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Copper-Catalyzed Alkylation of Aliphatic Amines Induced by Visible Light

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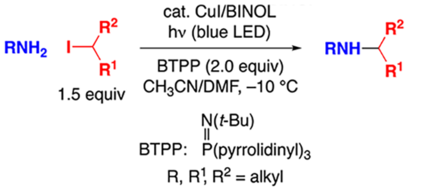
Supporting Information

ABSTRACT: Although the alkylation of an amine by an alkyl halide serves as a "textbook example" of a nucleophilic substitution reaction, the selective mono-alkylation of aliphatic amines by unactivated, hindered halides persists as a largely unsolved challenge in organic synthesis. We report herein that primary aliphatic amines can be cleanly mono-alkylated by unactivated secondary alkyl iodides in the presence of visible light and a copper catalyst. The method operates under mild conditions (−10 °C), displays good functional-group compatibility, and employs commercially available catalyst components. A trapping experiment with TEMPO is consistent with C−N bond formation via an alkyl radical in an out-of-cage process.

Because amines are a privileged functional group in bioactive molecules,[1] the development of more versatile methods for their synthesis is an important objective.[2] Whereas the alkylation of an amine by an alkyl halide via an S_N2 pathway is a classic transformation, at the same time the process represents an ongoing challenge in synthesis.[3] Thus, rather than the desired C−N bond formation, undesired pathways such as E2 reactions and over-alkylation often intervene. Furthermore, because S_N2 reactions are sensitive to steric effects, unactivated secondary and tertiary alkyl halides oftentimes do not serve as useful electrophilic partners. Due in part to these limitations, an array of methods other than the substitution reaction of an amine with an alkyl halide have been developed in order to selectively and efficiently introduce an alkyl group to an amine.[2]

Whereas transition-metal catalysis has been pursued very extensively to address the challenge of effecting substitution reactions of aryl halides by nitrogen nucleophiles,[4] until recently there were essentially no systematic investigations of corresponding metal-catalyzed substitution reactions of alkyl halides.[5] During the past few years, this deficiency has begun to be addressed, including through our work on photoinduced, copper-catalyzed processes (carbazoles, carboxamides, and indoles as nucleophiles)[6,7] and a study by Hartwig on palladium-catalyzed reactions (benzophenone imines as nucleophiles).[8]

Nevertheless, to date, a general method for transition-metal-catalyzed substitution of an alkyl halide by an aliphatic amine, which can be regarded as the prototypical nitrogen nucleophile, has not been described. In this study, we report a photoinduced, copper-catalyzed process that achieves the selective mono-alkylation of an array of aliphatic amines with unactivated secondary alkyl halides under mild conditions (−10 °C; eq 1).



(1)

In earlier work, we have described a variety of coupling reactions of nucleophiles with organic (aryl, alkenyl, alkynyl, and alkyl) electrophiles that are induced by light and catalyzed by copper;[6,9] an outline of one of the possible pathways for such processes is provided in Figure 1.[10,11] To date, all of our reported couplings have employed nucleophiles wherein the nucleophilic site is part of a π system (N: carbazole, indole, and imidazole; S: aryl thiol; O: phenol; C: cyanide). On the other hand, our initial efforts to utilize nucleophiles that lack this feature were unsuccessful. For example, under conditions in which carbazole[6a] and cyclohexanecarboxamide[6b] undergo alkylation by an unactivated secondary halide in good yield, the corresponding alkylation of a primary aliphatic amine does not proceed (eq 2 and eq 3). Having the nucleophilic site incorporated within a π system might be important for any of a variety of reasons, including determining the viability of the initial photoexcitation (**A** → **B** in Figure 1)[12] and/or of electron transfer from that excited state to the electrophile to generate a copper(II) complex (**B** → **C**).[13]

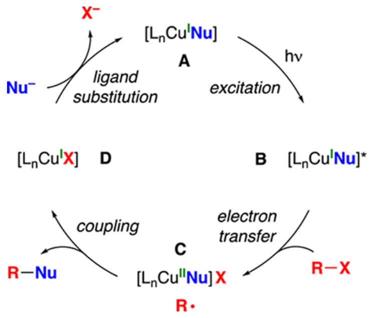


Figure 1. Outline of one of the possible pathways for photoinduced, copper-catalyzed coupling reactions.

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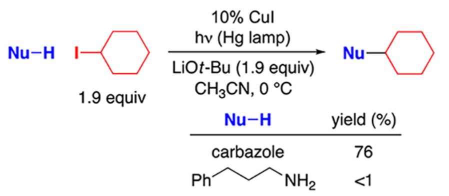
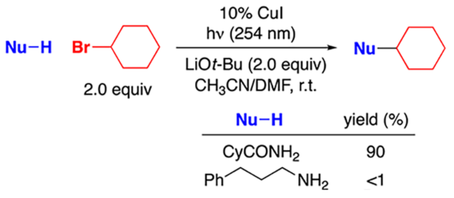
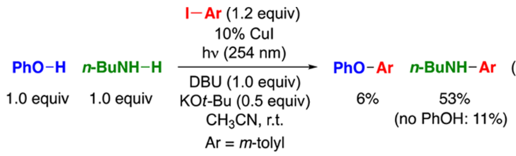


(2)



(3)

While examining the functional-group compatibility of a method that we developed for photoinduced, copper-catalyzed arylations of phenols,[9d] we discovered that the presence of 1.0 equiv of an aliphatic amine additive unexpectedly leads to predominant N-arylation of the aliphatic amine, rather than O-arylation of the phenol (eq 4; in the absence of n-BuNH$_2$: 80% yield of PhO–Ar).



(4)

One of the possible pathways by which phenol might enable the photoinduced, copper-catalyzed cross-coupling of an aliphatic amine is depicted in Figure 2. Thus, photoexcitation of a copper(I)–phenoxide complex (**E** → **F**) and then electron transfer to an electrophile (R–X) affords a copper(II)–phenoxide (**G**) and an organic radical ($R^•$). Ligand exchange of the copper(II)–phenoxide with an amine (NH$_2$R) leads to a copper(II)–amido (**H**)[14] that engages in C–N bond formation with the organic radical to furnish the cross-coupling product (R–NHR) and a copper(I) complex (**I**).[15] Ligand substitution then regenerates a copper(I)–phenoxide complex (**E**).

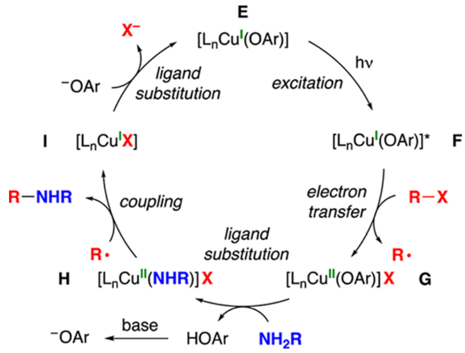
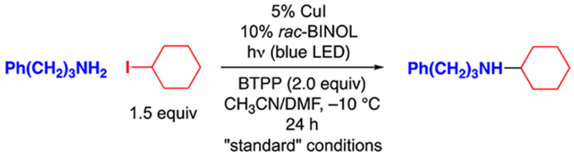


Figure 2. Simplified outline of one of the possible pathways for the photoinduced, copper-catalyzed coupling of an aliphatic amine in the presence of a phenol.

Given the paucity of systematic studies of metal-catalyzed substitution reactions of unactivated alkyl halides by aliphatic amines, we attempted to exploit our initial observation (eq 4) to devise a photoinduced, copper-catalyzed process that would address this deficiency. Indeed, building on this lead result, we have been able to develop a method that achieves the selective mono-alkylation of a primary aliphatic amine by an unactivated secondary alkyl halide under mild conditions (−10 °C) in good yield (92%; Table 1, entry 1).

Table 1. Effect of Reaction Parameters



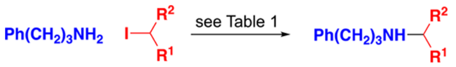
entry	variation from the "standard" conditions	yield (%)[a]
1	none	92
2	no CuI or no *rac*-BINOL or no hν or no BTPP	<1
3	no CuI, no *rac*-BINOL, no hν	<1
4	CuBr, instead of CuI	84
5	CuCl, instead of CuI	86
6	CuBr$_2$, instead of CuI	81
7	Cu(OTf)$_2$, instead of CuI	82
8	copper nanopowder, instead of CuI	<1
9	6% *rac*-BINOL	70
10	4% *rac*-BINOL	48
11	2-naphthol, instead of *rac*-BINOL	14
12	*rac*-BINOL dimethyl ether, instead of *rac*-BINOL	<1
13	1,1,3,3-tetramethylguanidine, instead of BTPP	50
14	LiO*t*-Bu, instead of BTPP	14
15	room temperature	56
16	1.2 equiv CyI	62
17	1.0 equiv BTPP	62
18	2.5% CuI, 5% *rac*-BINOL	54
19	CyBr or CyCl or CyOTs, instead of CyI	<1
20	under air (capped vial)	39
21	0.1 equiv H$_2$O added	78

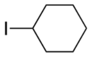
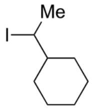
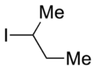
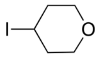
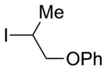
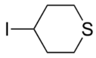
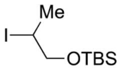
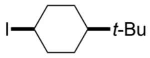
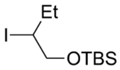
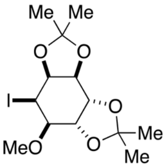
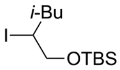
[a] Yields were determined via ^{1}H NMR analysis versus an internal standard (average of two experiments).

Control reactions establish that essentially none of the coupling product is generated in the absence of CuI, *rac*-BINOL, light, or BTPP (Table 1, entries 2 and 3). A variety of copper(I) and copper(II) sources furnish a good yield of the desired secondary amine, whereas copper nanopowder does not (entries 4–8). N-Alkylation proceeds less efficiently with less BINOL (entries 9 and 10), when BINOL is replaced with related ligands (entries 11 and 12), with other Brønsted bases (entries 13 and 14), at room temperature (entry 15), with less electrophile or BTPP (entries 16 and 17), and with less catalyst (entry 18; no further reaction after 24 h). Under our standard conditions, other cyclohexyl electrophiles (bromide, chloride, and tosylate) do not serve as suitable coupling partners (entry 19). Cross-coupling does occur in the presence of a small amount of air or water, although less effectively (entries 20 and 21).

An array of unactivated secondary alkyl iodides, both cyclic and acyclic, serve as suitable electrophiles in this photoinduced, copper-catalyzed mono-alkylation of aliphatic amines (Table 2).[16] The efficiency of the coupling is sensitive to steric effects, with more hindered electrophiles furnishing more modest yields (entries 6 and 7). Saturated oxygen and sulfur heterocycles are compatible with the reaction conditions (entries 8 and 9), and C–N bond formation can be achieved with excellent diastereoselectivity (entries 10 and 11; >20:1). In a gram-scale

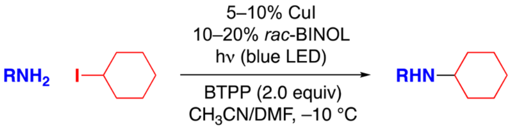
Table 2. Scope with Respect to the Electrophile

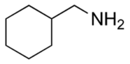
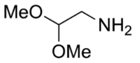
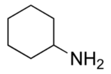
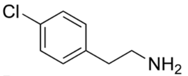
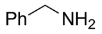
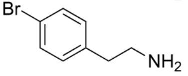
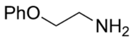
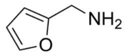
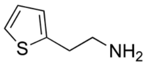
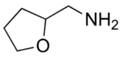


entry	electrophile	yield (%)[a]	entry	electrophile	yield (%)[a]
1		80	7[b]		41
2		70	8		82
3		65	9[b]		56
4		74	10[c]		54
5		55	11[d]		61
6		34			

[a] Yields of purified product (average of two experiments). [b] Catalyst loading: 10% CuI, 20% *rac*-BINOL. [c] Starting material: cis/trans = 5/1; product: trans/cis > 20/1. [d] Starting material: $\beta/\alpha > 20/1$; product: $\alpha/\beta > 20/1$.

Table 3. Scope with Respect to the Nucleophile

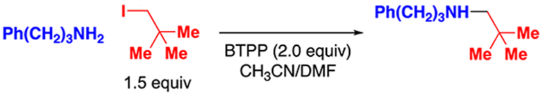


entry	nucleophile	yield (%)[a]	entry	nucleophile	yield (%)[a]
1		83	7[b]		75
2		71	8		64
3		70	9		52
4		61	10		54
5[b]		84	11		80
6		60			

[a] Yields of purified product (average of two experiments). [b] Isolated as the trifluoroacetamide derivative.

reaction, the alkylation illustrated in entry 1 proceeds in good yield with 10% CuI/20% BINOL (1.32 g, 81%).

Although many unactivated primary alkyl halides can serve as useful electrophiles in S_N2 reactions, neopentyl halides typically are poor substrates.[17] Nevertheless, the combination of a CuI/BINOL catalyst and blue-LED irradiation enables the alkylation of an aliphatic amine by neopentyl iodide in good yield at −10 °C (eq 5). In contrast, a simple S_N2 reaction proceeds very slowly even at 100 °C, and the addition of CuI/BINOL is not beneficial (eq 5).



(5)

conditions	yield (%)
10% CuI, 20% *rac*-BINOL hν (blue LED), −10 °C	70
−10 °C	<1
100 °C	4
10% CuI, 20% *rac*-BINOL, 100 °C	4

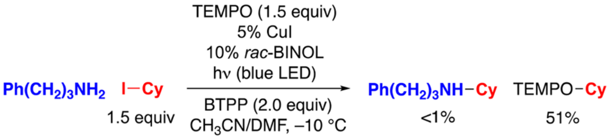
We have also examined the scope of this photoinduced, copper-catalyzed N-alkylation with respect to the nucleophile (Table 3). Thus, the efficiency of C−N bond formation does not appear to be highly sensitive to the steric demand of the aliphatic amine (entries 1 and 2). The method is compatible with a variety of functional groups, including an ether, an acetal, an aryl chloride, an aryl bromide, a furan, and a thiophene (entries 3−11).

Through an additive study, we have further assessed the functional-group compatibility of this method. For the coupling illustrated in entry 1 of Table 2, the addition of 1.0 equiv of an alcohol (5-nonanol), an alkyne (5-decyne), an ester (methyl octanoate), a ketone (2-nonanone), a cis olefin (*cis*-5-decene), and a trans olefin (*trans*-5-decene) has little impact on N-alkylation (>75% yield), and the additive is virtually unaffected (>90% recovery). On the other hand, addition of a nitroalkane (nitrocyclopentane) or an aldehyde (cyclohexanecarboxaldehyde) impedes coupling (<5% and 51% yield, respectively).

If desired, N-protection of the secondary amine can be affected in situ in good yield. For example, upon completion of the alkylation illustrated in entry 1 of Table 2, direct trifluoroacetylation followed by purification provides the TFA-protected amine in 86% yield. Similarly, a 73% yield of the purified carbamate can be obtained after in situ protection with Boc_2O.

Although reaction development is the primary focus of this investigation, we have also carried out preliminary mechanistic studies; as mentioned earlier, one of the possible pathways for this process is outlined in Figure 2. With regard to the identity of the primary photoreductant, ESI-MS of a reaction mixture after partial conversion reveals the presence of a copper(I)−binaphtholate complex; alternatively, deprotonated BINOL itself could also fill this role.[18,19] The illustrated mechanism includes d^9 copper(II) complexes as intermediates, and we have indeed detected such species via EPR spectroscopy by sampling a catalyzed coupling at partial conversion; at least two copper(II) species are evident (hyperfine coupling to copper), which together account for ~60% of the copper present in the reaction mixture.

According to the pathway depicted in Figure 2, C−N bond formation occurs through out-of-cage coupling of an organic radical ($R^\bullet$) with a copper(II)−amido complex.[15] Consistent with this hypothesis, the addition of TEMPO (1.5 equiv) to a reaction mixture leads to formation of a TEMPO adduct (eq 6).



(6)

In summary, we have determined that the combination of visible light and a copper catalyst provides the first general method for the transition-metal-catalyzed alkylation of aliphatic amines by unactivated secondary alkyl halides. This process addresses some of the deficiencies of the classic S_N2 approach,

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including its need for reactive electrophiles and its propensity for over-alkylation. With respect to our efforts to expand photoinduced, copper-catalyzed coupling reactions, this represents our first success with nucleophiles wherein the nucleophilic site is not part of a π system. With our optimized method, C−N bond formation proceeds without significant over-alkylation (<1%) under mild conditions (−10 °C) in the presence of a variety of functional groups, upon irradiation by blue-LED lamps of a catalyst derived from commercially available components. A preliminary mechanistic study is consistent with the formation of an alkyl radical that engages in out-of-cage C−N bond formation.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b09582.

Procedures and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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(3) For leading references, see: Marvin, C. C. In *Comprehensive Organic Synthesis*; Knochel, P., Molander, G. A., Eds.; Elsevier: Amsterdam, 2015; Vol. *6*, pp 34−99.

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(10) For mechanistic studies, see: (a) Johnson, M. W.; Hannoun, K. I.; Tan, Y.; Fu, G. C.; Peters, J. C. *Chem. Sci.* **2016**, *7*, 4091−4100. (b) Ahn, J. M.; Ratani, T. S.; Hannoun, K. I.; Fu, G. C.; Peters, J. C. *J. Am. Chem. Soc.* **2017**, *139*, 12716−12723.

(11) For leading references on photoredox catalysis, see: (a) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. *Chem. Rev.* **2013**, *113*, 5322−5363. (b) Skubi, K. L.; Blum, T. R.; Yoon, T. P. *Chem. Rev.* **2016**, *116*, 10035−10074.

(12) For example, see: (a) Lotito, K. J.; Peters, J. C. *Chem. Commun.* **2010**, *46*, 3690−3692. (b) Miller, A. J. M.; Dempsey, J. L.; Peters, J. C. *Inorg. Chem.* **2007**, *46*, 7244−7246.

(13) For examples of a role for the π system of the nucleophile in the electronic structure of copper(I) and copper(II) intermediates in photoinduced cross-couplings, see ref 10.

(14) For ease of discussion, the transformation of **G** → **H** in Figure 2 is drawn as a simple ligand exchange, whereas our data (e.g., out-of-cage C−N bond formation (vide infra)) point to a more complex pathway.

(15) In the case of a photoinduced, copper-catalyzed decarboxylative coupling, we have described evidence for out-of-cage C−N coupling after ligand exchange: Zhao, W.; Wurz, R. P.; Peters, J. C.; Fu, G. C. *J. Am. Chem. Soc.* **2017**, *139*, 12153−12156. See also ref 10b.

(16) Notes: (a) For all N-alkylations illustrated in Tables 2 and 3, no over-alkylation is observed (<1%). (b) Preliminary observations: this process can be conducted under flow conditions; an unactivated tertiary alkyl halide is not a suitable electrophile; in a light-on/light-off experiment, alkylation stops when irradiation stops, and alkylation resumes when irradiation resumes.

(17) Relative to Me−X, neopentyl−X can be 3.3×10^{-7} less reactive in S_N2 reactions. For example, see Table 11.5 in: Anslyn, E. V.; Dougherty, D. A. *Modern Physical Organic Chemistry*; University Science Books: Sausalito, CA, 2006.

(18) (a) Upon irradiation at 350 nm, 2-naphtholate has been reported to serve as a photoreductant of aryl and alkyl halides. For example, see: Argüello, J. E.; Peñeñory, A. B. *J. Org. Chem.* **2003**, *68*, 2362−2368. Legros, B.; Vandereecken, P.; Soumillion, J. P. *J. Phys. Chem.* **1991**, *95*, 4752−4761. (b) We have observed deprotonated BINOL can serve as a photoreductant of iodocyclohexane upon irradiation with a blue-LED lamp.

(19) For an example of a photoinduced, copper-catalyzed coupling wherein both a copper-bound and a copper-free nucleophile (carbazolide) appear to serve as photoreductants, see ref 10b.