Organic Letters

Tertiary Amines Acting as Alkyl Radical Equivalents Enabled by a P/N Heteroleptic Cu(I) Photosensitizer

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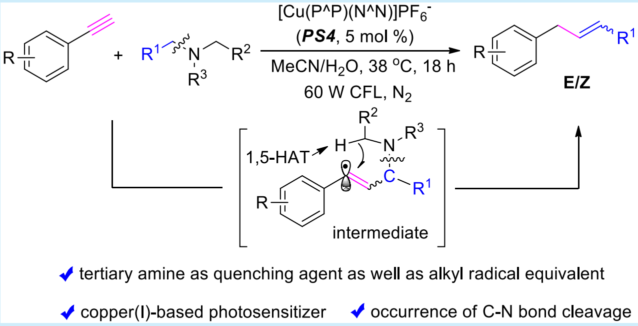
Cite This: https://dx.doi.org/10.1021/acs.orglett.0c03236 Read Online

ABSTRACT: An unprecedented exploration of tertiary amines as alkyl radical equivalents for cross-coupling with aromatic alkynes to access allylarenes has been achieved by a P/N heteroleptic Cu(I)-based photosensitizer under photoredox catalysis conditions. Mechanistic studies reveal that the reaction might undergo radical addition of in situ-generated α-amino radical intermediates to alkynes followed by 1,5-hydrogen transfer, C−N bond cleavage, and concomitant isomerization of the resulting allyl radical species.



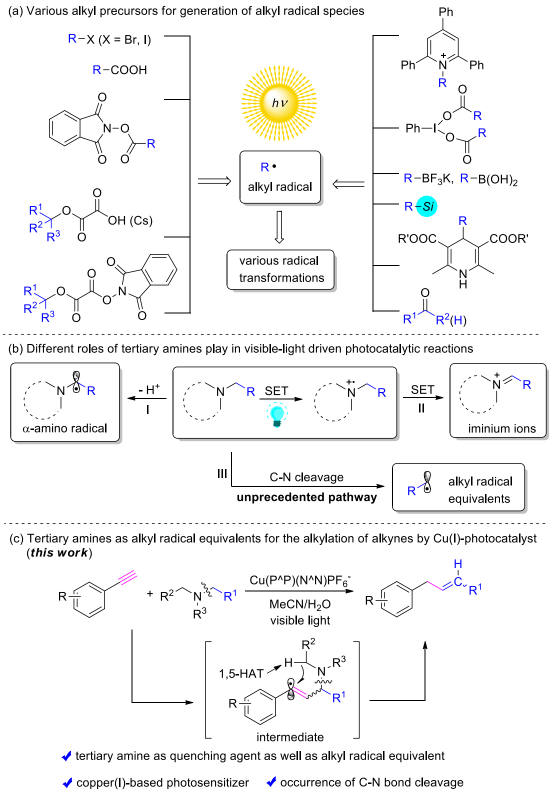
In the past two decades, visible-light-driven photoredox reactions have developed rapidly and emerged as an attractive and powerful platform for the construction of carbon−carbon or carbon−heteroatom bonds.[1] In this regard, most visible-light-driven photoredox catalysts predominantly rely on complexes of noble and heavy metals such as ruthenium or iridium. However, the fact that several innate limitations are associated with the metal centers of these photocatalysts, including poor reserves in the earth, high prices, and high toxicities, has stimulated chemists to explore alternative photocatalysts based on metals with characteristic features of lower costs, greater safety, and environmental friendliness. In this area, copper complexes represent the most attractive and promising alternative candidates.[2] Indeed, over the past two decades, there have been increasingly more reports about the copper-based photoactive complexes and their applications in visible-light-driven organic synthesis.[3−5] Despite the impressive progress, it is still highly desirable to develop novel and efficient organic transformations involving the direct use of copper-based photosensitizers under visible-light-driven catalysis conditions.

In view of the ubiquity of alkyl motifs in bioactive molecules,[6,7] the selective and efficient introduction of alkyl groups into organic molecules from alkyl precursors is very important, yet challenging due to the difficulty of introducing alkyl groups into organic molecules from alkyl precursors through the traditional transition-metal-catalyzed cross-coupling reactions.[8,9] It is well-known that transition-metal-catalyzed alkyl coupling partner-involved cross-couplings always suffer from a high energy barrier to activate alkyl precursors via the two-electron transfer process, easy β-hydride elimination, harsh reaction conditions, and environmentally unfriendly reaction conditions.[10] To circumvent these problems, recently, alkylation strategies involving active alkyl radical species produced from corresponding alkyl sources via the one-electron transfer process (SET) under visible-light-driven photoredox catalysis conditions have received special attention and become important tools for the incorporation of alkyl groups into organic molecules. So far, a variety of alkyl precursors have been explored to serve as active alkyl radical equivalents under visible-light-driven photoredox catalysis conditions, including alkyl halides,[10a,11] carboxylic acids and their derived esters,[12] alkyl alcohol-derived compounds,[13] Katritzky salts,[14] hypervalent iodine(III) reagents,[15] alkyl trifluoroborates,[10b,16] alkyl boronic acids,[17] organosilicon compounds,[18] Hantzsch esters,[19] ketones and aldehydes[20] (Scheme 1a), etc. Despite their merits, one or more limitations are still associated with some of these reagents with respect to the toxicity of halo-containing precursors, low atom economy, tedious preparation, high costs, explosiveness, production of undesired byproducts, etc. To realize efficient and practical alkylation reactions, exploring and developing cost-effective, easily available, safe, and low-toxicity alkyl radical equivalents are in high demand.

Tertiary amines play important roles in visible-light-driven photoredox catalytic reactions. In fact, tertiary amines were

Received: September 29, 2020

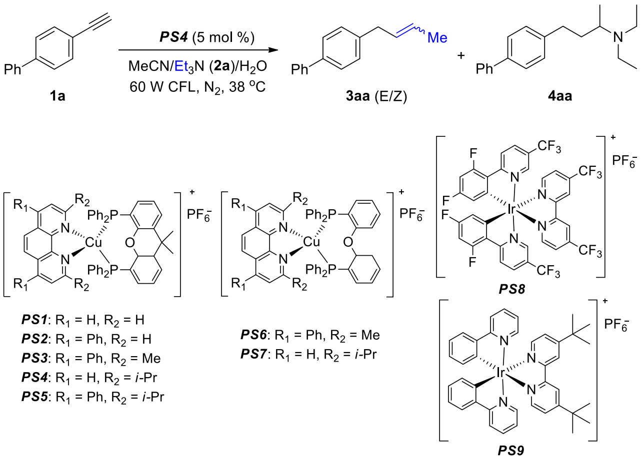
Scheme 1. Various Precursors Used as Alkyl Radical Equivalents in Visible-Light-Driven Photocatalytic Reactions



identified as faithful partners of excited photosensitizers and different types of reactivity have arisen from their combination (Scheme 1b): (1) merely used as electron sacrificial agents for the completion of a photocatalytic cycle in which they themselves are not incorporated into the final products,[4c,d,g−i,21] (2) acting as reductants for quenching photocatalyts as well as precursors for the generation of nucleophilic α-amino radicals that are capable of reacting with various electrophilic reagents (Scheme 1b-I),[21] and (3) used as two-electron donors to reduce photocatalysts as well as precursors for the generation of electrophilic iminium cations that are capable of reacting with various nucleophilic reagents (Scheme 1b-II).[22] To the best of our knowledge, to date, no studies of the utilization of tertiary amines as alkyl radical equivalents involving C−N bond cleavage under photoredox catalysis conditions have been reported (Scheme 1b-III). Very recently, we have realized alkyl aldehydes as alkyl radical equivalents in the cross-coupling with alkynes enabled by a P/N heteroleptic Cu(I) photosensitizer, mechanistically involving in situ-generated alkyl-substituted α-amino radical species.[4m] However, in the reaction, excessive amounts of dipropylamine and Hantzsch ester must be used. Because tertiary amines could be used as both quenching agents and precursors of alkyl-substituted α-amino radicals (Scheme 1b),[21,22] we envisioned that P/N heteroleptic Cu(I) photosensitizers might also enable cross-coupling of tertiary amines with alkynes to deliver allylarenes, thus leading to unprecedented exploration of tertiary amines as alkyl radical equivalents in photoredox catalytic reactions (Scheme 1b-III and Scheme 1c).[23]

Initially, 4-ethynyl-1,1′-biphenyl (**1a**) and Et_3N (**2a**) were selected as the model substrates for the optimization of reaction conditions (Table 1 and Table S1). When **1a** and ***PS4*** (5 mol %) were subjected to the mixture of MeCN (1.6 mL), Et_3N (1.2 mL), and H_2O (0.2 mL) and irradiated with a 60 W CFL at 38 °C for 18 h, allylbenzene **3aa** was obtained in an acceptable yield (GC yield, 75%; isolated yield, 72%), along with a small amount of C−N bond intact product **4aa** (13%, entry 1, Table 1). The most effective Cu(I) photosensitizer ***PS5*** previously reported for the cross-coupling of aldehydes and alkynes[4m] gave results inferior to those of ***PS4*** in the reaction presented here (64%, entry 2 vs entry 1, Table 1). Several other P/N heteroleptic Cu(I) photosensitizers (***PS1***-***PS3***, ***PS6***, and ***PS7***) generally gave results inferior to those of ***PS4*** (entries 3−6 vs entry 1, Table 1). Popular photocatalysts such as $Ru(bpy)_3Cl_2{\cdot}6H_2O$ (entry 8) and Ir(III) photosensitizers ***PS8*** (entry 8) and ***PS9*** (entry 9) all failed to deliver **3aa**, albeit a 35% yield of byproduct **4aa** was obtained with

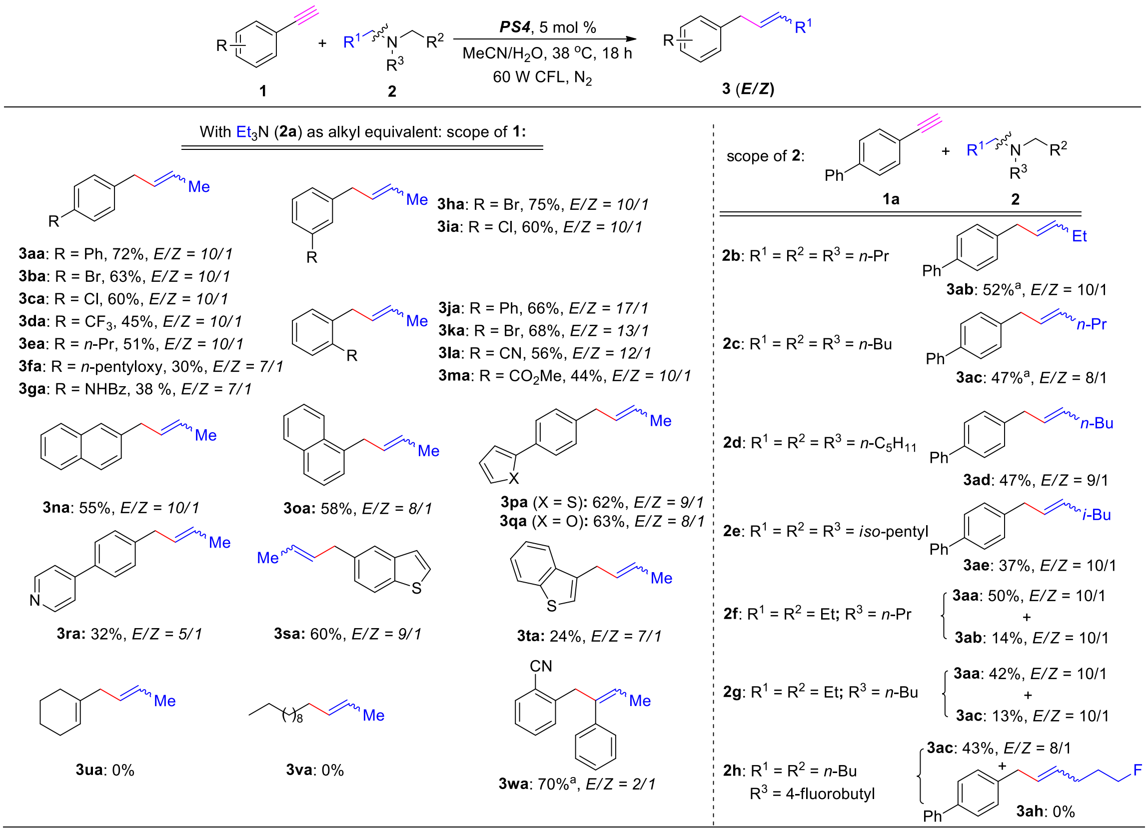
Table 1. Optimization of the Reaction Conditions[a]



entry	deviation from standard conditions	yield (%)[b] 3aa (E/Z)[b]	yield (%)[b] 4aa
1	none	75 (10/1), 72,[c] 67[d]	13
2	***PS5*** instead of ***PS4***	64 (10/1)	20
3	***PS1*** or ***PS2*** instead of ***PS4***	0	0
4	***PS3*** instead of ***PS4***	49 (10/1)	24
5	***PS6*** instead of ***PS4***	48 (10/1)	36
6	***PS7*** instead of ***PS4***	47 (10/1)	39
7	$Ru(bpy)_3Cl_2{\cdot}6H_2O$ instead of ***PS4***	trace	12
8	***PS8*** instead of ***PS4***	0	trace
9	***PS9*** instead of ***PS4***	0	35
10	Rose Bengal instead of ***PS4***	0	trace
11	4CzIPN instead of ***PS4***	35 (10/1)	trace
12	0.6 mL of Et_3N	57 (10/1)	11
13	0.1 mL of H_2O	45 (10/1)	13
14	3.0 mL of Et_3N was used in the absence of MeCN and H_2O	10	trace
15	THF instead of MeCN	50 (10/1)	31
16	1,4-dioxane instead of MeCN	66 (10/1)	18
17	without a photosensitizer	0	0
18	in the dark	0	0

[a] Standard conditions: **1a** (0.2 mmol), ***PS4*** (5 mol %), MeCN (1.6 mL)/Et_3N (**2a**) (1.2 mL)/H_2O (0.2 mL), irradiated with a 60 W CFL under a nitrogen atmosphere at 38 °C for 18 h unless otherwise noted. [b] Yields and E/Z ratios were determined by GC analysis using biphenyl as the internal standard. [c] Isolated yield. [d] Yield of 1 mmol-scale synthesis.

Scheme 2. Scope of Alkynes 1 and Amines 2[a]



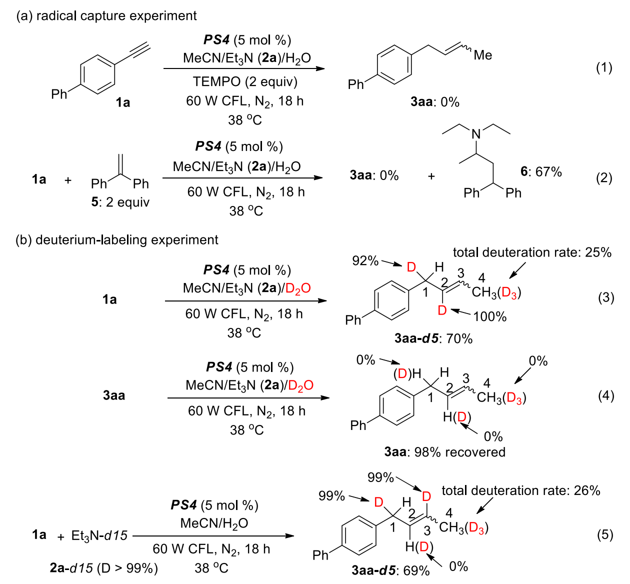
[a]Conditions: (a) 1,4-dioxane used instead of MeCN.

PS9 as a photocatalyst (entry 9, Table 1). For organophotosensitizers, Rose Bengal showed no catalytic activity for the reaction, while 4CzIPN [2,4,5,6-tetrakis(carbazol-9-yl)-1,3-dicyanobenzene] could exhibit some photocatalytic activity but delivering only a low yield of **3aa** (entries 10 and 11, Table 1). It was found that an appropriate ratio of Et_3N, MeCN, and H_2O is important for obtaining a satisfactory yield of **3aa** (entries 12−14, Table 1). Solvent screening experiments indicated that the combination of MeCN and water is the most suitable medium for the reaction (entries 15 and 16, Table 1). Controlled experiments indicated that the photosensitizer and light irradiation are indispensable for this alkylation reaction (entries 17 and 18, Table 1). Note that the *E*/*Z* ratios of **3aa** always remained around 10/1, not influenced much by the parameters investigated above.

With the optimized reaction conditions in hand, we next set out to investigate the scope of alkynes **1** and tertiary amines **2** (Scheme 2). A variety of aromatic terminal alkynes **1** were compatible with this transformation and could deliver corresponding products in acceptable yields with modest *E*/*Z* selectivities. Generally, aromatic terminal alkynes **1** bearing electron-withdrawing groups or a neutral group [e.g., Cl, Br, CF_3, CN, COOMe group, and phenyl (**1a**−**1d** and **1h**−**1m**, Scheme 2)] furnished the desired products in yields higher than the yields of those bearing electron-donating groups [e.g., *n*-propyl, *n*-pentyloxy, and acylamino (**1e**−**1g**, Scheme 2)]. It seems that the steric hindrance of substituents on phenyl rings had no significant influence on the reaction outcome in terms of yield (**1a** vs **1j** and **1b** vs **1k**). Aromatic alkynes **1** bearing a naphthalene ring (**1n** and **1o**), a heteroarene ring such as thiophene (**1p**), furan (**1q**), or pyridine (**1r**), or a benzothiophene backbone (**1s**, **1t**) were also viable substrates for the reaction. In addition, aliphatic alkynes (**1u** and **1v**) were used for the reaction; unfortunately, no desired products were obtained in these cases. Furthermore, internal alkyne **1w** was also proven to be a suitable candidate for this reaction, delivering the desired product **3wa** in 70% yield, but with a poor *E*/*Z* selectivity. Note that in the reaction of **1w** with Et_3N, the regioisomers predominantly arose from the addition of the α-amino radical to the more electron-deficient sp carbon of **1w** (see the Supporting Information). Finally, the substrate scope of tertiary amines **2** was explored. As shown in Scheme 2, for tertiary amines consisting of the same alkyl moieties (**2b**−**2e**), single desired products could be obtained in modest yields; however, the reaction may deliver different alkylated products when tertiary amines consisting of different alkyl moieties were used (**2f** and **2g**). Interestingly, when *N*,*N*-dibutyl-4-fluorobutan-1-amine (**2h**) was used, the reaction selectively delivered *n*-butyl-incorporated product **3ac** in 43% yield while no 4-fluorobutyl-incorporated product **3ah** was obtained. Note that 1,4-dioxane was a more suitable solvent in the cases of **2b** and **2c** as the substrates.

To gain some insights into the mechanism of the reaction presented here, several mechanistic experiments were carried out (Scheme 3). First, the reaction was performed in the presence of a radical scavenger. As a result, the reaction was suppressed thoroughly when 2 equiv of TEMPO (eq 1, Scheme 3) or 1,1-diphenylethylene **5** (eq 2, Scheme 3) was used. To our delight, the α-amino radical was successfully trapped by 1,1-diphenylethylene to produce **6** in 67%

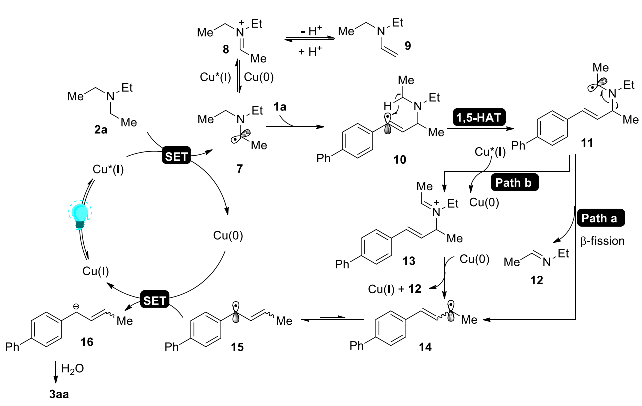
Scheme 3. Preliminary Mechanistic Experiments



yield.[22a,24] Next, when the reaction was conducted under the standard conditions except in MeCN and D_2O, deuterium-incoporated **3aa**-d_5 that comprises 92% D enrichment of one benzyl hydrogen at position 1, nearly 100% D enrichment of the vinyl hydrogen at position 2, and total 25% D enrichment of the methyl hydrogens at position 4 were obtained in 70% yield (eq 3, Scheme 3).[4m] As a comparison, no D/H exchange occurred when preparative **3aa** was subjected to the standard reaction conditions except with D_2O instead of H_2O (eq 4, Scheme 3). These results indicated that water participated in the reaction. Finally, a deuterium labeling experiment of the model reaction using deuterated Et_3N-d_{15} (>99% D enrichment) was carried out (eq 5, Scheme 3). It was found that a 99% D incorporation rate for one of the benzyl hydrogens at position 1 in the resulting **3aa**-d_5 was achieved, suggesting that the 1,5-HAT process should occur.[4m] Meanwhile, because we used H_2O in the reaction medium, an H/D exchange for the deuterated methyl group (CD_3) at position 4 of **3aa**-d_5 was also observed.

On the basis of the experiments presented above and previous studies,[4m,14,25−27] a plausible mechanism is presented in Scheme 4. First, the excited state of ***PS4*** Cu(I)* [$E_{1/2}(\mathrm{Cu^{I}}*/\mathrm{Cu^{0}})$ = 1.04 V vs SCE in MeCN (see the Supporting Information)] could be quenched by triethylamine **2a** [$E_{1/2}(\mathrm{Et_3N^{\bullet+}/Et_3N})$ = 0.83 V vs SCE in MeCN][25] to generate α-amino radical **7** and Cu(0) species. Addition of α-amino radical **7** to alkyne **1a** afforded vinyl radical species **10**, which could further undergo a key 1,5-HAT process to produce radical **11**.[4m,26] Subsequently, β-fission of **11** resulted in C−N bond cleavage and formation of radical intermediate **14** and imine **12** (path a).[4m,27] Alternatively, **11** might be oxidized by Cu(I)* to produce intermediate **13**, which was then reduced by the active Cu(0) species [$E_{1/2}(\mathrm{Cu^{I}/Cu^{0}})$ = −1.73 V vs SCE in MeCN (see the Supporting Information)] to yield **14** and imine **12** (path b).[4m,14,26a] **14** could be isomerized to **15**. Finally, the reduction of **15** by the active Cu(0) species via the SET process followed by the protonation of the resulting anion species **16** by H_2O delivered **3aa**.[4m]

Scheme 4. Proposed Mechanism



Allylarenes are versatile building blocks in organic synthesis and could be easily converted into valuable synthons and fine chemicals via various transformations.[28−30] With **3aa** as a model substrate, it could be epoxidized by *m*-CPBA to deliver epoxide **17** in 91% yield (see Scheme S1a) and hydroborylated by $B_2(pin)_2$ to afford **18** in 65% yield under the catalysis of $Fe(OAc)_2$ (Scheme S1b).[28c,d] **3aa** could also undergo oxidative cycloaddition with *N*-phenylmaleimide to deliver **19** in a stereoselective manner (Scheme S1c).[30c]

In summary, for the first time we have realized tertiary amines as alkyl radical equivalents exemplified in the alkylation of alkynes to access allylarene derivatives enabled by a P/N heteroleptic Cu(I) photosensitizer under photoredox catalysis conditions. In the reaction, tertiary amines play dual roles, namely, quenching agents for the photoexcited Cu(I) complex and alkylating equivalents for the cross-coupling with alkynes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03236.

Experimental details, full characterization data, mechanistic experiments, and copies of NMR spectra for compound **3** (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors thank the Natural Science Foundation of China (21772176 and 21372201) and the Natural Science Foundation of Zhejiang Province (LY20B020013) for financial support.

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https://dx.doi.org/10.1021/acs.orglett.0c03236
Org. Lett. XXXX, XXX, XXX–XXX