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Copper-Catalyzed Oxidative Benzylic C(sp³)-H Amination. Direct Synthesis of Benzylic Carbamates.

Shuai Liu,^a Raphael Achou,^a Coline Boulanger,^a Govind Pawar,^a Nivesh Kumar,^a Jonathan Lusseau,^a Frédéric Robert,^a and Yannick Landais*^a

University of Bordeaux, Institute of Molecular sciences (ISM), UMR-CNRS 5255, 351, Cours de la Libération, 33405 Talence Cedex, France.

E-mail : yannick.landais@u-bordeaux.fr

A new efficient strategy to access benzylic carbamates through C-H activation is reported. The use of a catalytic amount of Cu(I)/diimine ligand in combination with NFSI ((PhSO₂)₂NF) or F-TEDA-PF₆ as oxidants and H₂NCO₂R as an amine source, direct leads to the C-N bond formation at benzylic position. The mild reaction conditions, and broad substrate scope make this transformation a useful method for a late-stage incorporation of the ubiquitous carbamate fragment onto hydrocarbons.

The direct functionalization of the C(sp³)-H bond represents one of the most efficient, atom and step economic strategy to introduce functional groups on a carbon skeleton.¹ The selective C-H activation, however still remains an important challenge to synthetic organic chemists, due to the high bond energy of the C-H bond (BDE ~ 98-100 kcal/mol).² Over the past two decades, organic synthesis has made remarkable advances in this field and achieved direct functionalization of saturated C-H bonds of alkanes, alcohols, ketones, ethers, esters, to construct C-C and C-X bonds (X = N, O, S, etc.).³ Urethanes (carbamates) are an important family of nitrogen compounds that are widespread due to their biological activity,⁴⁻⁷ but also as a repeating unit in polyurethanes, the 6th class of commodity polymers.⁸ In addition, urethanes also play a prominent role as protecting groups for amines and amino acids.⁹ However, in spite of the many recent developments, the access to the urethane linkage still remains a burgeoning field. Traditional protocols for installing the carbamate group include additions of alcohols to carcinogenic isocyanates, available from acyl azides intermediates or toxic phosgene.¹⁰ Carbon dioxide was also shown to be an attractive alternative to phosgene, as it is non-toxic and widely available.¹¹⁻¹³

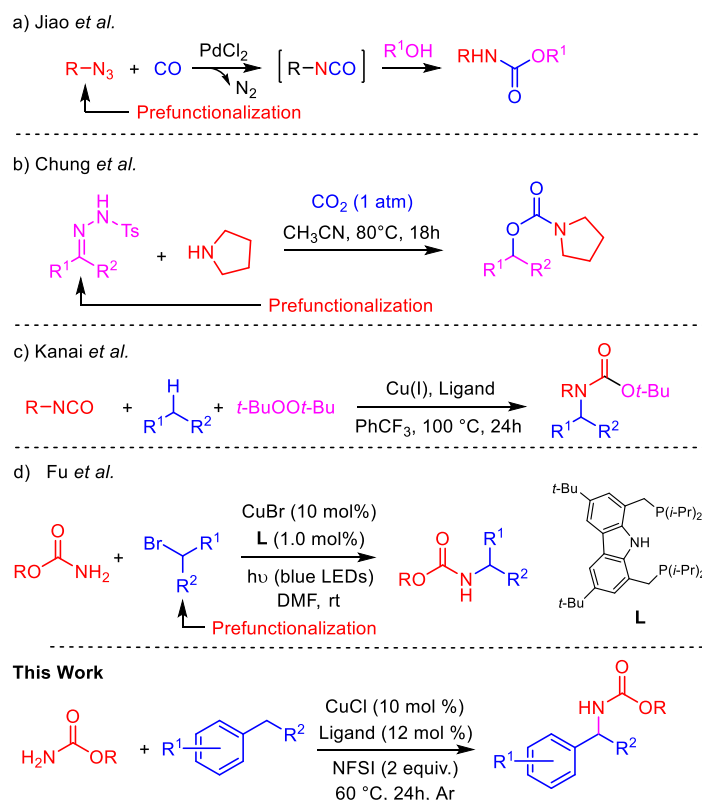


Figure 1 Reported protocol and present work for urethane synthesis

Several advancements have been made recently to efficiently construct urethanes. Jiao *et al.* thus reported a PdCl₂-catalyzed strategy for synthesis of urethanes, through a three-component process involving azides, CO, and alcohols (Figure 1a).¹⁴ In a similar vein, Jiang's group developed an alkali metal promoted coupling of CO₂, amines and N-tosylhydrazones, which led to a variety of carbamates in a single step.¹⁵ Similar, but greener conditions were later proposed by Chung's group (Figure 1b).¹⁶ Interestingly, Kanai *et al.* devised an original access to N-Boc carbamates through C-H activation in the presence of peroxide and isocyanates (Figure 1c).¹⁷ Finally, Fu and co-workers described a visible-light Cu(I)-catalyzed access to urethanes (Figure 1d).¹⁸ These strategies have their own merits but also limitations, such as expensive catalysts, the use of carcinogenic isocyanates or hazardous peroxides, the need for pre-functionalized substrates, and harsh reaction conditions. We thus describe here an alternative strategy relying on a Cu(I)-catalyzed oxidative amination of hydrocarbons benzylic C(sp³)-H position, which affords a regioselective access to simple carbamates under mild conditions. Preliminary studies were carried out using a Cu catalyst (10 mol%), ligand L1 (12 mol%)(for the choice of L1, see ESI), NFSI (2.0 eq.) as the oxidant and **2a** as the aminating agent (Table 1).^{3d,19} The reaction, first carried out using CuCl and ethylbenzene **1a** as a model substrate at 60°C in acetonitrile, led to carbamate **3a** in 33% yield (entry 1). Changing CH₃CN for HFIP provoked a severe drop in yield (entry 2), while, a mixture of both solvents in various ratio (entries 3-5) led to **3a** with improved yield. A 1:1 ratio was finally found to afford an optimal conversion (entry 5). Changing CuCl for CuOAc (Entry 6) did not improve the process, and iron catalyst proved to be totally inefficient in this context (entry 7).²⁰ A variety of other oxidants were also tried, including selectfluor and F-TEDA-PF₆ (ESI).^{3b} The former led to disappointing conversion (entry 8), while the latter led to **3a** in 53% yield (entry 9). It was later found that NFSI and F-TEDA-PF₆ were both efficient for this transformation depending on the nature of the substrate (*vide infra*). Photochemical activation of the deep green solution of NFSI-CuCl and L1 using red LEDs ($\lambda_{\text{max}} = 628 \text{ nm}$) was also tested, leading to **3a** in 43% yield at 25°C (entry 10). When the reaction was performed in the dark at 25°C, only 6% of **3a** was isolated (entry 11), indicating the importance of light. Our efforts to increase yields further using a photochemical activation however remained unsuccessful and the optimal thermal conditions in entry 5 were finally retained to extend the substrate scope, varying the nature of the hydrocarbons in the presence of **2a** (Scheme 1).

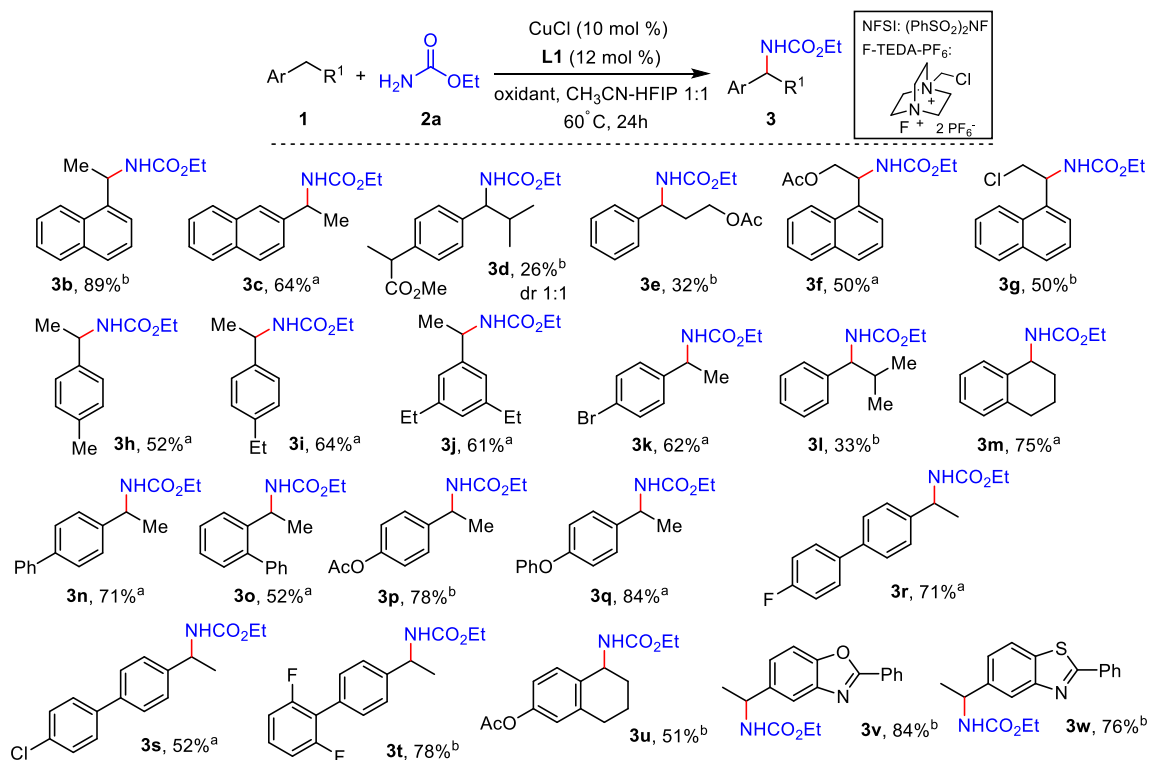


entr	1	Oxidant	Catalyst	Solvent	Yield (%) ^b
1	1a	NFSI	CuCl	CH ₃ CN	33
2	1a	NFSI	CuCl	HFIP	8
3	1a	NFSI	CuCl	CH ₃ CN-HFIP 7:3	54
4	1a	NFSI	CuCl	CH ₃ CN-HFIP 6:4	56
5	1a	NFSI	CuCl	CH ₃ CN-HFIP 1:1	72
6	1a	NFSI	CuOAc	CH ₃ CN-HFIP 1:1	68
7	1a	NFSI	Fe(OAc) ₂	CH ₃ CN-HFIP 1:1	-
8	1a	Selectfluor	CuCl	CH ₃ CN-HFIP 1:1	5
9	1a	F-TEDA-PF ₆	CuCl	CH ₃ CN-HFIP 1:1	53
10 ^c	1a	NFSI	CuCl	CH ₃ CN-HFIP 1:1	43
11 ^d	1a	NFSI	CuCl	CH ₃ CN-HFIP 1:1	6

^a Unless otherwise mentioned, all reactions were performed with **1a** (0.25 mmol), **2a** (0.5 mmol), oxidant (0.5 mmol) CuCl (0.025 mmol), L1 (0.03 mmol) in 1:1 MeCN/HFIP (1.0 mL) under argon atmosphere at 60°C for 24 h. ^b Isolated yields. ^c Reaction performed at 25°C under red-LEDs irradiation. ^d In the dark at 25°C

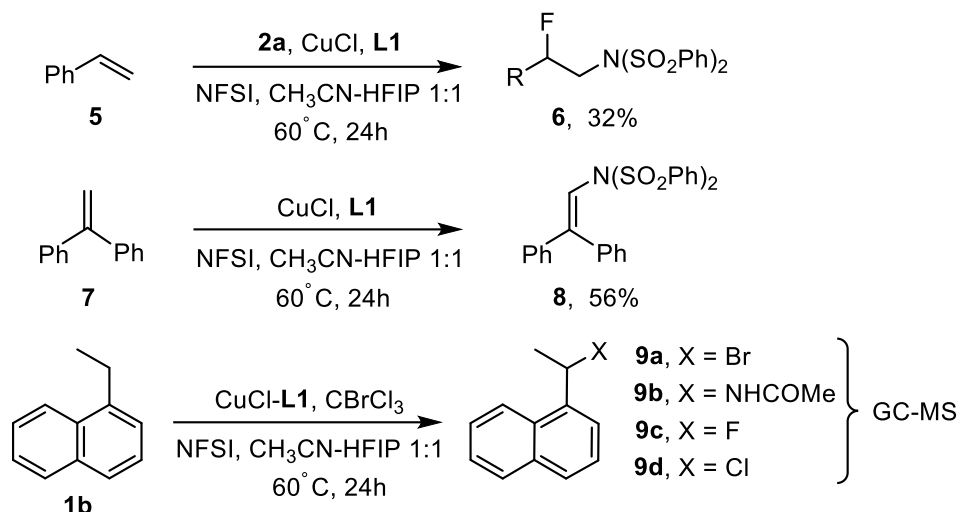
A variety of cyclic and acyclic benzylic systems were thus screened, and the corresponding carbamates obtained in moderate to good yields as summarized in Scheme 1. Functional groups including esters (in **3d**, **3f**, **3p**, **3u**) ether (**3q**), or halogens (Cl, Br, F) in **3g**, **3k**, **3r-t** are compatible with reaction conditions. Steric hindrance around the reacting center appears as a limiting factor as shown with the formation of **3d** and **3l** in moderate yield or comparing ortho- and para-substituted biphenyls **3n** and **3o**. Heterocycles are compatible with the C-H

amination conditions as shown by the access to **3v-w** in good yields. In some cases, NFSI was shown to provide lower conversion, being successfully replaced with F-TEDA-PF₆, which led to cleaner reactions and also proved to be easier to discard from the crude reaction mixture by chromatography.



Scheme 1 Scope of the C-H amination of benzylic substrates with carbamate **2a**. ^a NFSI used as oxidant. ^b F-TEDA-PF₆ used as oxidant.

Next, to broaden the variety of urethanes accessible through this approach, we varied the nature of the substituents on the carbamate, in order to access for instance to N-Cbz or N-Troc groups, typical amine protecting groups.⁹ Results summarized in Scheme 2, clearly show, as mentioned before, that yields decreased with the increasing steric hindrance of the carbamate moiety, the NBoc group being incorporated in very low yields (*i.e.* **4h**). Methyl, ethyl, benzyl and even iso-propyl carbamates **2a-d** react efficiently. The Troc (2,2,2-trichloroethoxycarbonyl) group was conveniently incorporated using **2g**, to give the desired carbamates **4i-j** in satisfying yields. 1,3-Oxazolidin-2-one **2h** also displayed a good reactivity, leading to the corresponding cyclic carbamates **4m-p** in moderate to excellent yields.



Scheme 3 Additional mechanistic study experiments.

Based on the above experimental evidence and previous literature reports,^{3d,19,22-24} a tentative mechanism for the benzylic C-H amination is finally proposed as depicted in Figure 2. We first anticipated a single-electron transfer from the Cu(I)-L complex to NFSI (or F-TEDA-PF₆), which would provide a Cu(II)-complex **A** along with a nitrogen-centered radical **B**. The latter would subsequently abstract the benzylic hydrogen of substrate **I** to generate a benzylic radical **C**. This may then evolve following two possible pathways, e.g. (1) through a combination with Cu-complex **A** to afford Cu(III) species **D**,²⁵ which could lead to intermediate **E** after ligand exchange with carbamate **II**, providing urethane **III** upon reductive elimination or benzyl halides **IV** in the absence of **II** (ESI). A radical-polar crossover process (2) should also be invoked through oxidation of **C** by Cu(II) species **A** into benzylic cation **F**.^{19b} The absence of enantioselectivity using chiral ligand **L1** in our experiments (ESI) and the formation of Ritter product **9b** point toward the formation of such a cation. Finally, a similar reasoning should apply to addition products **6** and **8**. The radical resulting from the addition of (PhSO₂)₂N onto **5** and **7** may be oxidized into a cation such as **F**, which would then evolve toward **8** though proton elimination or trapped by a fluoride anion leading to **6**. The absence of carbamate addition in the last case may be explained by the steric hindrance of the (PhSO₂)₂N group preventing the approach of **2a**, as observed above for hindered benzylic substrates (i.e. **3d**, **3l**). A Cu(II) complex such as **D** may also explain the formation of **6**.²³ Additional mechanistic studies to firmly distinguish between these pathways will however be required, which are currently ongoing.

In summary, we reported a direct Cu-catalyzed C-H amination of a variety of benzylic substrates, leading to carbamates in satisfying yields. The combination between strong oxidants, i.e. NFSI or F-TEDA-PF₆ and Cu(I)-catalyst/diimine system was found to be highly efficient to access carbamates including N-Cbz and N-Troc derivatives. This methodology avoiding carcinogenic isocyanates and unsafe peroxides should be useful for late-stage functionalization of hydrocarbons in medicinal chemistry where urethanes are widespread.

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