b] Reaction time: 6 h. [c] The ratio of *Z*/*E* within parentheses was determined by ^{1}H-NMR spectroscopy of the crude mixture. [d] CO_2 (2.0 MPa), 80 °C, DMSO (0.2 mL). [e] DBU as organocatalyst.

The substrate scope of the reaction was then explored using anhydrous THF as solvent at standard conditions (5.0 mol% TBD loading, 25 °C, and 1.0 bar of CO_2). The results are shown in Table 2. A range of propargylic amides with electron-donating (**2b** and **2c**) and electron-withdrawing (**2d-2k**) groups on phenyl ring, were tolerated in this process, providing the desired products in moderate to good yields with excellent stereoselectivity. Note that the nitro group attached on phenyl ring **1i** showed a relatively lower stereoselectivity to form **2i** in 80% isolated yield. Meanwhile, various functionalized alkyl (-R^2) amides were also found to be suitable reaction partners (Table

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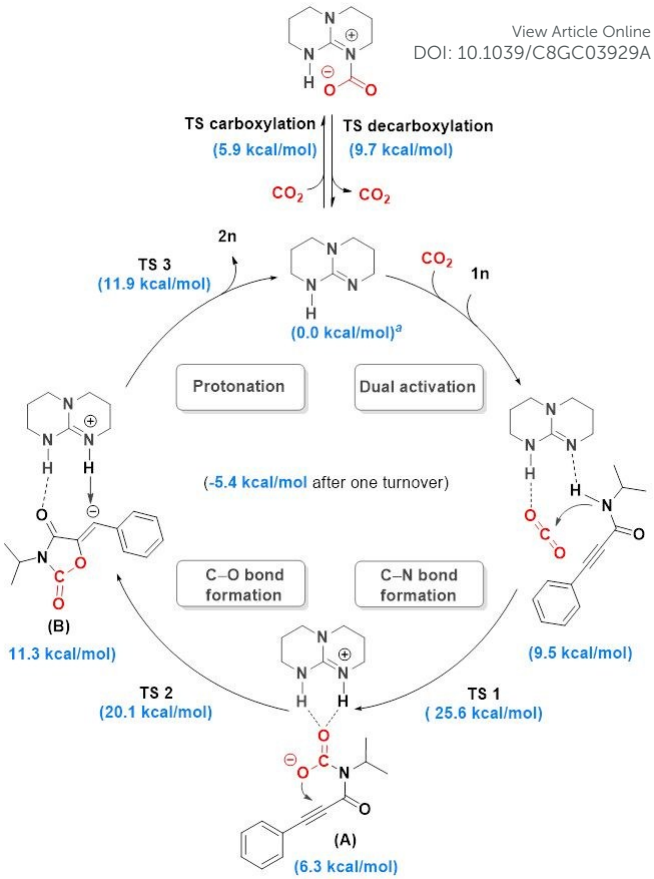
2, **2l-2q**). It is interesting to note that the reaction of *N*-propargylic precursor **1m** containing two carbon-carbon triple bonds, gave the desired oxazolidine-2,4-dione **2m** with high chemoselectivity, which could be applied for in vivo bioorthogonal reactions through the use of click chemistry.[8] In addition, the presence of a thiophene group on the acetylenic carbon atom did not hamper the successful preparation of **2n**, and an isolated yield of 98% could be obtained by a prolonging reaction time of 6 hours. When employing DBU as organocatalyst, proprargylic derivative **1s** with ester group was also applicable in this process. Furthermore, the absolute (*Z*) configuration of **2k**, **2m** and **2o** were clearly proved by X-ray crystallographic analysis, respectively.

To gain more insight into the reaction mechanism, a series of control experiments were investigated by means of In-situ FTIR and ^{1}H-NMR spectroscopy (Supporting Information. Figure S1-S5). Noting that CO_2 could be activated by strong organic bases, especially, organic guanidines,[9] and the corresponding TBD-CO_2 adduct was firstly isolated in THF solution due to the hydrogen bonding interaction.[10] Figure S1 showed that TBD also could rapidly react with free CO_2 in CH_2Cl_2 solution and the carbonyl peak of TBD-CO_2 adduct at 1713 cm^{-1} gradually increased within 2 hours. Meanwhile, TBD as organic base could also activate propargylic amides. In Figure S2, the peak associated to carbonyl group of **1a** smoothly shifts towards lower frequencies, from 1655 cm^{-1} after 2.0 h to 1622 cm^{-1}. Furthermore, the interaction of TBD and **1a** was proved by ^{1}H-NMR titration experiments, in which the -N*H*- signal (δ 6.20 ppm) completely disappears in the presence of 1.0 equivalent TBD, while the Ar*CH*$_2$- signal (δ 4.55 ppm) undergoes a modest downshift of -0.05 ppm (Figure S5). Moreover, propargylic amide **1a** due to the low nucleophilicity of the nitrogen atom, is very stable under CO_2 atmosphere, and no observable change in the absorption intensity at 1655 cm^{-1} was found (Figure S3). When TBD was subsequently added into the solution, the carbonyl peak of **1a** at 1655 cm^{-1} gradually decreased and the carbonyl peak of desired oxazolidine-2,4-diones **2a** at 1818 cm^{-1} and 1743 cm^{-1} simultaneously increased (Figure S4).

On the basis of preliminary mechanistic studies and previous reports,[11] a plausible mechanism is proposed to account for this transformation (Scheme 2). Meanwhile, density functional theory (DFT) B3LYP-D3(BJ) was employed to investigate the mechanism, and its potential energy curves are illustrated in Supporting Information, Figure S10. In the first step of this process, the hydrogen attached to the nitrogen of TBD activates the carbonyl group of free CO_2, and the imine nitrogen simultaneously activates the propargylic amides by attracting the hydrogen of its amide group through a lone pair interaction. Then, in the transition state **TS1** with an energy barrier of 25.6 kcal/mol, both C-N bond formation and proton transfer occur at the same time, and a new [TBDH]$^+$carbamate ionic pair intermediate **A** is formed. It is worth noting that the low transformation barriers for the CO_2 addition of TBD and the decarboxylation of TBD-CO_2 adduct show the reversible CO_2 binding with TBD under room temperature (Supporting Information, Figure S9). Because TBD-CO_2 adduct is sensitive to



Scheme 2. Plausible reaction mechanism. *a* The Gibbs free energy in solution are relative to the energy sum of TBD, CO_2, and **1n**

hydrolysis,[10, 12] which leads to form the corresponding [TBDH]$^+$ bicarbonate salt, it is necessary to carry out this process in an anhydrous reaction condition. During the subsequent attack of oxygen anion in the intermediate **A** on the C≡C bond of propargylic amide, the step should overcome an energy barrier of 20.1 kcal/mol to form an alkenyl anion intermediate **B**. Finally, the [TBDH]$^+$ cation provides the proton to the alkenyl anion *via* transition state **TS3** with an energy barrier of 11.9 kcal/mol, leading to generate 5-alkylidene cyclic oxazolidine-2,4-diones and the recovery of free TBD. The overall reaction is exothermic by 5.4 kcal/mol and the insertion step of free CO_2 to N-H bond of propargylic amides is the rate determining step *via* the dual activation by TBD through hydrogen bonding, which is in well agreement with the experimental results.

Conclusions

In conclusion, we have developed a high efficient cyclization of propargylic amides with atmospheric CO_2 employing commercially available TBD as organocatalyst, allowing a facile access to (*Z*) 5-alkylidene oxazolidinones in good yields with excellent chemo- and stereoselectivity. To the best of our knowledge, the reported system is the first metal-free catalyst for this transformation. The reaction operates under very mild reaction conditions (25 °C, p_{CO2}=1.0 atm, 5 mol% catalyst) and

tolerates a wide range of functional groups. Theoretical studies reveal that the hydrogen bonding of the TBD is crucial to accelerate the catalytic process.

Conflicts of interest

There are no conflicts to declare

Acknowledgements

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A facile and practical TBD-catalyzed carboxylative cyclization of propargylic amides with atmospheric CO_2 has been developed for the formation of (*Z*) 5-alkylidene 1,3-oxazolidine-2,4-diones.