JOC Article

General and Efficient Copper-Catalyzed Amidation of Saturated C−H Bonds Using *N*-Halosuccinimides as the Oxidants

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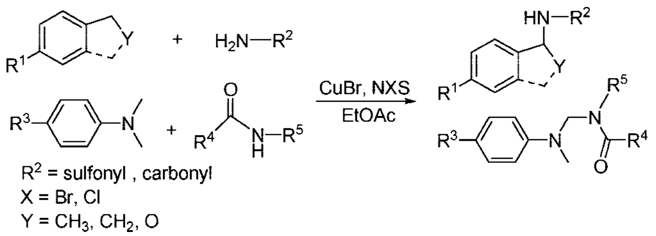

We have developed a general and efficient method for copper-catalyzed amidation of saturated C−H bonds under mild conditions, and the used substrates include benzylic reagents, the *N*,*N*-dimethylaniline derivatives, the free carboxamides, and sulfonamides. The protocol uses inexpensive and readily available CuBr/*N*-halosuccinimide (NBS or NCS) as the catalyst/oxidant, so it provides practical applications for synthesis of various amides via C−H activation.

Introduction

The direct C−N bond conversions of C−H bonds have attracted much attention because nitrogen-containing functional groups are prevalent in many natural products and pharmaceuticals.[1] However, the selective functionalization among many different C−H bonds remains a chellenge.[2] In the past two decades, great progress on intramolecular and intermolecular amidations of C−H bonds has been achieved, and the amidations of C−H bonds highly depend on metal catalysts and oxidants. The used metal catalysts include rhodium, ruthenium, sliver, iron, and other metal complexes.[3–6] Recently, several inexpensive copper-catalyzed amidations of C−H bonds have been reported.[7] $PhI(OAc)_2$ is a pupolar oxidant at present. Recently, other oxidants such as ^{t}BuOOAc[7d] and ^{t}BuOOH[7e] were also used in amidation of C−H bonds. In the reported methods, the amidations were usually performed by using nitrene-type intermediates[3–5] and alternative nitrene derivatives such as

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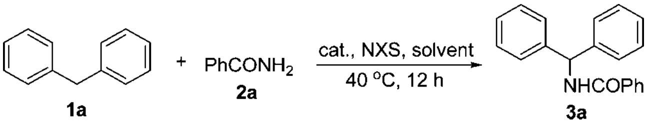
chloramines-T,[7a–c,8] bromamine-T,[9] and tosyloxycarbamates[10] as the primary nitrogen sources. Inspired by the previous good results, we are searching for a convenient, efficient, and general copper catalyst/oxidant system to reach the selective amidation of C−H bonds. Fortunately, an excellent CuBr/NXS (X = Br, Cl) system has been developed for amidations of saturated C−H bonds.

Results and Discussion

Copper-Catalyzed Amidation of Benzylic C−H Bonds. Because *N*-halosuccinimides (such as *N*-bromosuccinimide (NBS) and *N*-chlorosuccinimide (NCS)) are the oxidants[11] and free radical triggers,[12] we first chose diphenylmethane and benzamide as the model substrates and NBS or NCS as the oxidant to optimize the catalysis conditions, including optimization of copper catalysts, oxidants, and solvents at 40 °C without exclusion of air as shown in Table 1. Several copper salts, CuO, $Cu(OAc)_2$, $CuSO_4$, CuCl, CuBr, and CuI, were tested in CH_2Cl_2; Cu(I) salts showed better activity than Cu(II) salts in this amidation (see entries 1−6), and CuBr was found to be the most effective catalyst. The effect of solvents (CH_2Cl_2, hexane, 1,2-dichloroethane, CH_3OH, and EtOAc) (without any previous procedure for the commercial available solvents) was also investigated (compare entries 5 and 7−10); ethyl acetate provided the highest yield (see entry 10). In order to export whether the amidation reaction in entry 10 is from the catalysis of Cu(II) salt (oxidation of CuBr), we investigated the effect of $CuBr_2$ in ethyl acetate, and only 36% yield of product was obtained (entry 11). Slightly lower yields were given when NCS replaced NBS as the oxidant (see entry 12). Only a trace amount of amidation product was observed in the absence of copper catalyst (entry 13). The amidation led to a lower yield when a base (such as K_2CO_3) was added to the reaction system (entry 14). When the reaction temperature was increased to 60 °C, the reaction yield was slightly improved (compare entries 10 and 15). The use of excess of diphenylmethane (2 equiv) improved amide conversion and improved the yield of **3a** (compare entries 10 and 16). After the optimization process of catalysts, oxidants, solvents, and temperature, the following amidations were carried out under our standard conditions: CuBr as the catalyst, NBS as the oxidant (NCS was used as the oxidant for amidation of isochroman), and ethyl acetate as the solvent. The amidation temperature of benzylic sp^3 C−H bonds was maintained between room temperature and 80 °C without exclusion of air.

TABLE 1. Copper-Catalyzed Amidation of Benzylic sp^3 C−H Bond: Optimization of Conditions[a]



entry	catalyst	NXS	solvent	yield[b] (%)
1	CuO	NBS	CH_2Cl_2	22
2	$Cu(OAc)_2$	NBS	CH_2Cl_2	34
3	$CuSO_4$	NBS	CH_2Cl_2	15
4	CuCl	NBS	CH_2Cl_2	40
5	CuBr	NBS	CH_2Cl_2	56
6	CuI	NBS	CH_2Cl_2	51
7	CuBr	NBS	hexane	18
8	CuBr	NBS	ClC_2H_4Cl	64
9	CuBr	NBS	CH_3OH	trace
10	CuBr	NBS	EtOAc	75 (64[c])
11	$CuBr_2$	NBS	EtOAc	36
12	CuBr	NCS	EtOAc	68
13		NBS	EtOAc	trace[d]
14	CuBr	NBS	EtOAc	63[e]
15	CuBr	NBS	EtOAc	78[f]
16	CuBr	NBS	EtOAc	34[g]

[a] Reaction conditions: diphenylmethane (1 mmol), benzamide (0.5 mmol), catalyst (0.1 mmol), NBS or NCS (0.55 mmol), solvent (3 mL). [b] Determined by ^{1}H NMR using THF as the internal standard. [c] Isolated yield. [d] No addition of catalyst. [e] K_2CO_3 was used as the base. [f] Reaction temperature was maintained at 60 °C. [g] 0.55 mmol of diphenylmethane was used.

The scope of CuBr/NBS-mediated amidation of benzylic sp^3 C−H bonds was investigated under our standard conditions. As shown in Table 2, the coupling reactions could be performed for the substrates examined, and the desired amidation products were obtained in moderate to good yields. The activity order of the benzylic reagents is triphenylmethane > diphenylmethane > ethylbenzene > 4-bromoethylbenzene. For example, the amidation of triphenylmethane could be carried out at room temperature (entry 14), while the coupling reactions of 4-bromoethylbenzene with amides were not performed until the temperature was raised to 80 °C (entries 11 and 12). We also investigated amidation of isochroman; interestingly, NCS is a more effective oxidant than NBS, and the reactions selectively occurred on the benzylic C−H bond adjacent to the oxygen atom (entries 15−17). For the carboxamides and sulfonamides, the electron effect of the substrates are prime, the substrates containing the stronger electron-withdrawing groups showed higher reactivity, and their order of activity is sulfonamides > benzamides > aliphatic amides. In addition, the benzamides containing electron-withdrawing groups usually showed higher reactivity than those containing electron-donating groups (compare entries 1−5).

A possible mechanism for the amidation of benzylic sp^3 C−H bonds is proposed in Scheme 1. Reaction of carboxamide or sulfonylamide with NBS yields *N*-bromocarboxamide or *N*-bromosulfonamide (**A**),[13] exchange of copper(I) ion with proton in **A** gives **B**, and the exchange pathway of metal ion with proton in sulfonamides was proposed in the previous catalytic cycle.[14] It is worthwhile to note that **B** is similar to chloramines-T,[7a–c,8]

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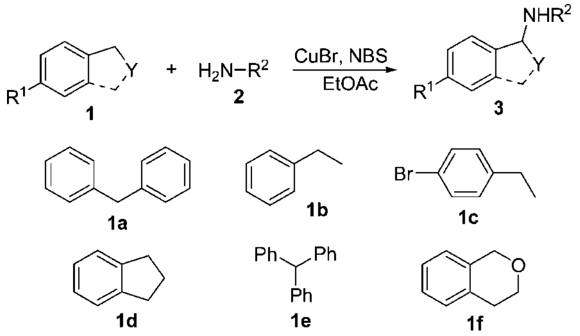
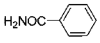
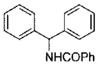
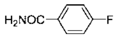
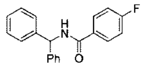
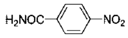
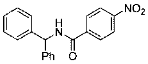
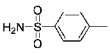
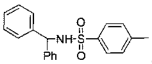
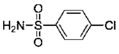
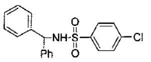
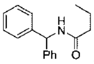
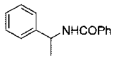
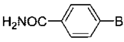
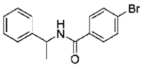
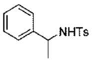
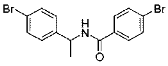
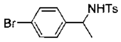
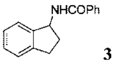
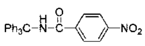
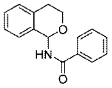
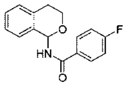
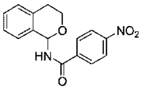
TABLE 2. CuBr/NBS-Mediated Amidations of Benzylic sp^{3}C−H Bonds[a]



entry	2	temp./time	product	yield (%)[b]
1	 **2a**	40 °C/12 h	 **3a**	64
2	 **2b**	40 °C/12 h	 **3b**	75
3	 **2c**	40 °C/12 h	 **3c**	78
4	 **2d**	40 °C/12 h	 **3d**	73
5	 **2e**	40 °C/12 h	 **3e**	79
6	$CH_3CH_2CH_2CONH_2$ **2f**	50 °C/12 h	 **3f**	49
7	n-$C_{17}H_{35}CONH_2$ **2g**	50 °C/12 h	 **3g**	42
8	**2a**	60 °C/12 h	 **3h**	50
9	 **2h**	60 °C/12 h	 **3i**	56
10	**2d**	60 °C/12 h	 **3j**	65
11	**2h**	80 °C/12 h	 **3k**	46
12	**2d**	80 °C/12 h	 **3l**	57
13	**2a**	50 °C/12 h	 **3m**	68
14	**2c**	rt/12 h	 **3n**	67
15	**2a**	60 °C/6 h	 **3o**	39[c]
16	**2b**	60 °C/6 h	 **3p**	43[c]
17	**2c**	60 °C/6 h	 **3q**	40[c]

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[a] Reaction conditions: benzylic reagent (4 mmol), amide (2 mmol), CuBr (0.4 mmol), NBS (2.2 mmol), EtOAc (8 mL). [b] Isolated yield. [c] Using NCS as the oxidant.

SCHEME 1. Possible Mechanism for CuBr/NBS-Mediated Amidation of Benzylic sp^{3}C−H Bonds

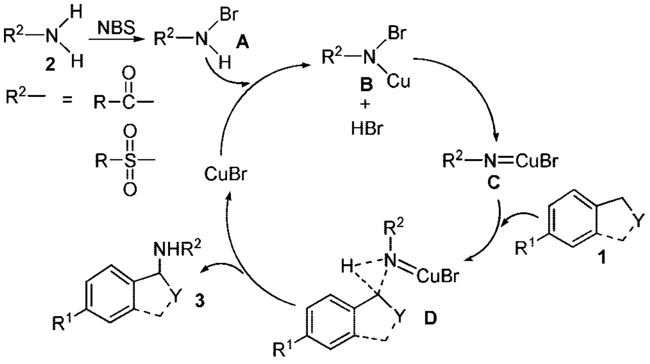
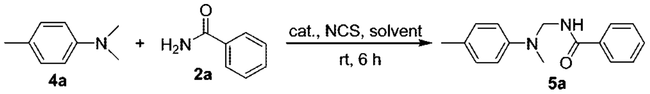


TABLE 3. Copper-Catalyzed Amidation of *N*,*N*-Dimethyl-*p*-toluidine: Optimization of Conditions[a]



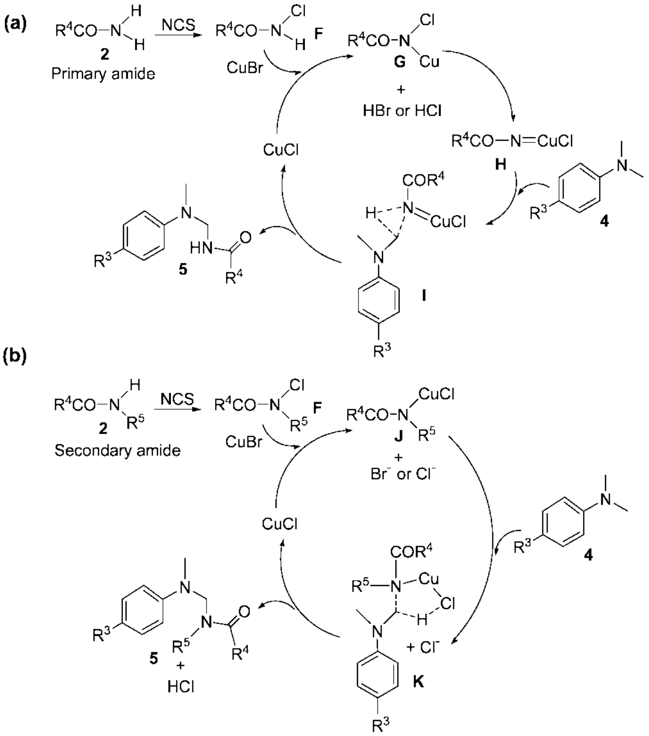
entry	catalyst	NXS	solvent	yield[b] (%)
1	$CuSO_4$	NCS	EtOAc	21
2	CuO	NCS	EtOAc	29
3	CuCl	NCS	EtOAc	13
4	CuI	NCS	EtOAc	51
5	CuBr	NCS	EtOAc	67
6	CuBr	NCS	CH_2Cl_2	36
7	CuBr	NCS	THF	63
8	CuBr	NCS	CH_3OH	16
9	CuBr	NCS	CH_3CN	43
10		NCS	EtOAc	trace[c]
11	CuBr	NBS	EtOAc	58
12	CuBr	NCS	EtOAc	51[d]
13	CuBr	NCS	EtOAc	31[e]

[a] Reaction conditions: *N*,*N*-dimethyl-*p*-toluidine (1 mmol), benzamide (0.5 mmol), NCS (0.55 mmol), catalyst (0.1 mmol), solvent (2 mL). [b] Yields were determined by ^{1}H NMR using THF or CH_3CN as internal standard. [c] No addition of copper catalyst. [d] Reaction temperature was maintained at 60 °C. [e] 0.55 mmol of *N*,*N*-dimethyl-*p*-toluidine was used.

bromamine-T,[9] and tosyloxycarbamates[10] used as the alternative nitrene sources, and isomerization of **B** provides copper−nitrene complex **C**. Treatment of **C** with benzylic C−H bonds yields intermediate **D**,[15] and release of CuBr in **D** gives the target product **3**.

Copper-Catalyzed Amidation of C−H Bonds Adjacent to a Nitrogen Atom. We also investigated amidation of C−H bonds adjacent to a nitrogen atom. At first, we chose *N*,*N*-dimethyl-*p*-toluidine and benzamide as the model substrates and 1.1 equiv of NCS or NBS (relative to benzamide) as the oxidant to optimize the catalysis conditions, and this screening process is similar to the amidation of benzylic C−H bonds (see Table 3). Several copper salts, $CuSO_4$, CuO, CuCl, CuI, and CuBr (20 mol % catalytic amount relative to benzamide), were tested in ethyl acetate (entries 1−5), and CuBr was the most effective catalyst. The effect of solvents (ethyl acetate, CH_2Cl_2, THF, CH_3OH, CH_3CN) was also investigated (entries 5−9), and ethyl acetate provided the highest yield. Only a trace amount of amidation product was observed in the absence of copper catalyst (entry 10). The reaction yield slightly decreased using NBS instead of NCS as the oxidant (entry 11). When the reaction temperature was increased to 60 °C, the conversion yield of the target product was lowered to 51% while some unknown byproduct were observed (entry 12). The use of excess of *N*,*N*-dimethyl-*p*-toluidine (2 equiv) improved amide conversion and improved the yield of **5a** (compare entries 5 and 13). After the optimization process for catalysts, solvents and temperature, the following amidation reactions were performed under our standard conditions: CuBr as the catalyst, NCS as the oxidant, and ethyl acetate as the solvent at room temperature (~25 °C) without exclusion of air.

SCHEME 2. Possible Mechanism for CuBr/NCS-Mediated Amidation of *N*,*N*-Dimethylaniline Derivatives Using Primary Amides (a) and Secondary Amides (b) as the Nitrogen Sources



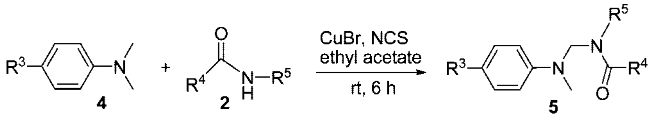
As shown in Table 4, the coupling reactions were performed for all the substrates examined, and the desired amidation products were obtained in moderate isolated yields. Aromatic amides showed better activity than aliphatic amides, the primary amides provided higher reaction yields than the secondary one (such as ϵ-caprolactam in entry 7), and succinimide is a good substrate (entries 8 and 13). All the reactions were carried out at room temperature without exclusion of air, the present catalyst system shows milder conditions than CuBr/tBuOOH one in our previous research (reaction temperature 80 °C),[7e] so it is of practical applications for amidations of C−H bonds.

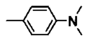
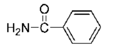
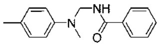
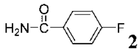
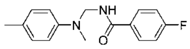
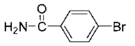
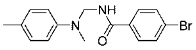
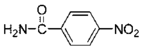
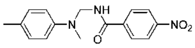
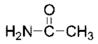
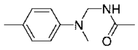
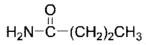
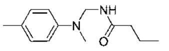
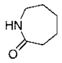
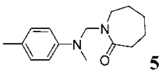
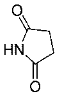
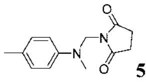
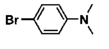
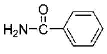
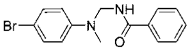
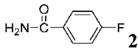
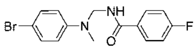
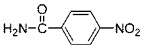
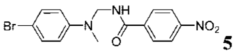
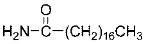
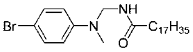
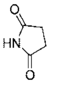
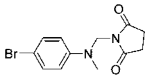
A possible mechanism for amidation of *N*,*N*-dimethylaniline derivatives is proposed in Scheme 2. When the primary amides were used as the nitrogen sources, the amidation of *N*,*N*-dimethylaniline derivatives undergoes the similar pathway to Scheme 1 (see Scheme 2a). However, the secondary amides are different to the former. The oxidative addition of copper(I) with N−Br bond provides **J**, treatment of **J** with *N*,*N*-dimethylaniline derivative forms complex **K**, and then reductive elimination of **K** gives the amidation product releasing CuCl (Scheme 2b).

Conclusion

We have developed a new copper-catalyzed method for the amidation of benzylic reagents and *N*,*N*-dimethylaniline deriva-

TABLE 4. Copper/NCS-Mediated Amidation of *N*,*N*-Dimethylaniline Derivatives[a]



entry	aniline	amide	product	yield (%)[b]
1	 4a	 2a	 5a	58
2	4a	 2b	 5b	54
3	4a	 2h	 5c	59
4	4a	 2c	 5d	58
5	4a	 2i	 5e	40
6	4a	 2f	 5f	43
7	4a	 2j	 5g	45
8	4a	 2k	 5h	63
9	 4b	 2a	 5i	61
10	4b	 2b	 5j	59
11	4b	 2c	 5k	54
12	4b	 2g	 5l	42
13	4b	 2k	 5m	64

[a] Reaction conditions: *N*,*N*-dimethylaniline derivative (4 mmol), amide (2 mmol), CuBr (0.4 mmol), NCS (2.2 mmol), ethyl acetate (8 mL). [b] Isolated yield.

tives via C−H activation. The protocol uses CuBr as the catalyst and nonexplosive NBS or NCS as the oxidant, and the amidations were efficiently performed under mild conditions. The reactions are insensitive to atmospheric moisture and oxygen, and neither dried solvent nor an inert atmosphere is required. The catalyst−oxidant (CuBr/NXS) system is an inexpensive and convenient example for amidation of the unactivated C−H bonds.

Experimental Section

General Procedure for Synthesis of Compounds 3a−q. A 25 mL round-bottom flask was charged with a magnetic stirrer, and 8 mL of ethyl acetate, benzylic reagent (**1**) (4 mmol), carboxamide or sulfonamide (**2**) (2 mmol), and CuBr (0.4 mmol, 58 mg) were added. After the mixture was stirred for 15 min, *N*-bromosuccinimide (NBS) (2.2 mmol, 392 mg) (2.2 mmol of NCS (294 mg) was used for amidation of isochroman) was added to the solution without extrusion of air. The mixture was stirred for 6 or 12 h at the indicated temperature as shown in Table 2. The reaction mixture was then cooled to room temperature and filtered. The solid was washed with ethyl acetate two times (2 × 5 mL), the combined filtrate was concentrated by the rotary evaporator, and the residue was purified by column chromatography on silica gel using hexane/ethyl acetate as eluent to give the desired product.

3d[16]**:** eluent, hexane/ethyl acetate = 8:1; white solid, yield 73% (492 mg); mp 153−154 °C; ^{1}H NMR (CDCl$_3$, 300 MHz, ppm) δ 7.54 (d, 2H, J = 7.9 Hz), 7.18−7.07 (m, 12H). 5.57−5.52 (m, 2H), 2.34 (s, 3H); ^{13}C NMR (CDCl$_3$, 300 MHz, ppm) δ 143.2, 140.7, 137.5, 129.4, 128.6, 127.6, 127.5, 127.3, 61.4, 21.5; HR-MS [M + H]$^+$ m/z calcd for $C_{20}H_{20}NO_2S$ 338.1215, found 338.1219.

General Procedure for Synthesis of Compounds 5a−m. A 25 mL round-bottom flask was charged with a magnetic stirrer, and 8 mL of ethyl acetate, *N*,*N*-dimethylaniline derivative (**4**) (4 mmol), amide (**2**) (2 mmol), and CuBr (0.4 mmol, 58 mg) were added to the flask. After the mixture was stirred for 15 min, *N*-chlorosuccinimide (NCS) (2.2 mmol, 294 mg) was added to the solution without extrusion of air. The mixture was stirred for 6 h at room temperature (~25 °C) as shown in Tables 3 and 4. The reaction mixture was filtered. The solid was washed with ethyl acetate two times (2 × 5 mL), the combined filtrate was concentrated by the rotary evaporator, and the residue was purified by column chromatography on silica gel using hexane/ethyl acetate as eluent to give the desired product.

5c: eluent, hexane/ethyl acetate = 10:1; white solid; yield 59% (395 mg); mp 135−137 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.50−7.59 (q, 4H, $J = 8.2$ Hz), 7.08 (d, 2H, $J = 8.2$ Hz), 6.78 (d, 2H, $J = 8.2$ Hz) 6.51 (s, br, 1H), 5.06 (d, 2H, $J = 5.5$ Hz), 3.01 (s, 3H), 2.26 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.0, 145.7, 133.0, 131.9, 130.2, 128.7, 128.1, 126.5, 113.9, 58.8, 38.2, 20.4; HR-MS $[M + H]^+$ m/z calcd for $C_{16}H_{18}BrN_2O$ 333.0603, found 333.0611.

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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.

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