EDGE ARTICLE

Copper-catalyzed intermolecular C(sp³)–H bond functionalization towards the synthesis of tertiary carbamates†‡

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We describe the development of an intermolecular unactivated C(sp³)–H bond functionalization towards the direct synthesis of tertiary carbamates. The transformation proceeded using a readily available, abundant first-row transition metal catalyst (copper), and isocyanates as the source of the amide moiety. This is a novel strategy for direct transformation of a variety of unactivated hydrocarbon feedstocks to N-alkyl-N-aryl and N,N-dialkyl carbamates without pre-functionalization or installation of a directing group. The reaction had a broad substrate scope with 3° > 2° > 1° site selectivity. The reaction proceeded even on a gram scale, and a corresponding free amine was directly obtained when the reaction was performed at high temperature. Kinetic studies suggested that radical-mediated C(sp³)–H bond cleavage was the rate-determining step.

Introduction

Carbamates are ubiquitous in nature, and are key functional and structural motifs in a broad range of important compounds, such as pharmaceuticals, agrochemicals, natural products, and functional materials. Molecules with N-alkyl-N-aryl and N,N-dialkyl motifs exhibit various biological properties (Fig. 1).[1,2] The biological significance of carbamates has inspired the development of novel and efficient carbamation reactions.

Catalytic C(sp³)–H amidation, amination, and carbamation of inert hydrocarbons is a challenging and attractive strategy for preparing nitrogen-containing compounds. Reactions such as these that do not require typical functional group manipulations have enormous economic benefits. The notable transformation of a C–H bond to a C–N bond occurs in nitrene chemistry (Scheme 1, route a).[3] However, intermolecular amidations using nitrenes are limited to reactions which produce secondary amides and functionalize benzylic or allylic positions. A more efficient copper-catalyzed Ritter-type C–H amidation was explored using a fluorine-based oxidant and acetonitrile as the nitrogen source (Scheme 1, route b); however, this reaction was limited to the synthesis of N-monoalkyl acetamides.[4] Hartwig's and Warren's copper-amide-based strategies constitute powerful synthetic methods (Scheme 1, route c); albeit, N-alkyl-N-aryl and N,N-dialkyl amides (tertiary amides) were obtained in low yields.[5] Some other intermolecular and intramolecular C–H amination reactions with or without the use of metal catalysts have also been reported.[6]

Despite remarkable progress in C–H amidation and amination reactions, the formation of tertiary carbamates from inert hydrocarbons remains underdeveloped and the synthesis of N-alkyl-N-aryl or N,N-dialkyl tertiary carbamates remains a challenge. Although several reagents are effective as nitrogen atom sources in amidation and amination reactions, isocyanates have not been used to synthesize carbamates. Herein we report a novel and efficient unactivated C(sp³)–H bond functionalization that produces N-alkyl-N-aryl and N,N-dialkyl tertiary
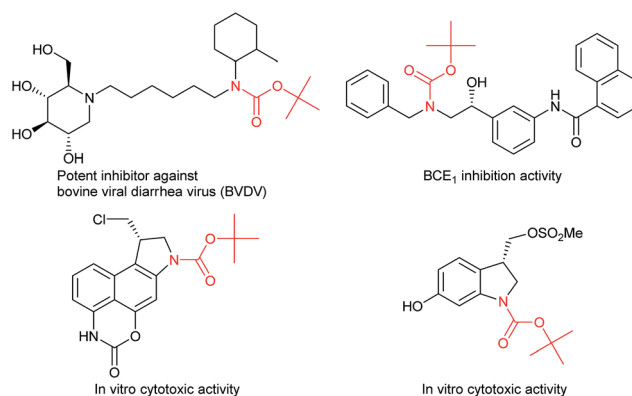
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† Dedicated to Professor Iwao Ojima on his 70th birthday.

‡ Electronic supplementary information (ESI) available: Experimental procedures, characterization data, and ¹H and ¹³C NMR charts. See DOI: 10.1039/c5sc00238a
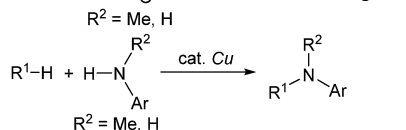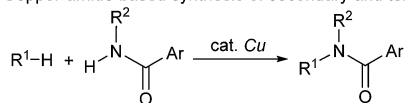

Fig. 1 Biologically active compounds with tertiary carbamate motifs.

(a) Nitrene-based synthesis of secondary amides by benzylic and allylic C(sp^3)-H amidation[3]

$$R^1-H + Ph-I{=}N-Ts \xrightarrow[Fe, \text{ or } Cu]{cat. \ Rh, \ Ru, \ Ag} R^1 \overset{H}{\underset{}{N}} Ts$$
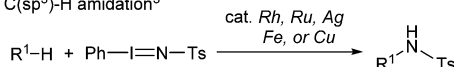
(b) Ritter-type synthesis of secondary acetamides[4]

$$R^1-H + MeCN \xrightarrow{cat. \ Cu} R^1 \overset{H}{N}\overset{O}{\underset{}{}}$$
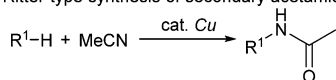
(c) Copper-amide based synthesis of secondary and tertiary amides and amines[5]

$$R^1-H + H-\overset{R^2}{\underset{O}{N}}-Ar \xrightarrow{cat. \ Cu} R^1-\overset{R^2}{\underset{O}{N}}-Ar$$
$$R^2 = Me, H$$

$$R^1-H + H-\overset{R^2}{\underset{Ar}{N}} \xrightarrow{cat. \ Cu} R^1\overset{R^2}{\underset{Ar}{N}}$$
$$R^2 = Me, H$$

(d) **This work:** Copper-catalyzed synthesis of tertiary carbamates and secondary amines using isocyanates

$$R^1-H + R^2-N{=}C{=}O + (^tBuO)_2 \xrightarrow{cat. \ Cu} R^1\overset{R^2}{\underset{O}{N}}O^tBu$$
$$R^2 = \text{alkyl, aryl}$$

$$\xrightarrow[\text{higher temperature}]{cat. \ Cu} R^1\overset{R^2}{\underset{H}{N}}$$
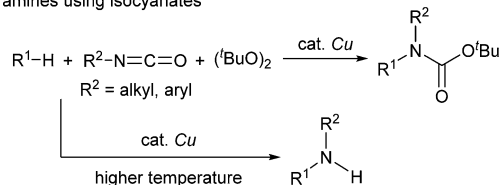
Scheme 1 Transition metal-catalyzed C(sp^3)−H bond transformations to construct C(sp^3)−N bonds.

Table 1 Development of optimized conditions for *N*-phenyl-carbamation of cyclohexane^a

Entry	Catalyst	Ligand	Yield^b (%)
1	CuI	1,10-Phen	30
2	CuCl	1,10-Phen	36
3	CuCl$_2$	1,10-Phen	35
4	CuOAc	1,10-Phen	32
5	[Cu(NCMe)$_4$]BF$_4$	1,10-Phen	47
6^c	[Cu(NCMe)$_4$]BF$_4$	1,10-Phen	0
7^d	[Cu(NCMe)$_4$]BF$_4$	1,10-Phen	0
8^e	[Cu(NCMe)$_4$]BF$_4$	1,10-Phen	20
9	[Cu(NCMe)$_4$]BF$_4$	(MeO)$_2$phen	60
10	[Cu(NCMe)$_4$]BF$_4$	Cl$_2$phen	51
11	[Cu(NCMe)$_4$]BF$_4$	^{t}Bu$_2$bipy	55
12	[Cu(NCMe)$_4$]BF$_4$	Bathocuproine	53
13	[Cu(NCMe)$_4$]BF$_4$	Neocuproine	67
14^f	[Cu(NCMe)$_4$]BF$_4$	Neocuproine	75

^{a} Reaction conditions: **1a** (5.00 mmol), **2a** (0.500 mmol), **3** (1.00 mmol), catalyst (0.0500 mmol), ligand (0.0500 mmol), C$_6$H$_6$ (1.0 mL), 100 °C, 36 h. ^{b} ^{1}H NMR yield using 1,1,2,2-tetrachloroethane as an internal standard. ^{c} TBHP (2.0 equiv.) was used as an oxidant. ^{d} TBPB (2.0 equiv.) was used as an oxidant. ^{e} DTAP (2.0 equiv.) was used as an oxidant. ^{f} Reaction in trifluorotoluene, Cu catalyst (5.0 mol%) and ligand (5.0 mol%), **3** (2.5 equiv.), 100 °C, 24 h. 1,10-Phen = 1,10-phenanthroline, (MeO)$_2$phen = 4,7-dimethoxyphenanthroline, Cl$_2$phen = 4,7-dichlorophenanthroline, ^{t}Bu$_2$phen = 4,7-di(*tert*-butyl) phenanthroline, bathocuproine = 2,9-dimethyl-4,7-diphenyl-1,10-phenanthroline, neocuproine = 2,9-dimethyl-1,10-phenanthroline.

carbamates and the corresponding secondary amines using a copper catalyst and isocyanates as carbamation reagents (Scheme 1, route d).

Results and discussion

First, we investigated transition metal complexes and oxidants for the reaction between cyclohexane (**1a**) and phenyl isocyanate (**2a**) (Table 1). In the presence of a copper(I) iodide–phenanthroline complex (10 mol%) and oxidant **3** in benzene solvent, *tert*-butyl *N*-cyclohexyl-*N*-phenylcarbamate (**4a**) was obtained in 30% yield (entry 1). Other copper salts were comparably active regardless of their counterions and oxidation states (entries 2–4). The cationic copper complex [Cu(NCMe)$_4$]BF$_4$ proved to be the best catalyst, giving **4a** in 47% yield (entry 5). Other peroxides, such as *tert*-butyl hydroperoxide (TBHP) and *tert*-butyl perbenzoate (TBPB), did not produce **4a**, and di-*tert*-amyl peroxide (DTAP) had lower reactivity (entries 6–8). Further screening of bipyridyl-type and phenanthrolyl-type ligands revealed that neocuproine was the best ligand, affording the desired product **4a** in 67% yield (entries 9–13). Extensive evaluation revealed that a reaction in the presence of 5 mol% of [Cu(NCMe)$_4$]BF$_4$ and 2.5 equiv. of oxidant **3** in trifluorotoluene as a co-solvent gave **4a** in 75% yield (entry 14). Other transition metal salts, however, such as Fe(OAc)$_2$, Co(OAc)$_2$, Ni(OAc)$_2$·4H$_2$O, and AgOAc, did not promote the carbamation reaction. In addition, the reaction in the absence of a ligand led to low yield (32%).

The substrate scope of isocyanates was investigated under the above optimal reaction conditions (Table 2). A variety of aryl and alkyl isocyanates were tested in cyclohexane (**1a**) or in a mixture of **1a**/trifluorotoluene. Aryl isocyanates possessing a halogen atom, such as a fluorine, chlorine, or bromine atom, afforded the desired products **4b–e** in excellent yields. Aryl isocyanates containing a trifluoromethyl group underwent carbamation of cyclohexane, affording the corresponding carbamates **4f** and **4g** in optimum yields. The carbamation reaction also proceeded from aryl isocyanates **4h–j** containing an electron-donating group, such as a methoxy, methyl, or *n*-butyl group; however, the isolated yields of the products were slightly lower than those of aryl isocyanates with an electron-withdrawing group. Aryl isocyanates containing an acetyl, methoxycarbonyl, or cyano group were also effective, and the corresponding tertiary carbamates **4k–m** were obtained in good yields. The carbamation reaction was next extended to more challenging substrates, alkyl isocyanates. Notably, reactions of **1a** also occurred with alkyl isocyanates, such as *n*-butyl, cyclopentyl, and cyclohexylisocyanates, giving the corresponding *N,N*-dialkyl carbamates (**4n–p**).
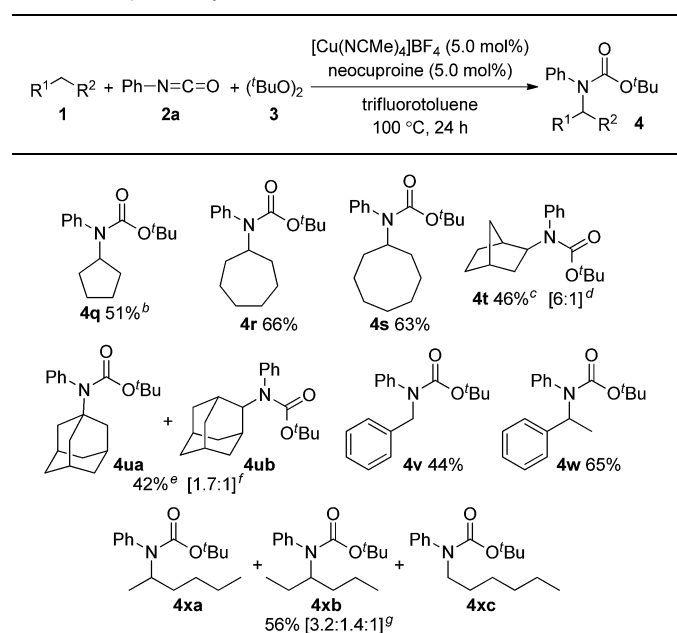
We next evaluated C(sp^3)–H carbamation of other cyclic and linear unactivated alkanes (Table 3). C(sp^3)–H carbamation of cycloalkanes such as cyclopentane, cycloheptane, and cyclooctane proceeded well, giving the corresponding tertiary

Table 2 C(sp^3)–H carbamation of cyclohexane with various isocyanates^{a,b}

4a 74% (76%) **4b** 75% (68%) **4c** 75% (83%)
4d 71% (77%) **4e** 62% **4f** 77% (85%)
4g 76% (87%) **4h** 54% (64%) **4i** 63% (70%)
4j 61% (70%) **4k** 68% (47%) **4l** 73% (70%)
4m 70% **4n** 33% (42%) **4o** 34% (34%) **4p** 30% (29%)
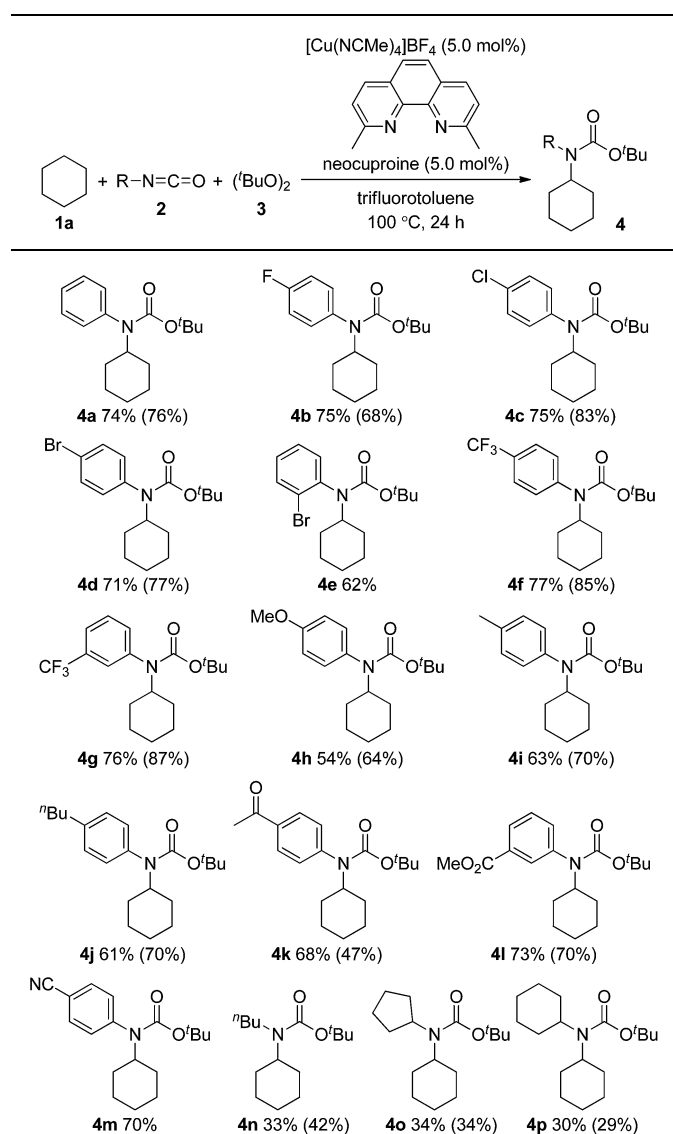
^{a} Reaction conditions: **1a** (5.00 mmol), **2** (0.500 mmol), **3** (1.25 mmol), [Cu(NCMe)$_4$]BF$_4$ (0.0250 mmol), neocuproine (0.0250 mmol), trifluorotoluene (0.5 mL), 100 °C, 24 h. ^{b} Yields in parentheses were obtained in cyclohexane (1.6 mL, 15.0 mmol).

Table 3 C(sp^3)–H aryl-carbamation of various alkanes^a

4q 51%^{b} **4r** 66% **4s** 63% **4t** 46%^{c} [6:1]^d
4ua + **4ub** 42%^{e} [1.7:1]^f **4v** 44% **4w** 65%
4xa + **4xb** + **4xc** 56% [3.2:1.4:1]^g

^{a} Reaction conditions: **1** (5.00 mmol), **2a** (0.500 mmol), **3** (1.25 mmol), [Cu(NCMe)$_4$]BF$_4$ (0.0250 mmol), neocuproine (0.0250 mmol), trifluorotoluene (1.0 mL), 100 °C, 24 h. ^{b} Cyclopentane (1.4 mL, 30 equiv.) was used. ^{c} Trifluorotoluene (1.5 mL) was used. ^{d} Ratio of *exo*- to *endo*-products. ^{e} Trifluorotoluene (2.0 mL) was used. ^{f} Ratio of **4ua** to **4ub**. ^{g} Ratio of **4xa** to **4xb** to **4xc**.

carbamates **4q–s** in good yields. C(sp^3)–H carbamation of norbornane proceeded with single-site selectivity and gave a mixture of stereoisomers **4t** in 46% yield (*exo* : *endo* = 6 : 1). The reaction of adamantane with phenyl isocyanate (**2a**) afforded a regioisomeric mixture (**4ua** and **4ub**) in 42% yield (**4ua** : **4ub** = 1.7 : 1). In the case of toluene, benzylic C(sp^3)–H amidation proceeded and **4v** was obtained in 44% yield. Ethylbenzene showed exclusive site selectivity, and furnished only a single carbamation product **4w** in good yield. The reaction of **2a** with a linear alkane (*n*-hexane), C(sp^3)–H carbamation, proceeded nicely and afforded a mixture of carbamates **4xa**, **4xb**, and **4xc**

(3.2 : 1.4 : 1) in good yield. This is a highly valuable transformation of hydrocarbon feedstocks to tertiary carbamates.

A proposed reaction mechanism is summarized in Scheme 2: (1) the copper(I) species-catalyzed[7] or thermal homolytic cleavage of a peroxide generates *tert*-butoxy radical, which reacts with an isocyanate and sequential oxidation of the copper(I) species to give Cu(II)–amide species; (2) abstraction of a hydrogen atom from the C(sp^3)–H bond of an alkane by *tert*-butoxy radical generates an alkyl radical with the release of ^{t}BuOH;[8] (3) combination of the alkyl radical with Cu(II)–amide species produces a Cu(III) intermediate with alkyl and amide ligands;[8a] and (4) reductive elimination of the Cu(III) species affords a tertiary carbamate and regenerates the Cu(I) species.
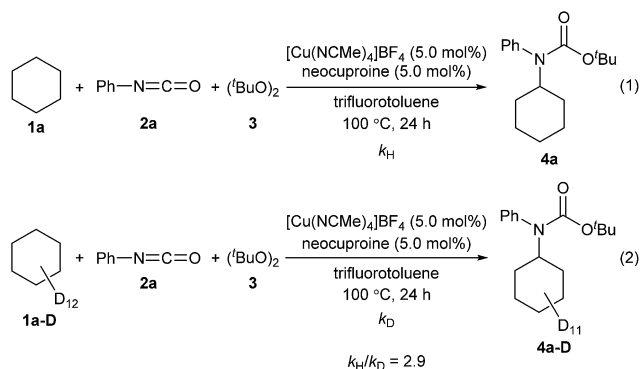
Next, kinetic isotopic effect studies with separate kinetic experiments were performed to gain insight into the rate-determining step for the amidation of cyclohexane (**1a**). Significant kinetic isotopic effects were observed ($k_H/k_D = 2.9$), suggesting that C–H bond cleavage was the rate-determining step of the reaction (Scheme 3, for details, see ESI‡).

We also examined the reactivity difference between carbamate **5n** and isocyanate **2n** in the carbamation reaction (Scheme 4). Treatment of *n*-butyl carbamate **5n** with cyclohexane (**1a**) under the optimized reaction conditions afforded **4n** in only 11% yield. On the other hand, *n*-butyl isocyanate (**2n**) gave **4n** in 42% yield under similar conditions. These results indicated that isocyanates are better carbamation reagents than secondary carbamates[5d] under the optimized conditions.
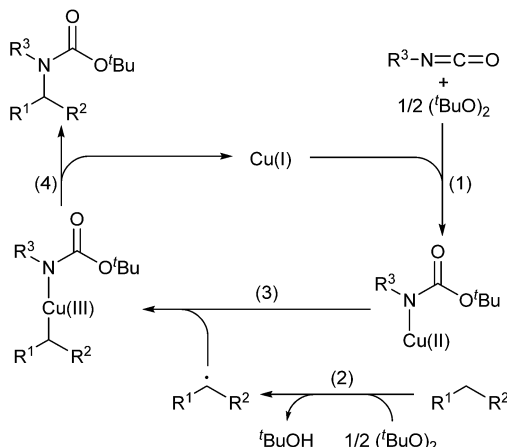
**Scheme 2** Proposed catalytic cycle for $C(sp^3)$–H carbamation of alkanes.

Scheme 3 Kinetic isotopic effect studies.

To address the reactivity difference between isocyanates and secondary carbamates, and to gain further support for the proposed reaction mechanism in Scheme 2, we performed several reactions as follows (Scheme 5): (1) A reaction of phenyl isocyanate (**2a**) with cyclohexane (**1a**) under the optimized conditions without using a copper catalyst was performed. As a result, carbamate **5a** was obtained in 76% yield, and tertiary carbamate **4a** was not formed at all (Scheme 5(1)). This result
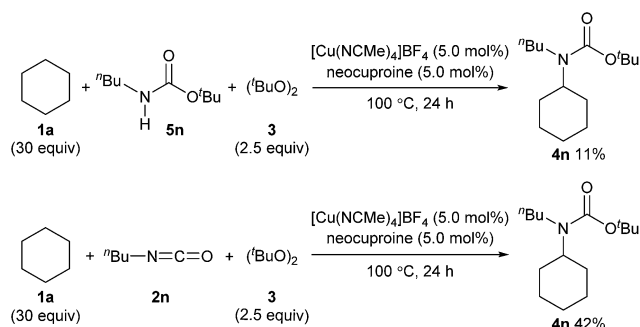

Scheme 4 Evaluation of reactivity difference between secondary carbamates and isocyanates.
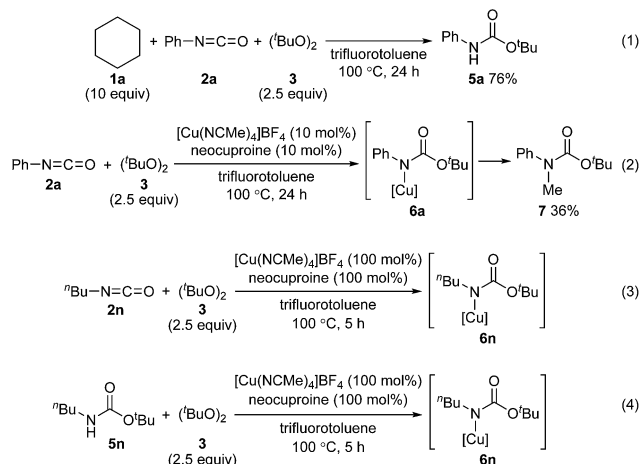

Scheme 5 Several experiments performed to understand the reaction mechanism: (1) a reaction between cyclohexane (**1a**), isocyanate **2a**, and peroxide **3** without using a copper catalyst; (2) a reaction between isocyanate **2a** and peroxide **3** without addition of cyclohexane (**1a**); (3) *in situ*-FT-IR study of a reaction between [Cu(NCMe)$_4$]BF$_4$, isocyanate **2n**, and peroxide **3**; (4) *in situ*-FT-IR study of a reaction between [Cu(NCMe)$_4$]BF$_4$, carbamate **5n**, and peroxide **3**.

showed that the copper catalyst was crucial for coupling between isocyanates and alkanes. (2) A reaction of phenyl isocyanate (**2a**) in the absence of **1a** under the optimized conditions afforded carbamate **7** in 36% yield (Scheme 5(2)). A methyl radical was generated through β-methyl elimination of a *tert*-butoxy radical, and sequential coupling with an *in situ* generated copper(II)–carbamate species (**6a**) would lead to the formation of carbamate **7**. (3) A reaction of *n*-butyl isocyanate (**2n**) with di-*tert*-butyl peroxide (**3**) in the presence of a stoichiometric amount of a copper complex was conducted in trifluorotoluene, and the course of the reaction was monitored by *in situ*-FT-IR (Scheme 5(3), see ESI‡ for details). As a result, an absorption band at 2266 cm^{-1} (assigned for the carbonyl group of isocyanate **2n**) started to disappear after 1.4 h (induction period), and a new absorption band, possibly assigned to the carbonyl groups of copper complex **6n**, appeared at 1725 cm^{-1}. The maximum absorbance intensity at 1725 cm^{-1} was 0.063 (A.U.). (4) Under similar conditions, the progress of a reaction between *n*-butyl carbamate **5n** and di-*tert*-butyl peroxide (**3**) and the formation of copper complex **6n** was monitored by *in situ*-FT-IR (Scheme 5(4), see ESI‡ for details). An absorbance band for the carbonyl group of carbamate **5n** was observed at 1720 cm^{-1}, and an absorbance band at 1725 cm^{-1} corresponding to **6n** started to appear after 3.9 h (induction period). The maximum absorbance intensity at 1725 cm^{-1} was 0.040
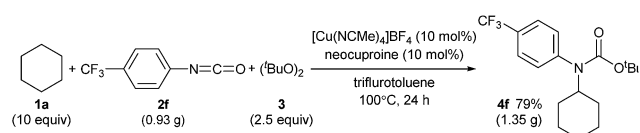
Scheme 6 Gram scale synthesis of *tert*-butyl *N*-cyclohexyl-*N*-(4-trifluromethylphenyl)carbamate (**4f**).
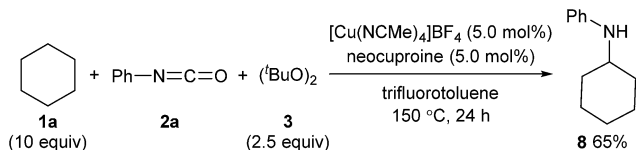
Scheme 7 One-pot direct synthesis of a secondary amine from an alkane.

(A.U., the absorbance intensity of **6n** must be less than 0.040 due to overlapping with an absorbance of **5n**). The differences in the induction period and absorbance intensity of the bands at 1725 cm^{-1} for reactions (3) and (4) correlated well with the result that n-butyl isocyanate (**2n**) was more reactive compared with n-butyl carbamate **5n**. In addition, the reaction of cyclohexane (**1a**) with phenylisocyanate (**2a**) was almost completely inhibited by 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO, 2 equivalents) under the optimized conditions. This result indicated that a radical pathway is involved as a key step in the catalytic cycle.

C(sp^3)–H carbamation could also be performed on a gram scale by treating cyclohexane (**1a**) and p-trifluoromethylphenyl isocyanate (**2f**) with a copper catalyst in trifluorotoluene solvent (Scheme 6, see also the ESI‡). As a result, **4f** was obtained in 79% yield (1.35 g), which was comparable to the yield of **4f** on a smaller scale (77% yield, 132 mg, Table 2).

The developed method can be further extended to the direct synthesis of valuable amines from alkanes in combination with thermal cleavage of the tert-butoxycarbonyl group at a higher temperature (Scheme 5). The reaction of cyclohexane (**1a**) with phenyl isocyanate (**2a**) and (^{t}BuO)$_2$ (**3**) at 150 °C gave N-cyclohexylaniline (**8**) in 65% yield (Scheme 7).

Conclusions

In summary, we developed a copper-catalyzed, non-nitrene-based C(sp^3)–H carbamation reaction. This new C(sp^3)–H to C(sp^3)–N bond transformation proceeded from unactivated alkanes and isocyanates. Although there are few examples of copper-catalyzed amidation or amination to afford secondary amides or amines, this novel protocol allowed us to obtain tertiary carbamates directly from hydrocarbon feedstocks. The reaction had a broad substrate scope, and the observed site selectivity was 3° > 2° > 1°. The reaction proceeded smoothly even on a gram scale, and a higher temperature directly produced the corresponding free amine without the addition of an acid. Kinetic studies suggested that radical mediated C(sp^3)–H bond cleavage was the rate-limiting step. The copper-catalyzed C(sp^3)–H carbamation reaction will be useful for rapid construction of synthetically useful and pharmaceutically valuable molecules bearing N-alkyl-N-aryl or N,N-dialkyl tertiary carbamate moieties.

Acknowledgements

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