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*n*Bu$_4$NI-catalyzed oxidative cross-coupling of carbon dioxide, amines, and aryl ketones: access to *O*-β-oxoalkyl carbamates

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The first *n*Bu$_4$NI-catalyzed oxidative cross-coupling reaction of carbon dioxide, amines and arylketones has been successfully developed by using TBHP as the oxidant, providing an efficient, atom-economical and metal-free strategy for the synthesis of a range of *O*-β-oxoalkyl carbamates.

Organic carbamates are compounds of great interest because they are key units of many natural products,[1] pharmaceuticals[2] and agrochemicals (Figure 1).[3] They also find increasing applications in organic synthesis as versatile building blocks or protecting groups for amines and amino acids.[4]

Traditionally, these important compounds can be prepared by the reaction of chloroformates with amines or the reaction of isocyanates with alcohols.[5] However, both chloroformates and isocyanates are commonly obtained from highly toxic phosgene. To address the environmental and safe issues associated with the use of phosgene, great efforts have been made to develop new and environmentally friendly methods for the synthesis of carbamates in the past decades.[6] Of particular note is the carbamation of amines using carbon dioxide (CO_2) as the raw material[7] since CO_2 is inarguably regarded as a non-toxic, abundant, inexpensive and renewable C1 resource.[8] Basically, these transformations rely on the in situ generation of carbamate anion via the reaction of amines and CO_2, followed by the reaction with electrophiles (Scheme 1, a). A variety of functional molecules, such as halohydrocarbons[7b, 7d, 7f] and alcohols,[7e, 7g, 7i] have been employed as the electrophile. Very recently, we have showed that *N*-tosylhydrazones[9a] and diaryliodonium salts[9b] could couple with CO_2 and amines to give the corresponding organic carbamates in the presence of bases. Although significant progress has been made in this research area, the development of more facile and atom-economical methods for the construction of carbamates is still highly desirable.

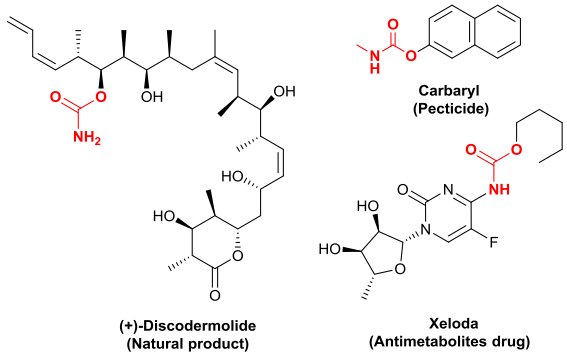
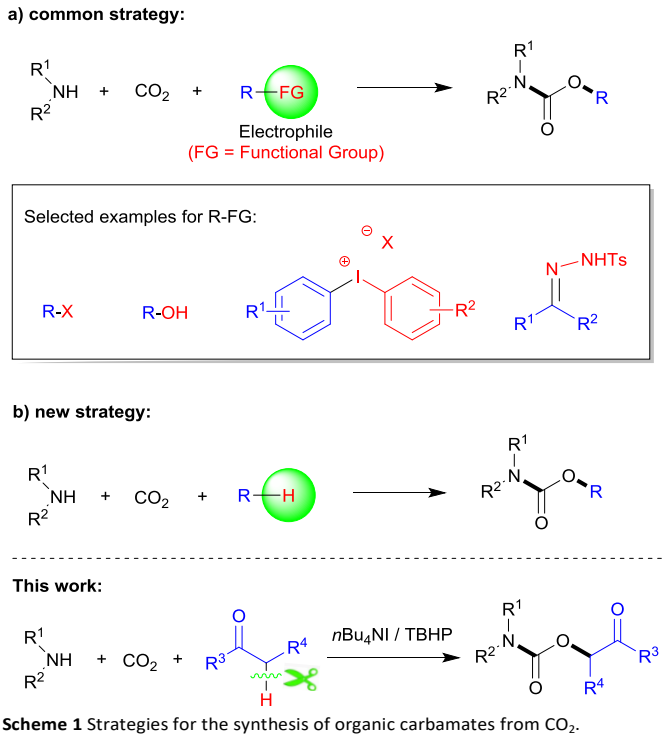


Figure 1 Representative carbamate-bearing molecules.



Scheme 1 Strategies for the synthesis of organic carbamates from CO_2.

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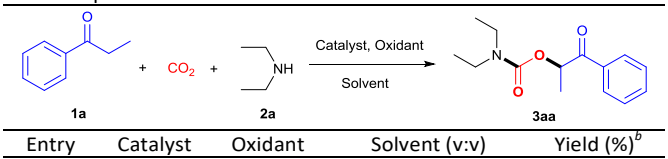
Over the past decades, catalytic functionalization of C-H bonds has become one of the most efficient strategies in organic synthesis because it avoids the requirement for prefunctionalization of substrates and thus shows improved atom- and step-economy.[10] However, to the best of our knowledge, the direct assembly of organic carbamates via C-H functionalization has not yet been developed. As part of our ongoing interest in developing efficient methods for the conversion of CO_2 into valuable chemicals,[9] herein, we wish to report a nBu$_4$NI-catalyzed direct α-carbamoyloxylation of arylketones with CO_2 and amines via C(sp^3)-H oxidative cross-coupling reactions, providing an efficient, atom-economical and metal-free protocol for the synthesis of a diverse range of *O*-β-oxoalkyl carbamates (Scheme 1, b).

Initially, propiophenone (**1a**) and diethylamine (**2a**) was chosen as the model substrates for the optimization of the reaction conditions, and the results are summarized in Table 1. When the reaction was carried out in DMF with nBu$_4$NI as catalyst and TBHP as the oxidant under 3 MPa of CO_2 at 90 °C for 12 h, the desired product **3aa** was formed in 77% yield (entry 1). DMSO also gave **3aa** in 60% yield while other solvents such as CH_3CN and DCE led to relatively low yields (entries 2, 4 and 5). Pleasingly, the yield of **3aa** was sharply increased to 92% when the reaction was conducted in a mixed DMF-DMSO (2:1) solvent (entry 3), which might be due to that the mixed solvent system could facilitate the formation of active intermediates of the reaction. Other iodides including KI, NH_4I, NIS, and even I_2 could also catalyse the reaction efficiently to furnish **3aa** in high yields (entries 6-9) while CuI exhibited exceedingly low catalytic activity (entry 10). Moreover, the reaction did not occur when nBu$_4$NBr was used as the catalyst (entries 11 and 12), implying that the use of iodides or iodine was critical for the reaction. Screening of different oxidants showed that the oxidant play an important role in this transformation. TBHP was the optimal oxidant; other oxidants, such as DTBP, TBPB, BPO and H_2O_2, were ineffective (entries 13-16). Both increasing and decreasing the reaction temperature decreased the yield of **3aa** (entries 17 and 18). Further optimization showed that a decrease in the pressure of CO_2 resulted in a decrease in the yield of the product (entry 19). The effect of the amount of oxidant and **2a** on the reaction was investigated, and the results showed that 6 equiv of TBHP and 7 equiv of **2a** were required to achieve high yield (see the Supporting Information for details). Finally, the control experiments showed that both nBu$_4$NI and TBHP are essential for the transformation (entries 20 and 21).

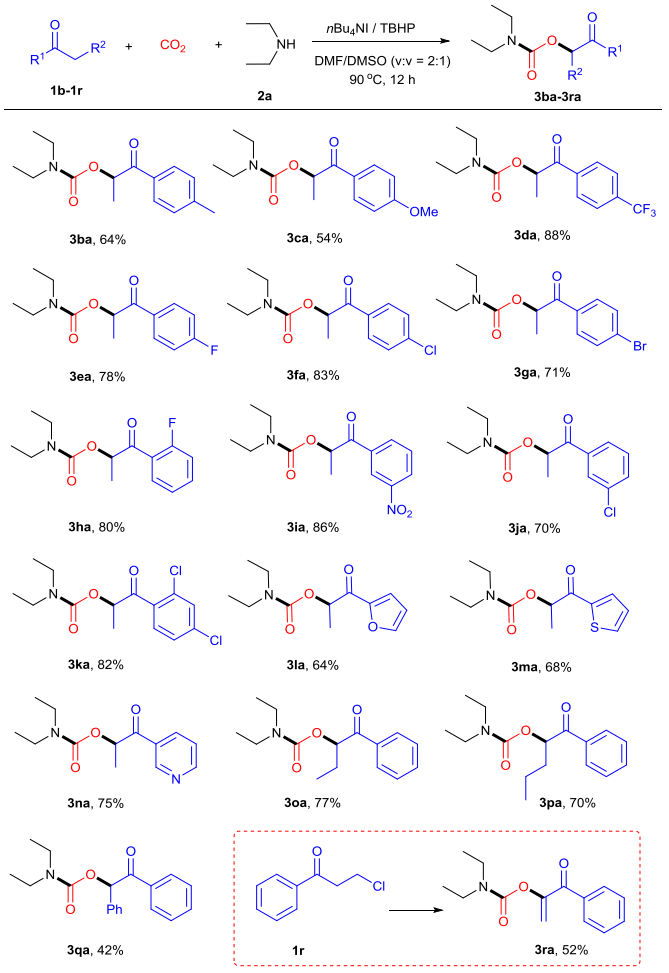
To examine the scope and limitations of the present carbamoyloxylation, a variety of aryl and heteroaryl ketones were examined as substrates to react with CO_2 and **2a** under the optimized reaction conditions (Scheme 2). Gratifyingly, various propiophenone derivatives bearing electron-donating

Table 1 Optimization of the reaction[a]



Entry	Catalyst	Oxidant	Solvent (v:v)	Yield (%)[b]
1	nBu$_4$NI	TBHP	DMF	77
2	nBu$_4$NI	TBHP	DMSO	60
3	nBu$_4$NI	TBHP	DMF/DMSO (2:1)	92 (87)
4	nBu$_4$NI	TBHP	CH_3CN	32
5	nBu$_4$NI	TBHP	DCE	9
6	KI	TBHP	DMF/DMSO (2:1)	86
7	NH_4I	TBHP	DMF/DMSO (2:1)	85
8	NIS	TBHP	DMF/DMSO (2:1)	83
9	I_2	TBHP	DMF/DMSO (2:1)	78
10	CuI	TBHP	DMF/DMSO (2:1)	10
11	nBu$_4$NBr	TBHP	DMF/DMSO (2:1)	n.d.
12	nBu$_4$NBr	$K_2S_2O_8$	DMF/DMSO (2:1)	n.d.
13	nBu$_4$NI	DTBP	DMF/DMSO (2:1)	n.d.
14	nBu$_4$NI	TBPB	DMF/DMSO (2:1)	trace
15	nBu$_4$NI	BPO	DMF/DMSO (2:1)	n.d.
16	nBu$_4$NI	H_2O_2	DMF/DMSO (2:1)	n.d.
17[c]	nBu$_4$NI	TBHP	DMF/DMSO (2:1)	76
18[d]	nBu$_4$NI	TBHP	DMF/DMSO (2:1)	73
19[e]	nBu$_4$NI	TBHP	DMF/DMSO (2:1)	46
20	-	TBHP	DMF/DMSO (2:1)	n.d.
21	nBu$_4$NI	-	DMF/DMSO (2:1)	n.d.

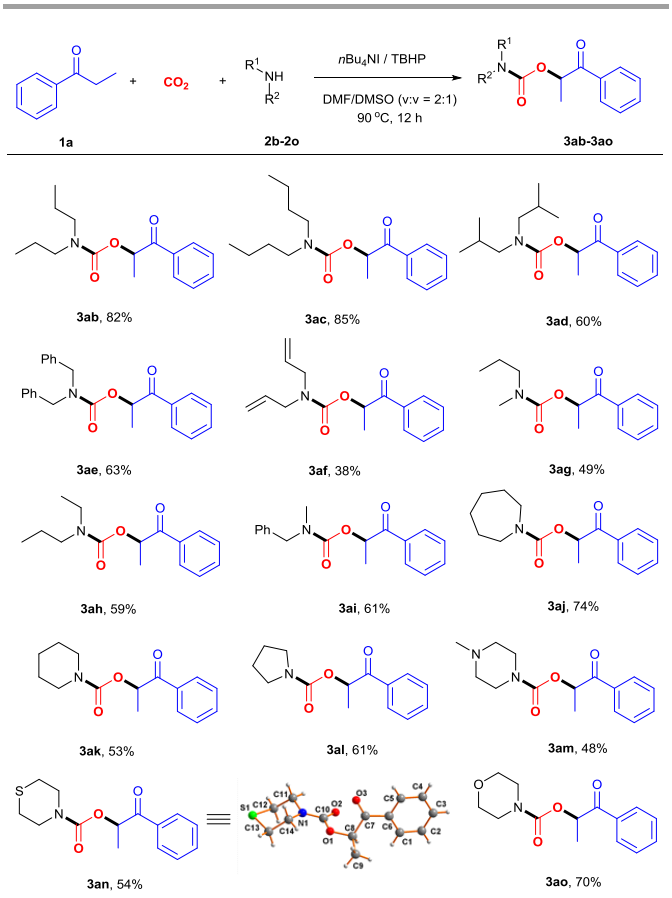
[a] Reaction conditions: **1a** (1.0 mmol), **2a** (7.0 mmol), CO_2 (3 MPa), nBu$_4$NI (0.2 mmol), TBHP (6.0 mmol), solvent (3 mL), 90 °C, 12 h. [b] Yields were determined by GC-MS analysis with n-dodecane as internal standard; number in parentheses is the yield of isolated product. [c] At 110 °C. [d] At 70 °C. [e] Under 1 MPa of CO_2.



Scheme 2 Substrate scope with respect to ketones. Reaction conditions: **1** (1.0 mmol), **2a** (7.0 mmol), nBu$_4$NI (0.2 mmol), TBHP (6.0 mmol), DMF/DMSO (v:v = 2:1, 3 mL), CO_2 (3 MPa), 90 °C, 12 h. Isolated yields based on **1**.

or electron-withdrawing groups at the ortho, meta, or para positions of the benzene ring, including methyl, methoxy, trifluoromethyl, halide (F, Cl and Br) and nitro groups, could undergo the reaction smoothly to give the desired products (**3ba**-**3ja**) in moderate to high yields. It was found that the electronic nature of the substituents has a great effect on the formation of the desired carbamates. In general, ketones with electron-withdrawing groups generated the desired products (**3da**-**3ja**) in higher yields than those with electron-donating ones (**3ba** and **3ca**). Besides mono-substitued propiophenones, the di-substituted substrate, 1-(2,4-dichlorophenyl)propan-1-one (**3k**) could also work well to furnish the expected product **3ka** in 82% yield. Notably, a variety of heteroaryl ketones containing the furan, thiophene and pyridine rings were all suitable substrates for the transformation, delivering the desired products (**3la**-**3na**) in good yields. Moreover, the substrates with longer alkyl chains (**1o** and **1p**) reacted smoothly to afford the corresponding products **3oa** and **3pa** in good yields. 1,2-Diphenylethanone could also enter into the reaction to give the desired carbamate **3qa** in a moderated yield. Interestingly, 3-chloro-1-phenylpropan-1-one (**1r**) generated an unsaturated carbamate **3ra**, which might be formed through the dehydrohalogenation of the desired product.[11] However, the reaction of acetophenone gave a complex mixture, and the desired product was not detected. Aliphatic ketones also failed to undergo the reaction, and the starting materials were recovered unchanged.

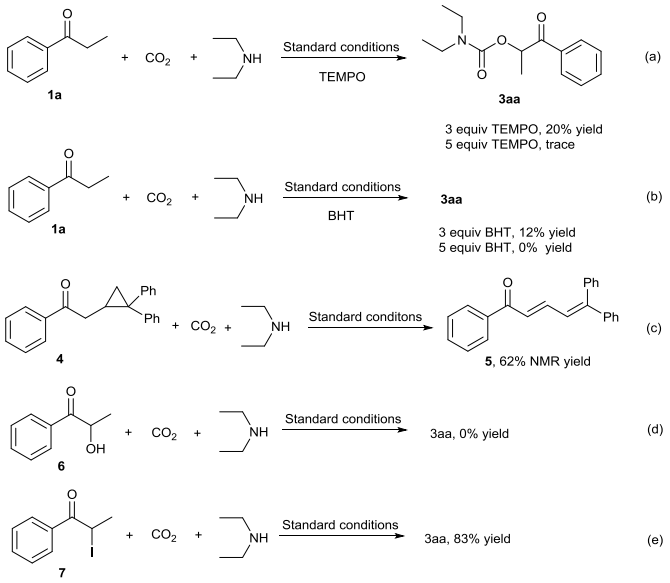
Subsequently, a wide range of amines were employed for coupling with propiophenone (**1a**) and CO_2 (Scheme 3).



Scheme 3 Scope of amines. Reaction condition: **1a** (1.0 mmol), **2** (7.0 mmol), nBu$_4$NI (0.2 mmol), TBHP (6.0 mmol), DMF/DMSO (v:v = 2:1, 3 mL), CO_2 (3 MPa), 90 °C, 12 h. Isolated yields based on **1a**.

Pleasingly, different dialkylamines, including symmetric and asymmetric ones, underwent the one-pot reaction smoothly and furnished the corresponding products (**3ab**-**3ai**) in moderate to excellent yield. Moreover, various types of cyclic secondary amines could also take part in the reaction, giving rise to the desired products in moderate to good yield (**3aj**-**3ao**). The structure of the product **3an** was unambiguously confirmed by means of X-ray crystallographic analysis.[12] Unfortunately, primary amines and anilines could not afford the desired products but resulted in the formation of a complex mixture of unidentified products under our conditions.

To understand the mechanism of the reaction, a series of control experiments were carried out as shown in Scheme 4. Firstly, it was found that the present reaction could be inhibited by the radical scavengers 2,2,6,6-teramethyl-1-piperidinyloxy (TEMPO) and 2,6-di-*tert*-butyl-4-methylphenol (BHT) (Scheme 4, a and b). Moreover, diphenylcyclopropyl ketone **4** could undergo ring-opening radical clock reaction under the standard conditions to afford the conjugated diene **5** in 62% NMR yield (Scheme 4, c).[13] These results suggest that a radical pathway should be involved in the reaction. Next, when 2-hydroxy-1-phenylpropan-1-one was employed as substrate to react with CO_2 and diethylamine under the standard conditions, no product **3aa** was detected (Scheme 4, d). However, the reaction of 2-iodo-phenylpropan-1-one with CO_2 and diethylamine could furnish the carbamate **3aa** in 83% yield (Scheme 4, e), indicating that 2-iodo-phenylpropan-1-one might be the intermediate for the reaction.



Scheme 4 Mechanism studies.

On the basis of aforementioned observations and previous reports,[7, 9a, 9b, 13, 14] a plausible mechanism of the reaction is depicted in Scheme 5. Initially, in the presence of nBu$_4$NI and TBHP, the propiophenone **1a** is oxidized to form a radical intermediate **A**, which could react with the in situ-generated iodine (I_2) to give the key intermediate 2-iodo-phenylpropan-1-one (**B**). Then, **B** undergoes nucleophilic attack by carbamate anion **C** generated in situ from CO_2 and diethylamine to afford the desired product **3aa** (Path a). Alternatively, the reaction might proceed through path b, in which **1a** is oxidized to form a cation intermediate **D** via radical **A**. Then the interaction of **D**

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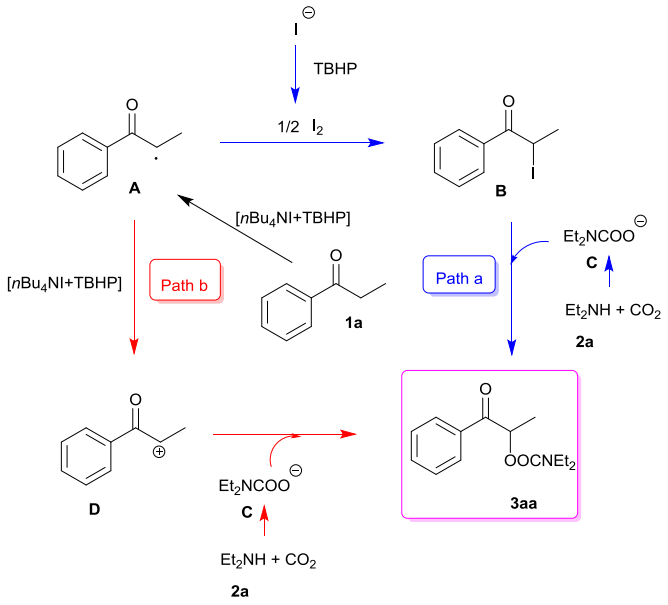

Scheme 5 A plausible mechanism of the transformation.

with the in situ generated carbamate anion **C** could also produce the final product **3aa**.

In summary, we have developed a *n*Bu$_4$NI-catalyzed oxidative cross-coupling of ketones, carbon dioxide and amines using TBHP as the oxidant. This reaction represents the first example of constructing organic carbamates via C-H bond functionalization strategy, and thus has many merits, such as the use of readily available substrates, high atom economy, and metal-free catalysis. Further investigation on the reaction mechanism and the application of this strategy to the synthesis of other kinds of carbamates are currently ongoing in our laboratory.

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12 CCDC 1520713 (**3an**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_reques/cif.

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