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Sunlight-Driven Forging of Amide/Ester Bonds from Three Independent Components: An Approach to Carbamates

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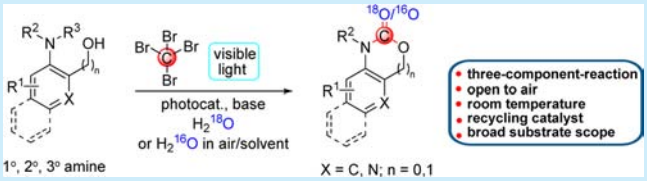
Supporting Information

ABSTRACT: A photoredox catalytic route to carbamates enabled by visible irradiation (or simply sunlight) has been developed. This process leads to a novel approach to the construction of heterocyclic rings wherein the amide or ester motifs of carbamates were assembled from three isolated components. Large-scale experiments were realized by employing continuous flow techniques, and reuse of photocatalyst demonstrated the green and sustainable aspects of this method.



Carbamates constitute a significant class of organic compounds in biological and medicinal science.[1] They are key building blocks in pharmaceutical and agrochemical products, such as the HIV inhibitor efavirenz,[2] progesterone antagonist,[3] and the analgesic Paraflex[4] (Figure 1 A). In addition

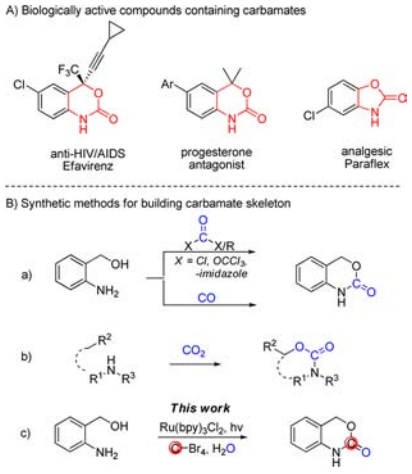


Figure 1. Biologically active compounds containing benzo-fused heterocycles and synthetic methods for building carbamate skeleton.

to their biological utilization, carbamates also have many applications in organic synthesis by serving as key synthetic intermediates[5] and specific directing groups.[6]

Therefore, numerous efforts have been made to establish such useful structures. The most conventional method to construct the carbonyl motif in carbamate generally resorted to hazardous phosgene and its derivates,[7] which would have a detrimental effect on the environment or create a stoichimetric amount of waste after the reaction (Figure 1 B, a). Alternatively, the carbonyl bond could be accessed by inserting CO directly into *o*-amino alchohols or *o*-aminophenols enabled by transition-metal catalyst.[4,8] In the aspects of green chemistry and natural abundance, CO_2 has always been considered an attractive and promising C1 building block in organic synthesis owing to its favorable properties such as being ubiquitous, inexpensive, and nontoxic. In addition, there are remarkable advances in incorporating CO_2 into organic compounds to yield carbamates, wherein CO_2 has been converted into the ester bonds in a straightforward pathway (Figure 1B, b).[9] However, the inherently high oxidation state of carbon in CO_2 makes it quite stable, which hampers its facile activation and the extension to substrate scope.[10] Furthermore, other phosgene-free approaches to carbamates have also been developed through elegant transformations of isocyanates, azides, aziridines, and so on.[11]

Among the mentioned versatile synthetic methods, the carbonyl moieties in carbamates were basically copied and pasted from starting agents that contained the same carbonyl bonds. Herein, we present an unconventional route to construct the amide or ester motifs of carbamates from three independent components under genuinely mild reaction conditions, wherein the C atom in carbonyl was derived from CBr_4 and the O atom was from moisture in solvent or air (Figure 1 B, c), using $Ru(bpy)_3Cl_2$ as the catalyst and sunlight as the energy source.

Initially, exposure of **1a** to blue LED irradiation in the presence of CBr_4 as an oxidant and $Ru(bpy)_3Cl_2$ (λ_{max} = 452 nm)[12] as photosensitizer under an atmosphere of CO_2 (balloon) afforded the heterocyclic carbamate **1b** in 45% yield (Table 1, entry 1). To our surprise, using ambient atmosphere (air) instead of purified CO_2 provided the same product **1b** in similar yield (entry 2). A control experiment was performed in the anhydrous and air-free conditions, which led to the recovery of starting material (entry 3). It was further established that the addition of base had a significant influence on the reaction

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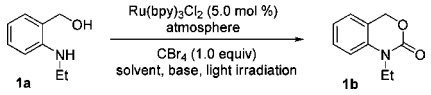
Table 1. Optimization of Reaction Conditions



entry[a]	base	solvent	atmosphere	yield[b] (%)
1[c]	none	MeCN	CO_2	45
2[c]	none	MeCN	air	45
3[c]	none	MeCN	N_2	trace
4[c]	K_2CO_3	MeCN	air	60
5	K_2CO_3	MeCN	air	62
6	**2,6-lutidine**	**MeCN**	**air**	**86**
7	2,6-lutidine	DMF	air	33
8	2,6-lutidine	DCM	air	65
9[d]	**2,6-lutidine**	**MeCN**	**air**	**81**

[a]Unless otherwise noted, reactions were carried out with **1a** (0.3 mmol, 1.0 equiv), CBr_4 (1.0 equiv), base (3.0 equiv), and $Ru(bpy)_3Cl_2$ (5.0 mol %) in undried solvent (0.1 M) under 8 W blue LED bulb irradiation for 16 h. [b]Isolated yields. [c]Dried solvent was used; reaction for 24 h. [d]Sunlight served as light source for 2 h.

outcomes (entries 4 and 6). Notably, employing hydrous MeCN did not diminish the reaction efficiency yet resulted in a very slight improvement of the yield of product (entry 5). Screening of solvents indicated MeCN to be the optimal medium for this transformation (entries 7 and 8). More specifically, replacement of blue LED with sunlight provided the same product **1b** in a much shorter reaction time, albeit with a negligible decrease in yield (entry 9), and it was speculated that the sunlight might provide not only the light but energy to warm the reaction system. These results therefore represent optimal reaction conditions to construct heterocyclic carbamate using *o*-amino alcohol as the carbonyl acceptor in the presence of CBr_4 (1.0 equiv), base (3.0 equiv), and $Ru(bpy)_3Cl_2$ (5.0 mol %) in undried MeCN with sunlight irradiation in an ambient atmosphere.

We next sought to test the scope of the carbonyl acceptors by subjecting a series of *o*-amino alcohols and phenols to the optimized reaction conditions (Figure 2). Various primary amines possessing substitution on the phenyl ring were evaluated, which afforded the corresponding heterocyclic carbamates in good to excellent yields (**2b** and **5b**−**10b**), demonstrating that both electron-donating and electron-withdrawing groups could be accommodated at diverse positions. Naphthalamine was also tolerant under the reaction conditions (**11b**). Significantly, this method was compatible with *o*-aminophenols to provide five-membered heterocycles in good yield (**12b**−**13b**). Furthermore, heteroaromatic substrates (**14b**) could also be employed. However, it should be noted that the presence of an aromatic amine, i.e., aniline, was critical to the success of the reaction. For example, no product was observed for the nonbenzo-fused heterocycle (**15b**). We proposed that the phenyl ring connected to amine might stabilize the amino radical that was formed in the process of the reaction.

We then investigated a diverse range of secondary amine substrates, and the results are outlined in Figure 2. Besides *N*-ethyl (**1b**), substrates with *N*-methyl, *N*-phenyl, and *N*-benzyl groups were equally accommodated, leading to corresponding products in moderate to good yields (**16b**−**21b**). Moreover, *N*-ethylamines bearing a substituent on the aromatic ring functioned proficiently as well (**26b** and **27b**). We further note that regardless of primary or secondary amine, *o*-amino

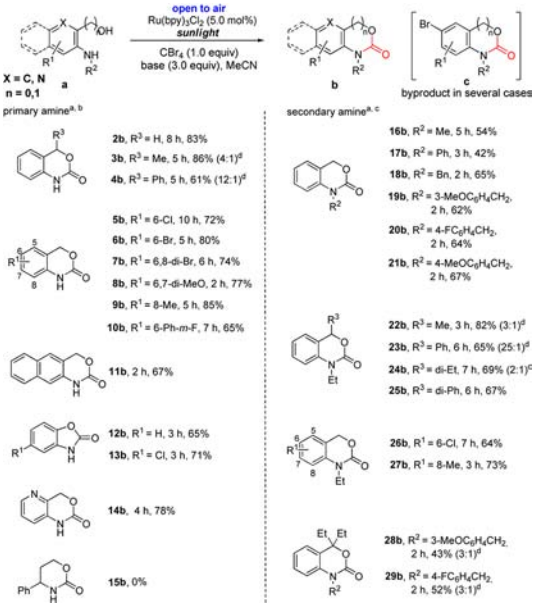


Figure 2. Scope of *o*-amino alcohols/phenols. (a) Isolated yields are indicated. (b) K_2CO_3 (3.0 equiv) was used as the base in all primary amine cases because 2,6-lutidine would result in a complex mixture. (c) 2,6-Lutidine (3.0 equiv) was used in all secondary amine cases. (d) Ratio in parentheses refers to the integrated ratio of **b** to **c** (**b**/**c**) in ^1H NMR spectra for cases in which the brominated product c was observed.

secondary or tertiary alcohol afforded not only **b** but also the Br-substituted product **c** (**3b**−**4b**, **22b**−**25b**, and **28b**−**29b**). Interestingly, the percentage of **c** in the mixed products was reduced when R^3 was phenyl instead of an alkyl group, and **25c** even could not be formed when R^3 was diphenyl (only **25b** was obtained). Compound **24c** was selected as a representative brominated product for determing the Br-substituted position, which was characterized on the *para*-position of the amine group based on NMR analysis (see the Supporting Information).

This protocol was further extended to tertiary amines (Table 2). Exposure of amines with both *N*-ethyl and *N*-benzyl substituents (entry 1) led to a mixture of products, with predominant fragmentation of the benzyl group to provide **1b** as the main product in 55% yield. Other tertiary amines bearing the same substituents on the amine were examined as well, providing products that resulted from the preferential loss of the benzyl substituent (entries 5−8). Switching *N*-ethyl to *N*-methyl with the same *N*-benzyl group led to the formation of the same debenzylated product **16b** (entry 9). We also examined the effect of electron-donating and electron-withdrawing groups on the reactivity of the *N*-benzyl substitutent in the reaction. We found that electron-donating groups favored the formation of the debenzylated carbamate products (entries 2 and 3). Furthermore, the *N*,*N*-dibenzyl substrate led to only a trace amount of **2b** with removal of both benzyl substituents (entry 10). However, the irradiation of substrates in which the amine is not benzylic led to the recovery of starting material (entry 4).

Photochemical reactions conducted under flow conditions enable more efficient light penetration and more efficient reaction.[13] We therefore applied continuous flow techniques to scale up the reaction for the synthesis of carbamate. We devised two strategies for the recycling of the heterogeneous $Ru(bpy)_3Cl_2$ catalyst. As depicted in strategy A of Table 3, the

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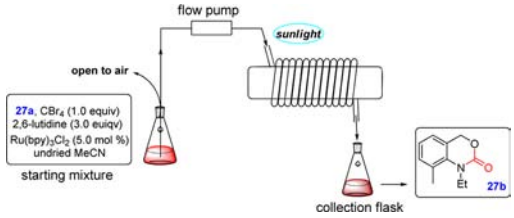
Table 2. Scope of Tertiary Amines

entry	substrate **a**	t (h)	product **b**[a]
1	R^3 = Bn	2	**1b**, 55% (**1b**:**18b** = 3:1)[b]
2	R^3 = Bn-p-F	3	**20b**, 45% (**1b**:**20b** = 1:4)[b]
3	R^3 = Bn-*p*-MeO	5	**1b**, 42% (**1b**:**21b** = 3:1)[b]
4	R^3 = Me	12	NR[c]
5	R^4 = Me	8	**22b**, 42%
6	R^4 = Ph	4	**23b**, 37%
7	R^1 = 6-Cl	4	**26b**, 52%
8	R^1 = 8-Me	2	**27b**, 54%
9	R^3 = Me	3	**16b**, 41%
10	R^3 = Bn-*p*-F	4	**2b**, <5%

[a]Main products and corresponding isolated yields. [b]Ratio in parentheses referred to the proportion of debenzylated product to ethyl removed product, determined by GC–MS. [c]No reaction.

Table 3. Scale-up Reaction Performed in Continuous Flow



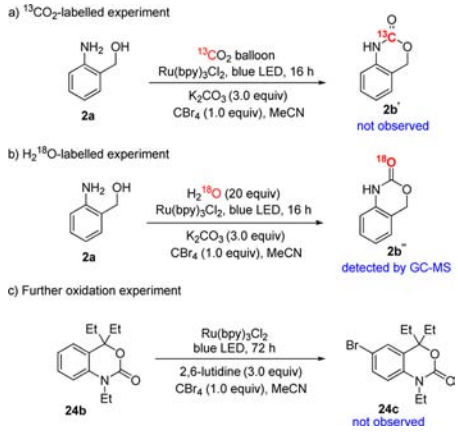
entry	*t* (h)	recovery of catalyst (%)	yield of **27b** (%)
Strategy A: Catalyst Was Recovered and Reused			
1[a]	2.5	86	67
2[b]	2.5	84	63
3[b]	2.5	81	64
Strategy B: Catalyst Was Reused in Situ without Recovery			
4[a]	2.5		
5[c]	4		
6[c]	4	89[d]	58[d]

[a]**27a** (300 mg) and the aforementioned reagents with $Ru(bpy)_3Cl_2$ in MeCN were pumped into flow reactor at a rate of 0.5 mL min^{-1}. [b]Recovered catalyst from entry 1 was used for entries 2 and 3 in an analogous manner. [c]Another batch of starting mixture at the same scale as entry 4, without $Ru(bpy)_3Cl_2$, was added directly into collection flask of entry 4, and entry 6 was completed in an analogous manner. [d]Calculated based on the total input of entries 4–6.

$Ru(bpy)_3Cl_2$ was readily recovered by filtration on completion of the reaction and reused in the subsequent entry (with only subtle effects on the yield of **27b**; entries 1–3). Moreover, the recycled catalyst maintained its efficiency with respect to reaction time. To avoid the recycling step, we have examined a second approach, strategy B, reusing the catalyst in situ without recovery to carry out the scale-up experiment in flow. After two cycles, the catalyst could be recovered in 89% yield, and the total yield of **27b** was reduced to 58% on prolonged irradiation (entries 4–6). The implementation of this continuous flow approach suggests that the reaction could be performed on a very large, i.e., industrial scale.

Initially, we postulated the carbonyl moieties in products presumably stemmed from CO_2 in air. To gain mechanistic insight into this transformation, several control experiments were therefore conducted. First, the starting mixture of **2a** was subjected to $^{13}CO_2$ atmosphere under similar reaction conditions (Scheme 1 a). However, the ^{13}C-labeled product

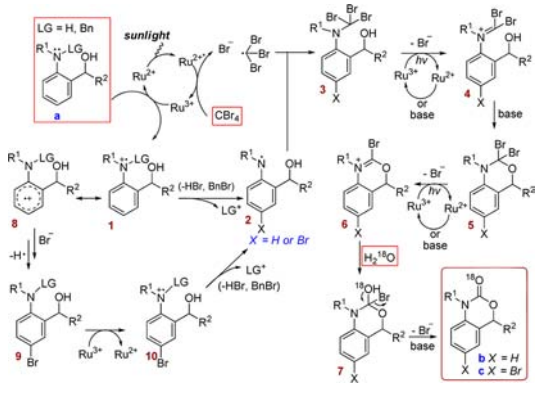
Scheme 1. Control Experiments



2b′ was not observed, while **2b** was obtained instead as the only product.[14] In addition, the $H_2{}^{18}O$-labeled experiment was also carried out (Scheme 1 b). With increasing amounts of $H_2{}^{18}O$, the ratio of ^{18}O-labeled product **2b″** increased accordingly (see the Supporting Information), which however, could not account for the distribution of the products with or without isotopic label. These isotopic labeling experimental results indicated that the carbonyl bond in the product was probably caused by hydrolysis of any sensitive intermediate during reaction rather than the incorporation of CO_2 to substrate. To gain more information about the conversion, we exposed **24b** to the standard reaction conditions to determine if **b** is converted to **c** (Scheme 1 c). However, **24b** remained intact after irradiation for 72 h, suggesting that the Br-substituted product **c** does not result from further reaction of **b**.

Based upon the above results, a mechanism was therefore proposed in Scheme 2. Having determined the reductive potential of **1a** (E_{red} = −0.97 V vs SCE) by cyclic voltammetry tests, we envisioned the reaction was started from single-electron reduction of CBr_4 by the photoexcited state $Ru(bpy)_3{}^{2+*}$ ($E_{1/2}{}^{III/*II}$ = −0.81 V vs SCE) to form $^{\bullet}CBr_3$ and $Ru(bpy)_3{}^{3+}$,[15] which could accept an electron from amine **a** to

Scheme 2. Proposed Mechanism



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regenerate the $Ru(bpy)_3^{2+}$ and deliver the radical cation **1**. With respect to the two kinds of products **b** and **c**, we proposed the removal of the leaving group (LG) of **1** could occur via one of two possible pathways. First, the LG could be removed directly from **1** to form HBr and/or BnBr as well as the amine radical **2** (X = H), which could couple with $^{\bullet}CBr_3$ to form the intermediate **3**. Afterward, the iminium **4** might result from debromonation of **3** by a base- or Ru-catalyzed photocyclic process, which would then proceed via intramolecular nucleophilic attack reaction by hydroxy to provide **5** in the presence of base. Subsequently, a similar debromonation process would occur to form iminium **6**, which then could be attacked by water to give **7**. At last, the final heterocyclic product **b** (X = H) could be formed by base-promoted intramolecular esterification. Alternatively, bromide ion could be regioselectively added to radical cation **8** to provide the Br-substituted amine **9** after the loss of $^{\bullet}H$ to rearomatize the ring system. Intermediate **9** would then undergo reaction via a pathway that was similar to that described above to form the final Br-substituted heterocyclic product **c** (X = Br).

In conclusion, we have demonstrated an unconventional strategy to construct the amide or ester motifs of carbamates from three isolated components via a sunlight-mediated photocatalytic approach. A wide range of *o*-amino alcohols and phenols were examined in this protocol to afford potentially bioactive heterocyclic carbamates with good efficiencies under very benign reaction conditions. Recycling and reutilization of precious photocatalyst highlighted the sustainable and economic advantages of this synthetic approach as well. Moreover, application of continuous flow techniques facilitated the scale-up experiment.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02811.

Experimental procedures, product characterization, and ^1H and ^{13}C NMR spectra for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(14) According to the results of entry 1 of Table 1, the carbonyl of carbamates derived from absorption of CO_2 could not be excluded, especially in the absence of H_2O.

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