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I_2-Mediated Oxidative Bicyclization of 4-Pentenamines to Prolinol Carbamates with CO_2 Incorporating Oxyamination of C=C Bond

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A metal-free oxyamination reaction of alkenes with ambient CO_2 is reported. In the presence of I_2 and DBU, CO_2 is applied in situ as protecting group to regulate nucleophilicity of amino group and facilitate the bicyclization of 4-pentenamines with high chemoselectivity. Moreover, this reaction provided a feasible approach to prepare prolinol carbamates with good tolerance of functional groups and high efficiency under mild conditions.

Prolinol and derivatives have been widely utilized in many asymmetric organic synthesis as ligands, catalysts or chiral auxiliaries.[1] Furthermore, the prolinol and derivatives are also significant scaffold frequently existing in the natural products[2] and pharmaceutical[3], for instance, (+)-allopumiliotoxin[2a] and stemonine[2f] as natural products contain prolinol skeletons. Iminoalditol served as reversible inhibitors of D-glycosidase[3b] and A-84543 displayed affinity for central neuronal nicotinic acetylcholine receptors[3a] (Figure 1). Consequently, many processes have been developed for efficient synthesis of prolinol derivatives. Traditionally, prolinol derivatives are often obtained from transformation of prolines. This method has a limitation for the synthesis of functionalized prolinols due to the weakness of getting functionalized prolines on the pyrrolidine.

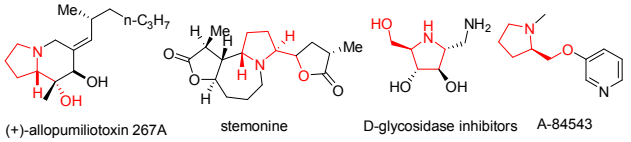

Fig.1 Selected biologically active prolinol derivatives

Due to the significance of alkenes for the past decades,[4] transition-metal-catalyzed oxyamination of alkenes has been reported for the construction of prolinol derivatives via sequentially intramolecular amination of alkene and oxygen-based nucleophiles. For example, Cu,[5a,5d] Os,[5b] Pd,[5c,5f] Au,[5e] and Mn[5g] were applied as catalyst to realize synthesis of prolinol derivatives in the presence of oxidant (Figure 2, a), which provided a straightforward method for the construction of the prolinol derivatives. Metal-free oxyaminations to construct this motif were also disclosed.[6] Although all works mentioned above for preparation of the prolinol derivatives are efficient, preprotected amine was required, which increase synthetic steps and decrease atom-economy. In addition, in some cases, reaction proceeded in both 5-exo and 6-endo cyclization modes to afford a mixture of products. Therefore, the development of a general and sustainable method for the synthesis of prolinol derivatives from easily available starting materials with good chemoselectivity and regioselectivity is highly desired.

Carbon dioxide (CO_2) is an abundant, low-toxic, environment-friendly and sustainable one-carbon synthons possessing great potential in preparation of value-added products. It has been utilized in the synthesis of carbamates[7] and various important heterocycles such as oxazolidones and cyclic carbonate.[8] However, relatively few chemical processes incorporating CO_2 were reported, which may be attributed to low reactivity of CO_2. Recently, combination of allylamines with CO_2 and some electrophiles to afford functionalized 2-oxazolidinones has been reported.[9] These works have well applied oxygen-based nucleophilic center generated from reaction of amine with CO2 and other electrophilic reagent such as *t*-BuOI,[9a] Togni's reagents,[9b] and perfluoroalkyl iodides[9c] to add to alkenes. We envisioned that 4-pentenamine to react with CO_2 may realize simultaneous oxyamination of C=C bond to form prolinol carbamate via tandem cyclization, which would provide a strategy to construct a variety of prolinol derivatives. Although oxyamination of 4-pentenamine using excess sodium bicarbonate in several days to form prolinol carbamate has been reported,[10] it is still a challenge for direct incorporation of CO_2 as synthon to form the prolinol carbamate via oxyamination of C=C. Inspired by the above-

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mentioned successes and our ongoing project on CO_2 chemistry,[11] herein, we reported a oxidative bicyclizcation of diverse 4-pentenamines with ambient CO_2 in the presence of I_2 and DBU at room temperature to produce prolinol carbamate, which are easily transferred into useful prolinol derivatives (Figure 2, b).

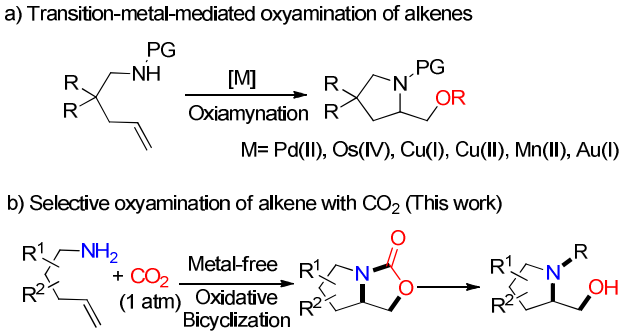
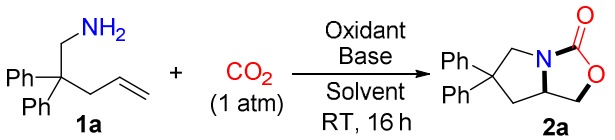


Fig.2 Oxyamination of alkenes

Initially, 2,2-diphenyl-4-pentenamine **1a** was selected as starting material. In principle, the oxidant is definitely needed to take away two redundant electrons for this reaction. We first examined the reaction of **1a** with CO_2 (1 atm) in the presence of $PhI(OAc)_2$ as an oxidant and DBU as the base in acetonitrile at room temperature (entry 1). Although trace desired product **2a** was observed by GC-MS, the oxidation of amine to the corresponding nitrile was obtained as major product in this case,[12] which means $PhI(OAc)_2$ was too reactive for this reaction to obtain the desired product. Other hypervalent iodine(III) reagents such as $PhI(OTf)_2$ and PhI(OH)OTs were employed and the reaction failed to give desired product. We thought that iodine as a milder oxidant might lead to desired product. To our delight, when iodine was added and the desired product **1a** was obtained in 94 % NMR yield (entry 4). Base might enhance the nucleophilicity of an amine or activate CO_2. Several bases such as ^{t}BuOK, TBD, Cs_2CO_3 and Et_3N were explored (entries 4-8), we were delighted to identify DBU as the best choice (entry 4). When DMF, THF, EtOH, and EtOAc were used as solvent, the yield of **2a** decreased (entries 9-12), nevertheless, EtOH and EtOAc demonstrate potential to replace MeCN as greener solvents. Furthermore, when H_2O was used as solvent, the yield of **2a** was obtained in 9% (entry 13). When the temperature was increased, **2a** diminished (entry 14). When amount of I_2 or DBU was reduced, yield of **2a** decreased (entries 15-16), which suggested that sufficient amount of I_2 and base were necessary to facilitate the bicyclization. The structure of **2a** was confirmed by X-ray crystallography (see supporting information).[13]

With optimal reaction condition (Table 1, entry 4) in hand, we explored the substrate scopes and the representative results are summarized in Scheme 1. Substituent effect of R^1 and R^2 was first investigated. Starting material bearing phenyl (**1a**), benzyl (**1b**), allyl (**1c**), *p*-tolyl (**1d**), *p*-flurophenyl (**1e**), 2-thiophene (**1f**), ester (**1g**) of R^1 and R^2 proceeded smoothly to afford the desired products **2a-2g** in good yields. Substrates with five-membered (**1h**) and six-membered (**1i**) cycloalkeneamines could also generate the corresponding spiro-bicyclic carbamates **2h** and **2i** in 81% and 70% yield, respectively. Substrate containing different substituents of R^1 and R^2 (**1j**, **1k**) were also tested. Monosubstituted substrate **1j** afforded a product with high diastereoselectivity. The NOE spectrum showed the major one

Table 1 Optimization of reaction conditions[a]



Entry	Oxidant	Base	Solvent	Yield %[b]
1	$PhI(OAc)_2$	DBU	MeCN	5
2	$PhI(OTf)_2$	DBU	MeCN	0
3	PhI(OH)OTs	DBU	MeCN	0
4	I_2	DBU	MeCN	94 (84)
5	I_2	^{t}BuOK	MeCN	84
6	I_2	TBD	MeCN	85
7	I_2	Cs_2CO_3	MeCN	50
8	I_2	Et_3N	MeCN	24
9	I_2	DBU	DMF	80
10	I_2	DBU	THF	83
11	I_2	DBU	EtOH	89
12	I_2	DBU	EtOAc	85
13	I_2	DBU	H_2O	9
14[c]	I_2	DBU	MeCN	75
15[d]	I_2	DBU	MeCN	46
16[e]	I_2	DBU	MeCN	50
17[f]	I_2	DBU	MeCN	76

[a]Reaction conditions: **1a** (0.5 mmol), 1 atm CO_2, oxidant (0.5 mmol, 1.0 equiv.), base (1.0 mmol, 2.0 equiv.), solvent (5 mL), room temperature (rt), 16 h. [b]NMR yields were detected with dibromomethane as an internal and isolated yield was demonstrated in parenthesis. [c]60 °C. [d]I_2 (0.25 mmol, 0.5 equiv.). [e]Base (0.5 mmol, 1.0 equiv.). [f]8 h. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, TBD = 1,5,7-triazabicyclo[4.4.0]dec-5-ene , DMF = *N*,*N*-dimethylformamide, DCM = dichloromethane, THF = tetrahydrofuran.

is large group (Ph versus H) in the *cis* product. When disubstituted substrate **1k** was employed and the product **2k** was isolated in 69% yield with diastereoselectivity in 5:4 ratio. Electronic effect of R^1, R^2 was obvious in this reaction. Substrate with electron-donating group such as methyl (**1h**) in benzene ring was more reactive to produce the product **2d** in 88% isolated yield while electron-withdrawing group such as fluorophenyl (**1e**) and ester group (**1g**) gave the products **2e** and **2g** in 65% and 47% yield, respectively. Except for substrates with different functional groups of R^1 and R^2, cyclosubstrates **1l** and **1m** also underwent tandem cyclization smoothly and afforded tricyclic carbamates **2l** and **2m** in good yields, but moderate diasteroselectivity were obtained. Notably, the two isomers could be easily seperated by flash chromatography on silica gel. We further explored the substrates with more steric hindrance in C=C bond, which is more challenging in difunctionalization reaction. When 1,1-

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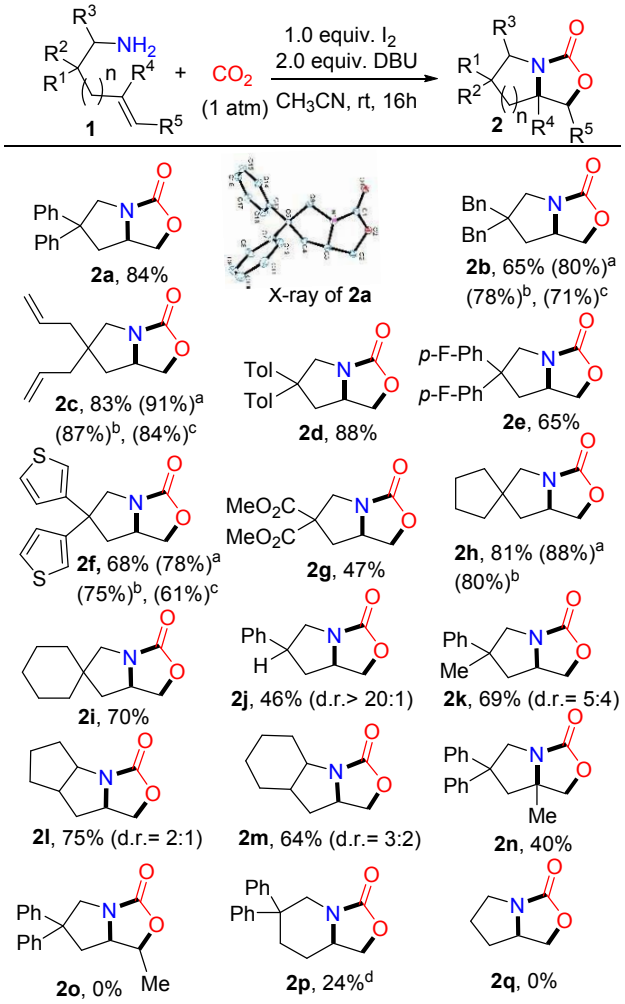
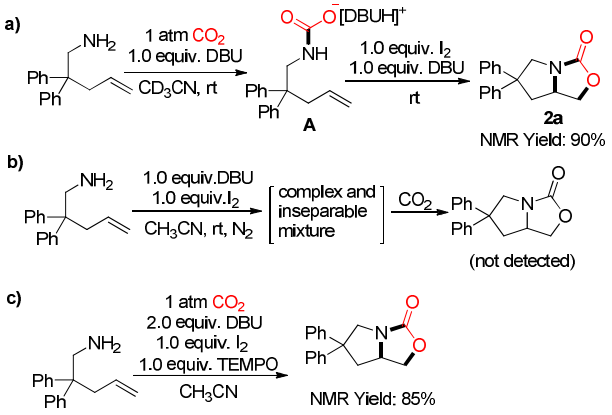
disubstituted alkeneamine **1n** was treated with CO_2 under the conditions and expected carbamate **2n** was formed in 40% yield. When 1,2-disubstituted alkenylamine **1o** was employed, the reaction failed to give the desired product **2o**. Notably, substrate with longer carbochain such as 5-hexenamine **1p** was used and tetrahydro-1H-oxazolo[3,4-a]pyridin-3(5H)-one **2p** was obtained in 24% yield even at 60 °C for 36 h. When non-substituted 4-pentenamine **1q** was employed, the reaction failed to afford the corresponding product **2q**, which may be contributed to flexibility of chain without substituents. Furthermore, **2b**, **2c**, **2f**, and **2h** could also be generated in good yields when the reaction was conducted in EtOH or EtOAc.



Scheme 1 Scope of 4-pentenamines.[a] [a]The standard reaction conditions, yields are those of the isolated products, the NMR yields are shown in parentheses. [b]The reaction proceed in the EtOH. [c]The reaction proceed in the EtOAc. [d]60 °C, 36 h.

Additional experiments were performed to gain more insight of this reaction. According to previous work, it is suspected that

carbamic salt **A** generated from amine with CO_2 might be the possible intermediate in this reaction. As a result, we first mixed 2,2-diphenyl-4-pentenamine **1a** with one equivalent of DBU under ambient CO_2 in CD_3CN at room temperature, the reaction was monitored by NMR. The NMR data showed that substrate **1a** was totally transformed to carbamic salt **A**. ESI data also supported formation of compound **A** (see supporting information). Subsequently, addition of another one equivalent of DBU and one equivalent of I_2 to the reaction mixture containing carbamic salt **A** and desired product **2a** was obtained in 90 % yield (Scheme 2, a). Secondly, when the reaction of **1a** was proceeded under the standard conditions in the absence of CO_2, any well-defined products were not observed,[14] unfortunately. Whereafter, CO_2 was injected to the above reaction mixture and no any product was obtained (Scheme 2, b). These experiments demonstrated that CO_2 is necessary to tune the reactivity of amino group in this tandem oxidative cyclization. Finally, radical scavengers such as TEMPO were added in the reaction under the standard conditions, the desired product **2a** was also observed in 85% yield (Scheme 2, c), which rules out the possibility of radical pathway in this reaction.



Scheme 2 Control experiments

In light of all results, we proposed a possible mechanism for this reaction (Scheme 3). First, in the presence of DBU, amino group is trapped by CO_2 to generate the carbamic salt **A**, which has been identified by NMR and ESI. Then, C=C bond may be activated by I_2 to generate intermediate **B**, and meanwhile reversible proton exchange occurs to generate active intermediate **C,** which leads to iodonium intermediate **D** and releases $[DBUH]^+I^-$. The nitrogen atom attacks the C=C bond *via* 5-*exo*-trig to form compound **E**. However, possible intermediate with N-I bond generated from nucleophilic substitution of N atom and I_2 directly could not be excluded, which is capable of yielding compound **E** via iodocyclization. Then, another molecular DBU captures the proton from carbamic acid **E** to form intermediate **F**.[15] The iodine of intermediate **F** is intramolecularly substituted by the oxygen of the carbamate **F** to give oxyamination product **2**.

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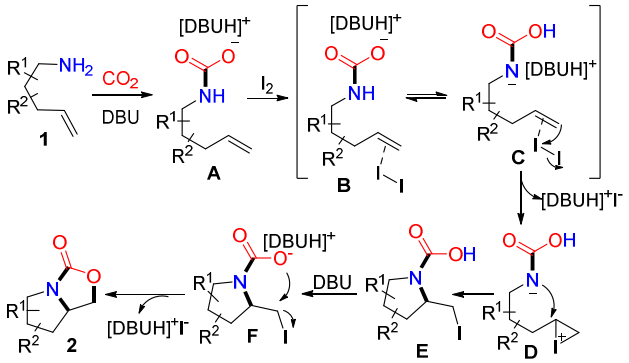
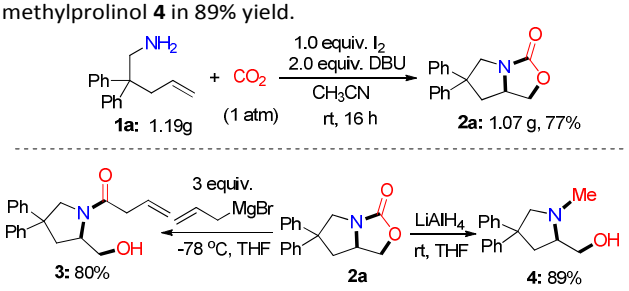


Scheme 3 Proposed reaction mechanism

Considering significance of prolinol and derivatives in organic synthesis, gram-scale experiment and transformation starting from prolinol carbamate are worthy of investigation. We conducted the reaction in gram-scale and obtained prolinol carbamate in comparable yield (Scheme 4). The reaction of **2a** with allyl Grignard reagent afforded the amide prolinol **3** in 80% yield. Treatment of **2a** with $LiAlH_4$ obtained *N*-methylprolinol **4** in 89% yield.



Scheme 4 Gram-scale synthesis and transformations of **2a**. See the Supporting information for details.

Conclusions

In summary, metal-free oxidative oxyamination of 4-pentenamines with ambient CO_2 was realized efficiently to generate privileged prolinol carbamates *via* bicyclization under a mild condition. CO_2 plays a vital role in tuning the reactivity of amine to achieve oxyamination of alkene with excellent regioselectivity. This reaction is scalable and compatible with various functional groups. Furthermore, prolinol carbamates could be easily transformed into prolinol derivatives.

Acknowledgements

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13 CCDC 1553780 (**2a**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

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