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Multifunctional 1,3-diphenylguanidine for the carboxylative cyclization of homopropargyl amines with CO_2 under ambient temperature and pressure†

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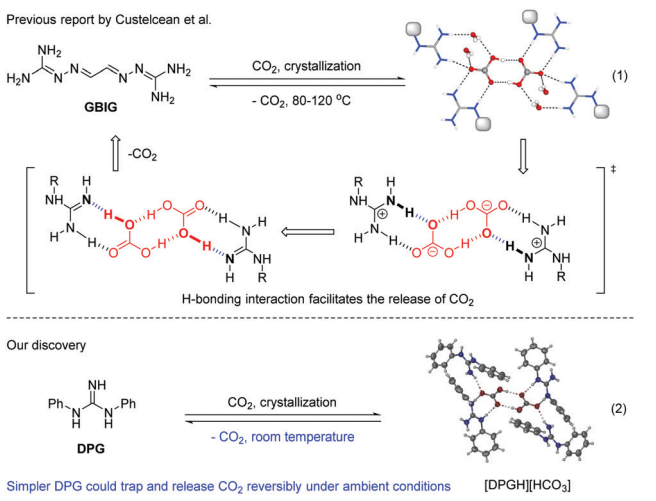
Herein, we report that 1,3-diphenylguanidine (DPG) could be utilized for the carboxylative cyclization of homopropargyl amines with CO_2 under ambient temperature and pressure, in combination with $AgSbF_6$, which enabled the synthesis of both chiral and achiral 2-oxazinones efficiently. A mechanistic study revealed that the multi-functionality of DPG is critical to the success of the reaction.

The development of green carbon science, which focuses on the transformations of carbon-containing compounds in the entire carbon cycle, is of great importance for the sustainable development of our society.[1] In this context, the recycling of CO_2 as an inexpensive, nontoxic and renewable C1 synthon for the efficient synthesis of industrially attractive fuels and value-added chemicals has attracted ever-increasing attention.[2] However, due to the inherent thermodynamic stability and kinetic inertness, many chemical transformations of CO_2 require high pressures to increase its concentration in the system, which results in indirect production of additional CO_2, and thus these transformations are net CO_2 emitters rather than consumers.[3] Therefore, the development of efficient protocols which can capture and release CO_2 under ambient conditions allowing the facile and effective fixation of CO_2 into complex molecules is highly desirable but challenging.

Currently, most organic CO_2 capture materials involve amine moieties, taking advantage of their strong binding with CO_2 *via* the formation of a carbamate or (bi)carbonate anion.[4] However, also because of the strong binding interaction, although the capture of CO_2 could be performed under mild conditions, the release of CO_2 typically requires high temperatures, especially for the (bi)carbonate involved process.[4c,d] On the other hand, if the capture materials are capable of hydrogen-bonding with (bi)carbonates anions, a low-temperature CO_2 release path might be realized, in which the anions could be activated toward neutralization by proton transfer along the H-bonds, thus resulting in the formation of easily decomposed carbonic acid dimers. Based on this concept, Custelcean and co-workers gave an elegant example just recently, in which the simple aqueous guanidine glyoxal-bis(iminoguanidine) (GBIG), bearing four N–H bonds, could capture CO_2 under room temperature and release CO_2 by mild heating (eqn (1), Scheme 1).[5]

Inspired by this fascinating study and based on our research on the chemical fixation of CO_2,[6] we found that the simpler 1,3-diphenylguanidine (DPG), bearing three N–H bonds and two phenyl substituents, could efficiently trap and release CO_2 reversibly under ambient conditions in the form of crystalline H-bonded bicarbonate dimers (eqn (2), Scheme 1). This novel



Scheme 1 The trapping and release of CO_2.

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† Electronic supplementary information (ESI) available: Experimental procedures, mechanism studies, characterisation data, NMR spectra, X-ray crystal structures. CCDC 1894496 and 1907983. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c9cc07671a

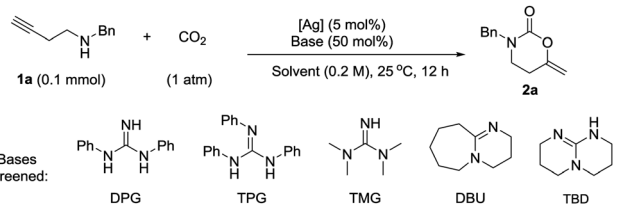
discovery along with the fact that guanidine type superbases have been used in many applications in CO_2 capture and conversion,[7] promote us to see whether DPG could be used to realize some challenging CO_2 chemical transformations under ambient conditions.

Among the diverse routes for chemical fixation of CO_2 developed to date, the carboxylative cyclization of alkynyl amines is one of the most promising strategies as it enabled the construction of cyclic carbamates effectively (Scheme 2).[8] Since the seminal work of Mitsudo and Watanabe,[9] the cyclization of α-propargyl amines with CO_2 to access 2-oxazolidinones has been intensively studied.[10] However, the use of this strategy to construct six-membered 2-oxazinones,[11] an important class of heterocycles present in a variety of natural products and bioactive molecule as well as useful building blocks in organic synthesis, is rarely reported.[12] Until now, to the best of our knowledge, it is still challenging to develop 6-membered carboxylic cyclization of homopropargyl amines and CO_2 under ambient conditions (25 °C, 1 atm of CO_2).[13]

Herein, we wish to report that DPG could be utilized for the carboxylative cyclization of a homopropargyl amine with CO_2, with the combination of $AgSbF_6$, which enables the synthesis of both chiral and achiral six-membered 2-oxazinones efficiently at ambient temperature and pressure. More importantly, a mechanistic study revealed that the multi-functionality of DPG is critical to the success of the reaction.

The reaction of *N*-benzyl amine **1a** and CO_2 was undertaken for the evaluation. The reactions were run at 25 °C in 1,2-dichloroethane (DCE), with CO_2 held within a balloon. To our delight, under the catalysis of 5 mol% AgOBz and 50 mol% DPG, the reaction worked well to give the desired 2-oxazinone **2a** in 69% yield (entry 1, Table 1). The performance of other types of organic bases was then studied. The use of analogous TPG and TMG resulted in a greatly diminished 35% and 37% yield for **2a**, respectively (entries 2 and 3). The commonly used base DBU and TBD showed inferior 46% and 40% yields, respectively (entries 4 and 5). The performance of GBIG[6] was also studied, but no reaction occurred (entry 6). Considering that metal counterions are of critical importance in impacting the catalytic activity, different silver salts were evaluated in combination with DPG and $AgSbF_6$ was found to be the most efficient one, giving **2a** in 91% yield (entries 7–9). Further screening of solvents, such as CH_3CN, DMF failed to improve the result (entries 10 and 11). In the absence of $AgSbF_6$ or DPG, no reaction occurred at all (entries 12 and 13).

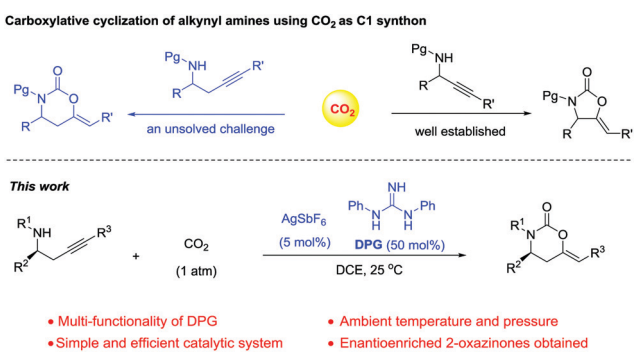
Table 1 Carboxylative cyclization reactions



Entry	[Ag]	Base	Solvent	Yield[a] (%)
1	AgOBz	DPG	DCE	69
2	AgOBz	TPG	DCE	35
3	AgOBz	TMG	DCE	37
4	AgOBz	DBU	DCE	46
5	AgOBz	TBD	DCE	40
6	AgOBz	GBIG	DCE	No reaction
7	AgOAc	DPG	DCE	66
8	AgTFA	DPG	DCE	82
9	$AgSbF_6$	DPG	DCE	91
10	$AgSbF_6$	DPG	CH_3CN	37
11	$AgSbF_6$	DPG	DMF	6
12	—	DPG	DCE	No reaction
13	$AgSbF_6$	—	DCE	No reaction

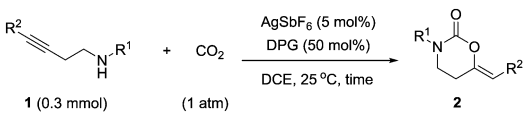
[a] Determined *via* GC-MS with decane as the internal standard.

Based on the aforementioned screenings, we determined to evaluate the substrate scope with respect to differently substituted homopropargyl amines by running the reaction at room temperature in DCE, in the presence of 5 mol% $AgSbF_6$ and 50 mol% DPG under 1 atm of CO_2, as shown in Table 2. In general, all the terminal *N*-benzyl type homopropargyl amines **1a–f** worked well to give the desired products **2a–f** in 86–92% yield (entries 1–6). The *N*-^{n}butyl and phenylpropyl terminal amines **1g–h** were viable substrates as well (entries 7–8). The *N*-cyclohexyl amine **1i** was less active possibly due to steric hindrance (entry 9). Internal homopropargyl amines **1j–k**, with an electron-withdrawing



Scheme 2 The carboxylative cyclization of alkynyl amines.

Table 2 Reactions with achiral 2-oxazinones



Entry	1	R^1	R^2	Time (h)	2	Yield[a] (%)
1	**1a**	Bn	H	12	**2a**	89
2	**1b**	4-$MeOC_6H_4CH_2$	H	12	**2b**	89
3	**1c**	4-$BrC_6H_4CH_2$	H	12	**2c**	92
4	**1d**	4-$MeC_6H_4CH_2$	H	13	**2d**	90
5	**1e**	3-$MeC_6H_4CH_2$	H	13	**2e**	91
6	**1f**	2-$MeC_6H_4CH_2$	H	13	**2f**	86
7	**1g**	^{n}Bu	H	57	**2g**	66
8	**1h**	$BnCH_2CH_2$	H	39	**2h**	74
9	**1i**	Cyclohexyl	H	57	**2i**	40
10	**1j**	Bn	$CO_2{}^i$Pr	22	**2j**	54
11	**1k**	Bn	$PO(OEt)_2$	20	**2k**	74
12[b]	**1l**	Bn	Me	80	**2l**	40

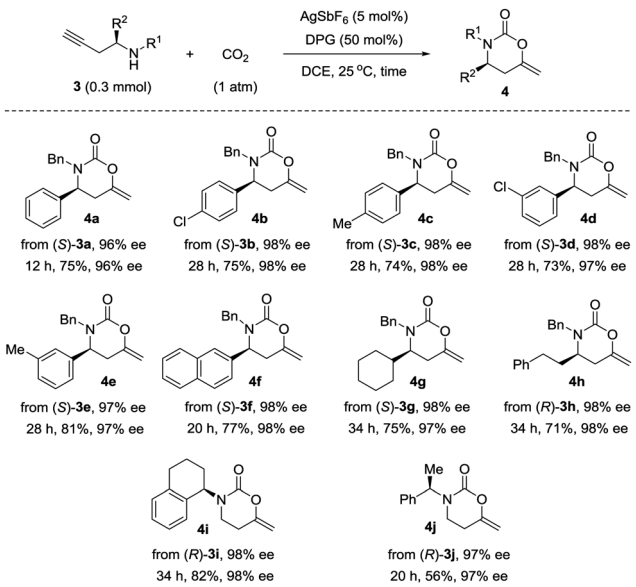
[a] Isolated yield. [b] $AgSbF_6$ was replaced by IPrAuCl (20 mol%), 10 atm CO_2, 50 °C.

ester or phosphate ester group, underwent the carboxylative cyclization smoothly (entries 10 and 11). The reaction of amine **1l** bearing an unactivated alkyne moiety could also give product **2l** in 40% yield (entry 12).

The high efficiency and mild conditions of the DPG catalyzed cyclization is very impressive, offering the promise of synthesizing chiral 2-oxazinones from easily available optically active homopropargyl amines *via* the carboxylative cyclization. Gratifyingly, all the chiral amines **3a–j** could afford the desired enantioenriched 2-oxazinones readily under standard conditions, without the erosion of ee values (Table 3). First, the reaction of optically pure homopropargyl amines featuring differently α-phenyl groups and α-naphthyl proceeded well to furnish chiral 2-oxazinones efficiently. Optically active amines bearing an α-aliphatic substituent, such as α-cyclohexyl and α-phenethyl, were also viable substrates. (*R*)-1-Aminotetralin together with (*R*)-1-phenylethylamine derived homopropargyl amines were also tried, and the corresponding chiral 2-oxazinones **4i** and **4j** could be facilely obtained.

The superiority of DPG over other organic bases in the carboxylative cyclization of CO_2 with both *N*-alkyl homopropargyl amines and *N*-aryl propargylamines[14] is very intriguing. Accordingly, a variety of analysis was conducted to gain more insight into the role of DPG. Initially, the detail for the trapping and releasing of CO_2 by DPG was studied. When CO_2 was bubbled into a solution of DPG in DCE at 0 °C, a white precipitate gradually formed, which could be obtained *via* a quick filtration. If the temperature was raised above 25 °C, the precipitate in the solution gradually disappeared with the release of CO_2 bubbles, which indicated that atmospheric CO_2 could be reversibly captured by DPG (for detail, see ESI†). NMR analysis of the precipitate in D_2O revealed that a bicarbonate salt [DPGH][HCO_3] was formed. Fortunately, a single crystal of the bicarbonate adduct was obtained, which showed that a centrosymmetric dimer was formed by the ''anti-electrostatic'' hydrogen-bonding between the oxygen atoms of the bicarbonate

Table 3 Reactions with optically active 2-oxazinones



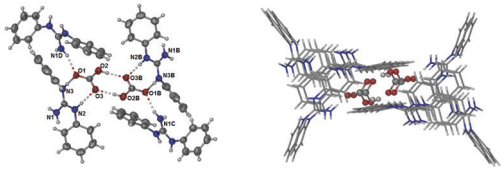
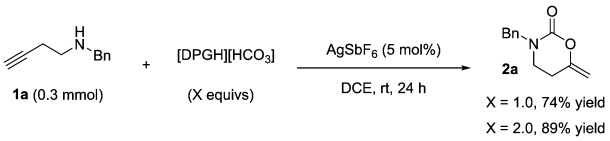


Fig. 1 The X-ray crystal structure of [DPGH][HCO_3].

anion [HCO_3]$^-$, and in each monomer the bicarbonate anion associated with the cation [DPGH]$^+$ through three hydrogen bonds between the oxygen and nitrogen atoms. In addition, the cationic stacks flank the anionic cluster in a close-packed arrangement (Fig. 1).

Then the reaction of homopropargyl amine **1a** with the bicarbonate adduct was performed in the presence of 5 mol% of $AgSbF_6$ under N_2 atmosphere at room temperature. By using 1.0 or 2.0 equivalents of bicarbonate salt, the desired product **2a** could be obtained in 74% and 89% yield, respectively. These results clearly revealed that DPG could reversibly trap CO_2 by forming the bicarbonate salt [DPGH][HCO_3].



The interaction of DPG with $AgSbF_6$ was also studied. NMR analysis revealed that with the addition of $AgSbF_6$, the characteristic peaks of DPG shifted gradually, supporting the binding of DPG to $AgSbF_6$ (for details, see the ESI†). In addition, HRMS analysis of the DPG–Ag(I) complex with different molecular ratios was conducted, and a signal at *m*/*z* 529.1248 was observed in all cases, consistent with a 1/2 complex cation, [$(DPG)_2$ + Ag]$^+$. Fortunately, we also obtained a single crystal of the DPG–$AgSbF_6$ complex upon crystallization of the 1/2 mixture of $AgSbF_6$ and DPG from CD_2Cl_2, which revealed that DPG served as a neutral monodentate ligand and bound to the silver center *via* a head-to-head fashion (Fig. 2). This is consistent with the HRMS analysis, and casts further light on the coordination fashion of DPG to $AgSbF_6$.[15]

To further probe the role of DPG during the reaction course, we further conducted the NMR analysis of the reaction mixture (for details, see the ESI†).

Based on these studies, a mechanism for the DPG/$AgSbF_6$ catalyzed carboxylative cyclization of homopropargyl amines with CO_2 was proposed tentatively, as shown in Scheme 3. The coordination of DPG to $AgSbF_6$ readily gave DPG–Ag complex **A**.

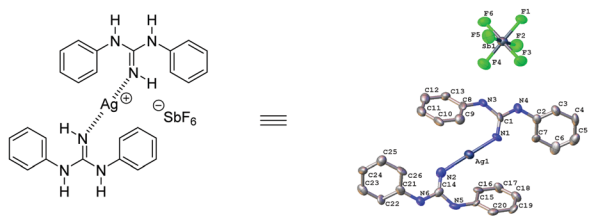
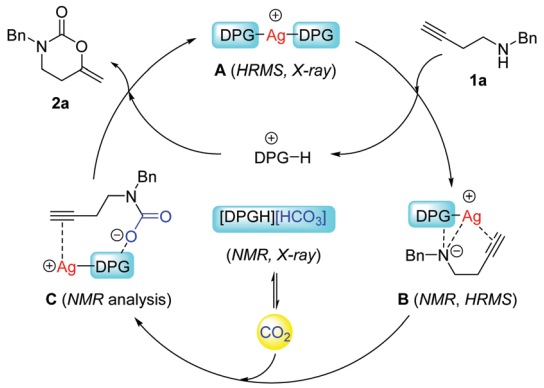


Fig. 2 The X-ray crystal structure of the DPG–Ag(I) complex.



Scheme 3 The proposed mechanism.

With the deprotonation of **1a** by DPG, the *in situ* generated homopropargyl amine anion coordinated to the DPG–Ag(I) to form the intermediate **B**. Then the reaction with CO_2 gave the carbamate intermediate **C**, which could be stabilized by DPG *via* possible H-bonding interactions. The simultaneous interaction of the carbamate and alkyne moiety with the DPG–Ag(I) complex facilitated the subsequent nucleophilic addition, affording the desired 2-oxazinone **2a** effectively. Notably, during the reaction, CO_2 could be reversibly trapped by DPG, thus enhancing the effective concentration of the reaction system, and finally enabled the reaction to proceed effectively.

In summary, we have found that the simple and easily available DPG, bearing three N–H bonds, could trap and release CO_2 under ambient conditions *via* the formation of crystalline H-bonded bicarbonate dimers. Based on this discovery, the unprecedented highly efficient carboxylative cyclization of homopropargyl amine with CO_2 under ambient temperature and pressure was realized. The combination of DPG with $AgSbF_6$ enabled the facile synthesis of both chiral and achiral 2-oxazinones in good to excellent yields with CO_2 as the C1 synthon. A mechanism study revealed that the multifunctionality of DPG is critical. Apart from enhancing the effective concentration of CO_2 in solution *via* trapping and releasing CO_2 under ambient conditions, it could also serve as a neutral monodentate ligand to coordinate with $AgSbF_6$ in a head-to-head fashion, as demonstrated by X-ray diffraction data, thus improving the efficiency of the reaction. The development of other novel CO_2 participating chemical transformations for the synthesis of value-added chiral chemicals is now in progress in our laboratory.

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Conflicts of interest

There are no conflicts to declare.

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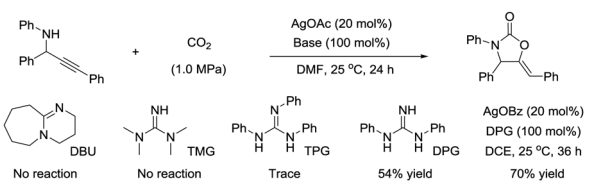
14 In our previously reported carboxylative cyclization of *N*-aryl propargylanilines with CO_2, DPG also showed unique activity compared to other bases, such as DBU, TMG and TPG. The representative results are shown below, for details see ref. 6b



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