ORGANIC LETTERS

2007
Vol. 9, No. 19
3813−3816

Copper-Catalyzed Amidation of sp^3 C–H Bonds Adjacent to a Nitrogen Atom

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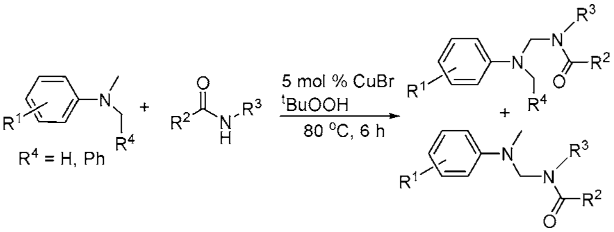
Received July 19, 2007

ABSTRACT



We have developed a novel copper-catalyzed amidation of unactivated sp^3 C–H bonds adjacent to a nitrogen atom by using an inexpensive catalyst–oxidant (CuBr/^{t}BuOOH) system under mild conditions. The *dephenylation* was first found for *N*-benzylaniline, and the new class of products provide diverse structures for pharmaceuticals and combinatorial chemistry.

Direct and selective formation of C−C, C−O, and C−N bonds from unactivated carbon−hydrogen bonds is an important and long-standing goal in chemistry. These conversions have wide potential in synthetic organic chemistry because C−H bonds are ubiquitous in organic molecules. However, achieving selectivity among many different C−H bonds remains a challenge.[1] The formation of C−N bonds is very important in organic synthesis because many bioactive and medicinal molecules are nitrogen-containing compounds.[2] The vast majority of methods for the introduction of C−N bonds depends on functional group interconversions for their synthesis, thus the direct utilization of only C−H bonds is highly desirable.[3] In the past several years, great achievements have been made on amidation via a C−H activation strategy, particularly with regards to allylic and benzylic C−H bonds,[4−6] and most of them were performed through the metal−nitrene-type amidation. Although great

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(4) Representative intramolecular metal−nitrene-type amidations: (a) Kim, M.; Mulcahy, J. V.; Espino, C. G.; Du Bois, J. *Org. Lett.* **2006**, *8*, 1073−1076. (b) Lebel, H.; Huard, K.; Lectard, S. *J. Am. Chem. Soc.* **2005**, *127*, 14198−14199. (c) Cui, Y.; He, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 4210−4212. (d) Espino, C. G.; Fiori, K. W.; Kim, M.; Du Bois, J. *J. Am. Chem. Soc.* **2004**, *126*, 15378−15379. (e) Liang, J.-L.; Yuan, S.-X.; Huang, J.-S.; Yu, W.-Y.; Che, C.-M. *Angew. Chem., Int. Ed.* **2002**, *41*, 3465−3468. (f) Espino, C. G.; Wehn, P. M.; Chow, J.; Du Bois, J. *J. Am. Chem. Soc.* **2001**, *123*, 6935−6936. (g) Espino, C. G.; Du Bois, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 598−600.

(5) Representative intermolecular metal−nitrene-type amidations: (a) Fructos, M. R.; Trofimenko, S.; Díaz-Requejo, M. M.; Pérez, P. J. *J. Am. Chem. Soc.* **2006**, *128*, 11784−11791. (b) Thu, H.-Y.; Yu, W.-Y.; Che, C.-M. *J. Am. Chem. Soc.* **2006**, *128*, 9048−9049. (c) Leung, S. K.-Y.; Tsui, W.-M.; Huang, J.-S.; Che, C.-M.; Liang, J.-L.; Zhu, N. *J. Am. Chem. Soc.* **2005**, *127*, 16629−16640. (d) Pelletier, G.; Powell, D. A. *Org. Lett.* **2006**, *8*, 6031−6034.

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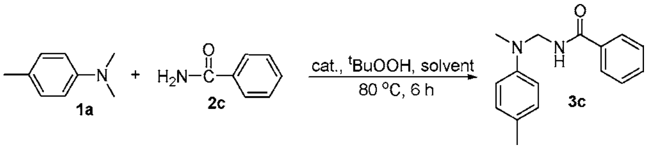
10.1021/ol701715m CCC: $37.00

progress has been made in intramolecular[4] amidation reactions, intermolecular[5] couplings remain limited, and some expensive metal catalysts, such as Ru and Rh, were generally used. Herein, we report an efficient copper-catalyzed amidation of sp^3 C−H bonds adjacent to a nitrogen atom.

Since *tert*-butyl hydroperoxide (^{t}BuOOH) is a suitable oxidant in the copper-catalyzed formation of C−C bonds by directly using C−H bonds,[7] we first chose *N*,*N*-dimethyl-*p*-toluidine and benzoylamide as the model substrates and 1.5 equiv of ^{t}BuOOH (relative to benzoylamide) in decane as the oxidant to optimize the catalysis conditions, including optimization of the copper catalysts and solvents in amidation at 80 °C as shown in Table 1. Several copper salts, CuCl, CuBr, CuI, CuO, and $CuSO_4$ (5 mol % catalytic amount relative to benzoylamide), were tested in DMSO, and CuBr was found to be the most effective catalyst in this amidation. The reaction did not proceed in the absence of either a copper catalyst or ^{t}BuOOH (entry 12). We also studied the effect of solvents (compare entries 1, 6−10). Decane provided the highest yield (see entry 11); DMSO (see entry 14) and mixed solvents (mixture of decane and other solvents) gave lower yields. When the reaction temperature was lowered to room temperature, no product was found (entry 13). The amidation led to a lower yield in the absence of a nitrogen atmosphere (entry 15). The use of 2 equiv of aniline increased the amide

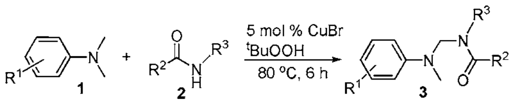
Table 1. Copper-Catalyzed Amidation of sp^3 C−H Bonds: Optimization of Conditions[a]

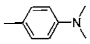
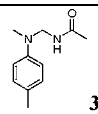
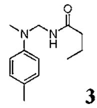
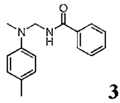
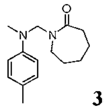
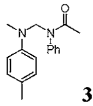
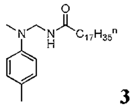
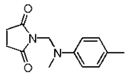
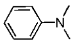
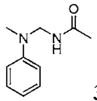
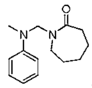
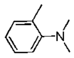
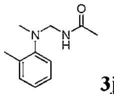
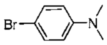
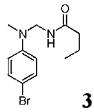
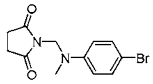


entry	catalyst	additional solvent	yield[b] (%)
1	CuCl	DMSO	20
2	CuBr	DMSO	61
3	CuI	DMSO	52
4	CuO	DMSO	16
5	$CuSO_4$	DMSO	3
6	CuBr	DMF	48
7	CuBr	CH_3CN	25
8	CuBr	CH_2Cl_2	35
9	CuBr	CH_3OH	25
10	CuBr	THF	42
11	CuBr		82 (77[c])
12		DMSO	0[d]
13	CuBr		0[e]
14	CuBr	DMSO	57[f]
15	CuBr		60[g]

[a] Reaction conditions: under nitrogen atmosphere, *N*,*N*-dimethyl-*p*-toluidine (2 mmol), benzoylamide (1 mmol), ^{t}BuOOH (1.5 mmol, 5−6 M in decane), catalyst (0.05 mmol), solvent (0.5 mL). [b] Reported yields were determined by NMR using THF or CH_3CN as internal standard, and were based on benzoylamide. [c] Isolated yield. [d] No addition of copper-catalyst or ^{t}BuOOH. [e] Room temperature. [f] Pure ^{t}BuOOH was used as a dehydrogenative reagent instead of ^{t}BuOOH in decane. [g] Without nitrogen atmosphere.

Table 2. Copper-Catalyzed Amidation of *N*,*N*-Dimethylaniline Derivatives[a]



entry	aniline	product	yield %[b]
1	 **1a**	 **3a**	76
2	**1a**	 **3b**	67
3	**1a**	 **3c**	77
4	**1a**	 **3d**	63
5	**1a**	 **3e**	22
6	**1a**	 **3f**	78
7	**1a**	 **3g**	77
8	 **1b**	 **3h**	59
9	**1b**	 **3i**	71
10	 **1c**	 **3j**	20
11	 **1d**	 **3k**	35[c]
12	**1d**	 **3l**	52[c]

[a] Reaction conditions: under nitrogen atmosphere, anilines (4 mmol for entries 1−3, 6, 8, 10−11, 13, 14; 3 mmol for others), amides (2 mmol), CuBr (0.1 mmol), ^{t}BuOOH (3 mmol, 5−6 M in decane). [b] Isolated yield. [c] DMSO (1 mL) as the additional solvent.

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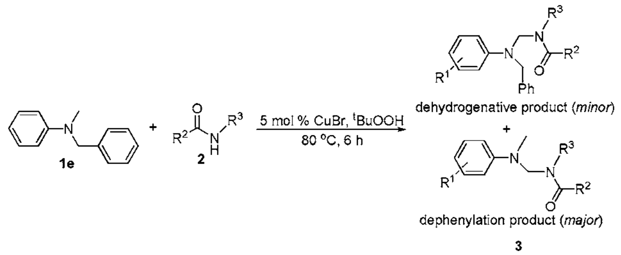
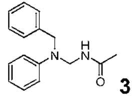
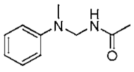
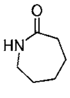
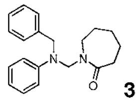
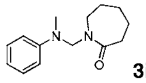
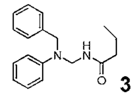
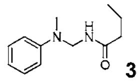
(7) (a) Li, Z.; Bohle, D. S.; Li, C.-J. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 8928−8933. (b) Li, Z.; Li, C.-J. *Org. Lett.* **2004**, *6*, 4997−4999. (c) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2004**, *126*, 11810−11811. (d) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2005**, *127*, 3672−3673.

Table 3. Copper-Catalyzed Amidation of *N*-Methyl-*N*-benzylaniline[a]



entry	amide	product	yield %[b]
1	CH_3CONH_2 **2a**	 **3m**	28
		 **3h**	56
2	 **2d**	 **3n**	17
		 **3i**	45
3	$CH_3CH_2CH_2CONH_2$ **2b**	 **3o**	23
		 **3p**	43

[a] Reaction conditions: under nitrogen atmosphere, anilines (4 mmol), amides (2 mmol), CuBr (0.1 mmol), ᵗBuOOH (3 mmol, 5−6 M in decane). [b] Isolated yield.

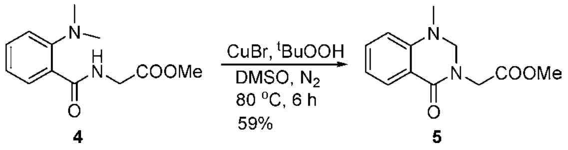
conversion and improved the yield. After the optimization process for catalysts, solvents and temperature, we decided to carry out the following reactions under our standard conditions: 5 mol % CuBr as the catalyst relative to amides and decane or decane/DMSO mixture as the solvent (the mixed solvent was used for insoluble substrates in decane) at 80 °C.

The scope of the copper-catalyzed amidation was explored under our standard conditions. As shown in Table 2, the coupling reactions could be performed for all of the substrates examined, and the desired amidation products were obtained in various yields. The substituted anilines containing electron-rich groups showed higher reactivity than those containing electron-deficient groups. The ortho-substituted aniline (**1c**) gave a low yield (entry 10) because of steric hindrance. However, the electron-deficient amides gave higher reaction yields than the electron-rich ones, the primary amides provided higher reaction activity than the secondary ones, and *N*-arylamide was a poor substrate (entry 5).

Interestingly, reactions of amides with *N*-methyl-*N*-benzylaniline led to both dehydrogenative and *dephenylation* coupling products, and the latter product was major (see Table 3). To our knowledge, the dephenylation is the first such example in metal-catalyzed direct amidation of C−H bonds reported thus far.

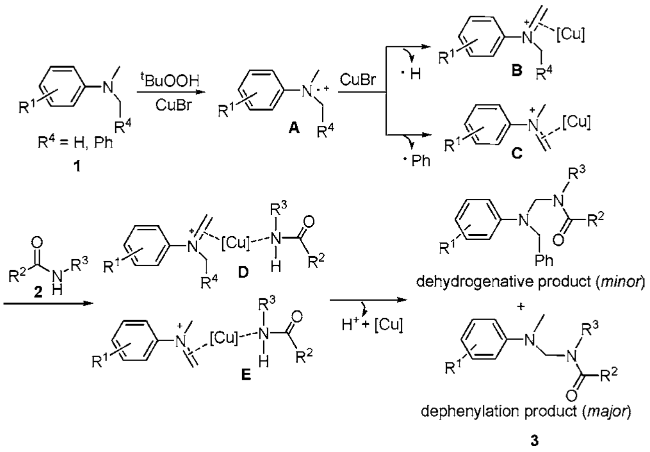
We also attempted intramolecular amidation under our standard coupling conditions as shown in Scheme 1, and the six-membered cyclic compound **5** was obtained in 59% yield. This might be a favorable process to construct complex nitrogen-containing heterocycles in pharmaceuticals and combinatorial chemistry.

Scheme 1. Synthesis of the Six-Membered Cyclic Compound



A tentative mechanism for product formation is proposed in Scheme 2. Reaction of the *N*-substituted aniline with ᵗBuOOH under catalysis of CuBr produced the free radical **A** through a single-electron transfer. The resulting iminium type intermediate **B** or **C** was then generated, leaving a hydrogen[7,8] or phenyl free radical. Combination of **B** or **C** and amide with copper formed the complex **D** or **E**, and removal of the copper catalyst yielded the amidation product **3** (dehydrogenative product or dephenylation product).

Scheme 2. Tentative Mechanism for the Direct Oxidative Coupling of *N*-Substituted Aniline with Amide



In summary, we have developed a novel copper-catalyzed amidation of unactivated sp^3 C−H bonds adjacent to a nitrogen atom via cross-dehydrogenative-coupling reaction by using an inexpensive catalyst-oxidant (CuBr/ᵗBuOOH) system under mild conditions. The dephenylation of *N*-benzylaniline first was disclosed, and the new products may provide diverse structures for pharmaceuticals and combi-

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(8) (a) Wang, F.; Sayre, L. M. *J. Am. Chem. Soc.* **1992**, *114*, 248−255. (b) Leonard, N. J.; Leubner, G. W. *J. Am. Chem. Soc.* **1949**, *71*, 3408−3411.

natorial chemistry. The scope, mechanism, and synthetic application of this reaction is under investigation.

Acknowledgment. This work was supported by the National Natural Science Foundation of China (Grant Nos. 20472042 and 20672065), Programs for New Century Excellent Talents in University (NCET), Changjiang Scholars and Innovative Research Team in University (PCSIRT) (No. IRT0404) in China, and the Key Subject Foundation from Beijing Department of Education (XK100030514).

Supporting Information Available: Synthetic procedures, characterization data, and ^{1}H and ^{13}C NMR spectra of these synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL701715M