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Visible-Light-Induced Copper-Catalyzed Intermolecular Markovnikov Hydroamination of Alkenes

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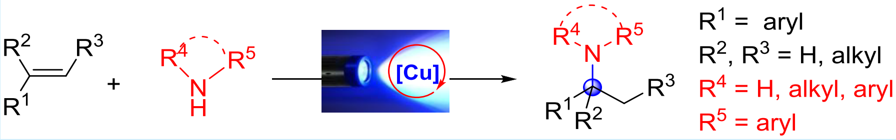
Supporting Information



ABSTRACT: A visible-light-induced copper-catalyzed intermolecular hydroamination of alkenes using commercially accessible primary and secondary amines has been established. This effective method exhibits good tolerance of a broad range of functional groups and provides a facile access to an array of valuable amines with Markovnikov regioselectivity. The process can be positively expected to be used in bioactive amines, and it may provide new potential in the discovery of copper-catalyzed hydrofunctionalization reactions.

Amines are fundamentally important frameworks in natural products, synthetic drugs, agrochemicals, biological probes, and functional materials.[1] To date, considerable endeavor has been devoted to the discovery and development of new strategies for the formation of this critical organic compound.[2] Hydroamination of alkenes, combining two commercially accessible and structurally diverse feedstocks in a highly valuable and atom-economical way, is one particularly significant method of such transformations. Marvelous progress, especially metal-catalyzed alkene hydroamination, has been achieved over the past decades.[3] Among the various metal-catalyzed hydroamination reactions, the direct copper-catalyzed addition of amines to alkenes is considered to be an intriguing and practical technique.[4] For instance, recently, the Miura[5] and Buchwald[6] groups have established the efficient hydroamination of alkenes with electrophilic amines in the presence of a copper catalyst. Meanwhile, in spite of the great development and vibrant expansion of photochemistry during the past decades,[7] it seems only recently has success been achieved in photodriven intermolecular hydroamination of alkenes. In this regard, the Nicewicz group has realized the novel and general approach to anti-Markovnikov olefin hydroamination reactions by using a dual organic catalyst system consisting of an acridinium photooxidant.[8] The Knowles group has developed an innovative and robust method of visible-light photoredox protocols for the anti-Markovnikov hydroamination of olefins through catalytically generated aminium radical intermediates.[9] However, the more general and economic method for the direct coupling of common and commercially available amines and olefins in a green and easy-to-handle way remains a challenging synthetic task.

Given many readily accessible copper salts serving as photochemical catalysts,[10] the development and expansion of their applications in other attractive areas such as hydroamination are highly desired. Inspired by the impressive pioneering work of Fu and Peters,[10d−g] also consistent with our research interest in radical chemistry,[11] we focused our attention toward the addition of simple amines to readily available alkenes catalyzed by copper salt in photochemistry. Here, we describe a distinct pathway of a visible-light-induced protocol for copper-catalyzed hydroamination of alkenes, which could enable the rapid construction of valuable amines in a Markovnikov regioselective manner with convenient and environmentally benign reaction conditions. In this catalytic strategy, the copper complex, which is generated in situ, is supposed to function as the photocatalyst and coupling catalyst without sacrificing reagents.

In our previous study, we found that the hydroamination product 9-(1-phenylethyl)-9*H*-carbazole, **c1**, could be obtained in 40% yield by using 9*H*-carbazole, 2-bromo-2-methylpropane, and styrene under the reported reaction conditions.[11b] The unpredicted discovery of the photoinduced protocol has attracted our interest, due to the significance of the carbazole motif which frequently occurs in natural products, drug molecules, and chiral ligands.[12] We started to optimize the reaction conditions. The 9-(1-phenyl-ethyl)-9*H*-carbazole was isolated in 60% yield using CuCl and LiO^{t}Bu in CH_3CN (1.5 mL) (Table 1, entry 1). When other bases were tested (Table 1, entries 2−3), LiO^{t}Bu was found to be the most effective in this reaction.[13] The hydroamination also proceeded in other solvents; however, the yields of **c1** were considerably decreased

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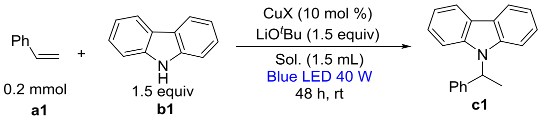
Table 1. Optimization of the Reaction Conditions



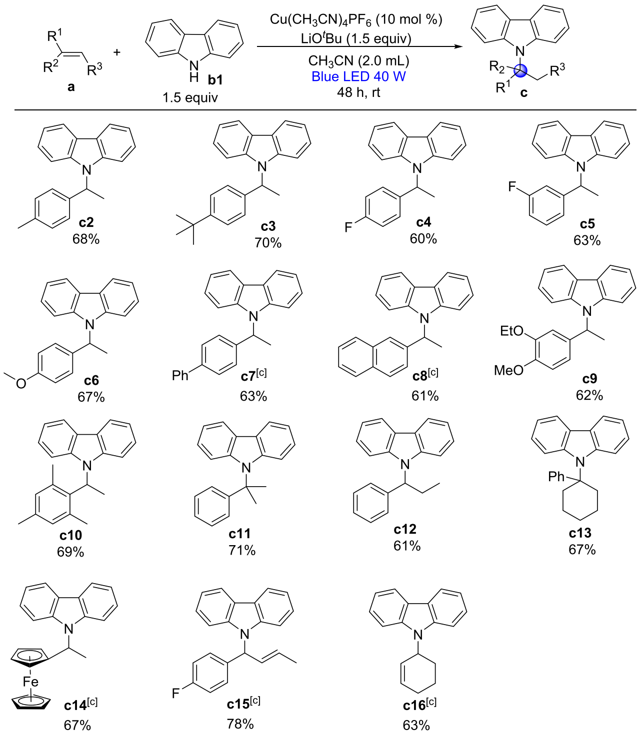
entry[a]	catalyst	base	solvent	yield (%)[b]
1	CuCl	LiO^{t}Bu	CH$_3$CN	62 (60)[c]
2	CuCl	NaO^{t}Bu	CH$_3$CN	ND
3	CuCl	KO^{t}Bu	CH$_3$CN	ND
4	CuCl	LiO^{t}Bu	DMAC	40
5	CuCl	LiO^{t}Bu	MeOH	ND
6	CuCl	LiO^{t}Bu	Toluene	ND
7	CuCl	LiO^{t}Bu	THF	ND
8	CuBr	LiO^{t}Bu	CH$_3$CN	60
9	Cu(CH$_3$CN)$_4$PF$_6$	LiO^{t}Bu	CH$_3$CN	70
10[d]	Cu(CH$_3$CN)$_4$PF$_6$	LiO^{t}Bu	CH$_3$CN	83
11[d]	Cu(OTf)$_2$	LiO^{t}Bu	CH$_3$CN	82
12	No	LiO^{t}Bu	CH$_3$CN	20
13	Cu(CH$_3$CN)$_4$PF$_6$	No	CH$_3$CN	ND
14[e]	Cu(CH$_3$CN)$_4$PF$_6$	LiO^{t}Bu	CH$_3$CN	ND
15[f]	Cu(CH$_3$CN)$_4$PF$_6$	LiO^{t}Bu	CH$_3$CN	76[c]

[a]0.2 mmol scale. [b]Measured by ^{1}H NMR analysis, using diethyl phthalate as internal standard. [c]Isolated yield. [d]CH$_3$CN (2.0 mL), 0.1 M. [e]No light, 50 °C, 16 h. [f]0.4 mmol scale, 0.1 M. DMAC is Dimethylacetamide

(Table 1, entries 4−7). In addition, testing of different copper salts showed that a higher yield could be obtained by using Cu(CH$_3$CN)$_4$PF$_6$ or Cu(OTf)$_2$ (Table 1, entries 8−11). The control experiments demonstrated the essential roles of the copper salt, LiO^{t}Bu, and light in the reaction[13] (Table 1, entries 12−14). Lastly, under the optimized reaction conditions, **c1** could be obtained in 76% isolated yield (Table 1, entry 15).

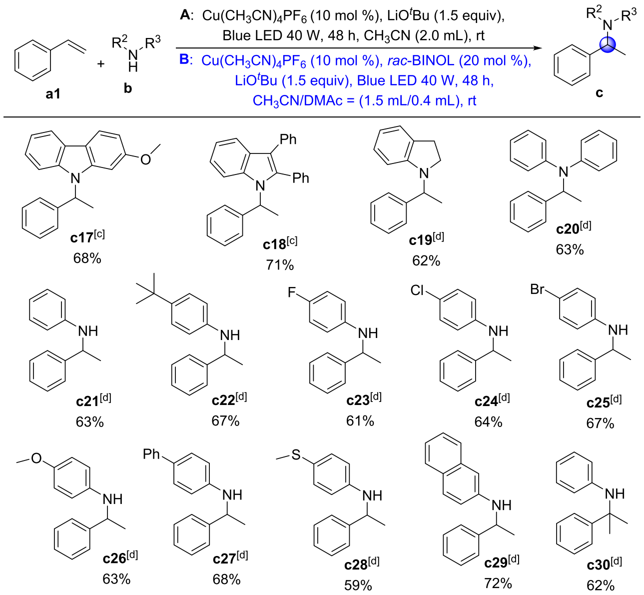
With the optimized reaction conditions established, we evaluated the substrate scope of alkenes (Scheme 1). In the reaction, electron-donating or -withdrawing substituents on the aryl ring of styrenes could afford the products **c2** to **c8** in satisfactory yields. The styrenes bearing functional groups of halides and ether could be well tolerated. The di- or trisubstituted styrenes proceeded efficiently to provide the amines **c9** and **c10**. Moreover, *α*- or *β*-substituted styrenes could also afford the desired products **c11** and **c12**. Even *α*,*β*-disubstituted styrene underwent the photoinduced process to provide **c13** in a high yield, demonstrating the generality of the procedure. Interestingly, the introduction of the ferrocene motif in alkene could be allowed to yield the desired product **c14**. Additionally, the 1,3-dienes both reacted well to give the functionalized products (**c15** and **c16**) in good 1,4-selectivity. The strategy may pave a promising way toward transformation of 1,3-dienes into allylic compounds. The reaction of aliphatic alkenes with 9*H*-carbazole under the standard conditions did not give the desired products probably because of the lower reactivity of the nonactivated double bond.

Scheme 1. Scope Studies with Alkenes[a,b]



[a]0.2 mmol scale. [b]Isolated yield. [c]Cu(OTf)$_2$ was used as the copper salt.

Scheme 2. Scope Studies with Amines[a,b]

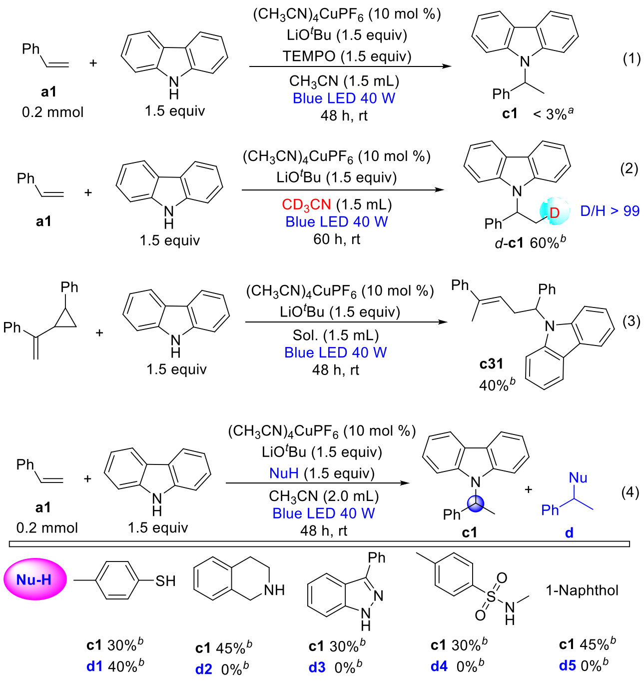


[a]0.2 mmol scale. [b]Isolated yield. [c]According to the reaction condition A. [d]According to the reaction condition B.

Next, we investigated the generality of the amines (Scheme 2). The substituted 9*H*-carbazole and representative indole derivatives, which are common elements in bioactive compounds and natural products,[14] could be converted to **c17** and **c18** in good yields. However, the application of the standard hydroamination process to the simple indoline, with a further decreased *π*-system, was not successful. We reasoned that the Cu−Nu complex may be less effective in the activation of the substrate or the stabilization of the intermediate in the photoexcitation. Inspired by the elegant work of Fu and Peters[15] using BINOL as the cocatalyst and according to our previous study,[11b] after extensive optimization of the reaction conditions, to our delight, the desired product **c19** was obtained in 62% yield using *rac*-BINOL (20 mol %) and CH$_3$CN/DMAc (1.5 mL/0.4 mL) as the solvent. The modified process has been proven to be general for an array of aryl amines. The reaction of diphenylamine proceeded efficiently to give the product **c20**. Anilines containing electron-donating or -withdrawing groups could smoothly react to afford the products **c21** to **c29**. Meanwhile, functional groups such as halides (F, Cl, Br), ether, and thioether were tolerated to offer the desired products which bear a handle for further C–C, C–O, and C–S cross-coupling reactions. The 1,1-disubstituted styrene also showed good reactivity to provide the product **c30** in 62% yield.

Finally, to acquire a good understanding of the possible mechanistic pathway of this reaction, a series of control experiments have been conducted. When the radical quencher, TEMPO (1.5 equiv), was added in the reaction, the yield of desired product **c1** was less than 3% (measured by ^{1}H NMR) [Scheme 3, eq 1]. Then, by using CD_3CN as solvent, the deuterated product *d*-**c1** (D/H > 99, measured by ^{1}H NMR) could be obtained in 60% yield [Scheme 3, eq 2]. Additionally, the amine **c31** was obtained in 40% yield by a ring-opening route of the cyclopropane unit [Scheme 3, eq 3]. The above-mentioned experimental results indicate that the radical intermediates[16a] and the hydrogen atom abstraction of the solvent[8,16b] may be involved in the present hydroamination reaction pathway. When other nucleophiles (1.5 equiv), such as naphthol, the isoquinoline, indazole, and benzenesulfonamide, were added in the reaction respectively, the additives were almost recovered and no hydrofunctionalization products could be found, except 4-methyl-benzenethiol[10f] [Scheme 3, eq 4]. Those results suggest that the involvement of cationic intermediates in the formation of the C–N bond is less likely.

Scheme 3. Preliminary Mechanistic Studies



[a]Measured by ^{1}H NMR analysis, using diethyl phthalate as an internal standard. [b]Isolated yield.

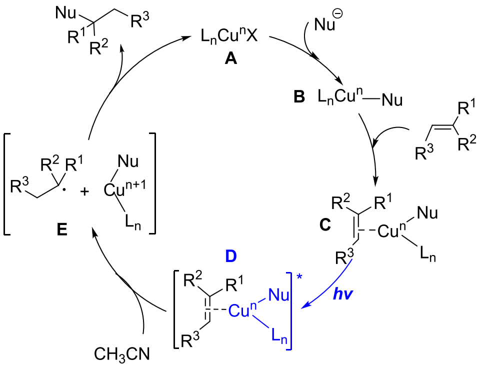


Figure 1. Simplified outline of the proposed reaction mechanism.

According to the literature[8,10,13,16] and our preliminary experiments, one of the plausible reaction pathways is outlined in Figure 1. First, in the presence of the base, L_nCu^nNu was formed by the ligand exchange of L_nCu^nX with the nucleophile. Then the copper–nucleophile complex **B** was coordinated with the alkene to generate the complex **C**.[17] After irradiation with light, the complex **C** could be transformed into the excited complex **D**.[17] The capability of initial photoexcitation of copper complex **C** may depend on the strong π-system of the nucleophilic site (carbazole and the indole).[15] In the case of a simple aryl amine with reduced photoactivity, the copper–binaphtholate complex may act as the primary photocatalyst.[15a] Next, the intermediate **E** (the benzyl radical and the organocopper^{n+1}) could be generated via SET with the excited complex **D** and the hydrogen atom abstraction of CH_3CN.[10d−g,13,16] Lastly, the benzyl radical is captured by the organocopper^{n+1} to afford the desired hydroamination product and regenerate the copper catalyst **A**.[10g] Regarding the copper–binaphtholate complex, the copper–amido complex is forged with the ligand exchange to a simple amine[15] before capture.

In summary, we have established a green and expedient method for Cu-catalyzed hydroamination reaction of an alkene induced by visible light. This highly effective process was compatible with a variety of functional groups and provides a facile access to a range of aryl amines. Considering the commercial availability of chemical substrates, highly operational flexibility, and comparatively simple and mild conditions, this general platform described here not only could further be applied to the hydrofunctionalization of complex amines but also may pave a new pathway toward the discovery of photoinduced copper-catalyzed hydro-amination reactions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02863.

Research details, experimental procedures, full characterization of products, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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