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Visible-Light-Mediated Deacylated Alkynylation of Unstrained Ketone

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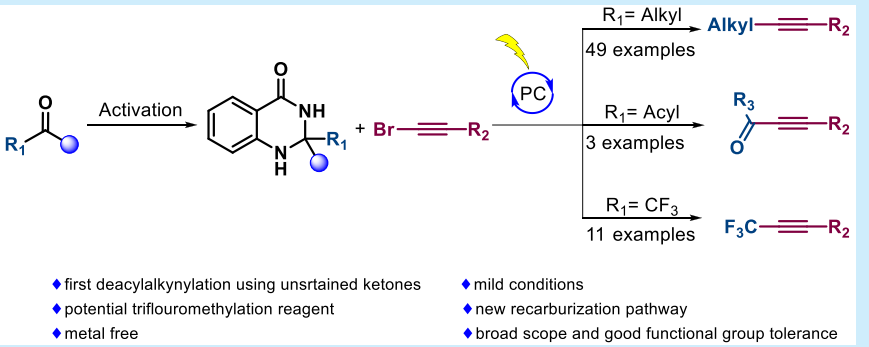

ABSTRACT: Deconstructive alkynylation of an unstrained ketone catalyzed by an organic photocatalyst under blue light irradiation is reported for the first time. A broad substrate scope with up to 63 examples, excellent functional group tolerance, and gram scale reaction demonstrated the practicality of this novel alkynylation method. The dihydroquinazolinone derivative of trifluoroacetophenone had been proved to have potential as a novel trifluoromethylation reagent after working well for the trifluoromethylation reaction with various alkynyl bromides.

Alkynes are widely found in natural products,[1] pharmaceutical molecules, and bioactive compounds; meanwhile, applications as fundamental feed stocks and building-block alkynes also have been widely utilized to prepare various antibiotics,[2] antimycotics,[3] polymers, optical or electronic materials, and liquid crystals.[4] Due to its powerful practicality in chemical science, many kinds of methods have been created to synthesize alkynes; Sonogashira coupling is the most general and widely used pathway to provide Csp^2−Csp products using terminal alkynes and arylhalides.[5] In 2003, Fu's group expanded this Pd/Cu cocatalytic system to construct the Csp^3−Csp bond,[6] and thereafter, various catalysts based on ruthenium,[7] gold,[8] nickel,[9] copper,[10] and iron[11] have been reported to synthesize alkynes (Scheme 1a). Unfortunately, the requirements of high temperature and appropriate ligands not only reduce the functional group tolerance but also increase the reaction cost, and competition reactions initiated by homocoupling and β-elimination are also Gordian knots for those transition metal catalyzed Csp^3−Csp processes. Obstructions mentioned above pushed chemists to develop alternative novel mild methods in this research field.

In recent years, photoredox catalysis has emerged as a powerful tool to realize various chemical transformations including the Csp^3−Csp coupling via radical pathway in accord with the demands for green and sustainable chemistry. So far, aliphatic alkane,[12] amine,[13] alcohol,[14] halide,[15] and acid[16] all have been applied as radical precursors to undergo alkynylation (Scheme 1b), but deconstructive alkynylation of unstrained ketone via deacylatedation is still not reported, probably largely due to the fact that the C−C bond of a ketone is more inert to manipulation. Although the high C−C bond-strength of the ketone makes its activation challenging,[17] ketones as alkynylation precursors still possess unique features. First, a diversity of methods to prepare ketones and their prevalence in natural products and commodity chemicals make them ideal candidates for alkynylation.[18] Second, it is convenient to introduce various functional groups to α, β, or even remote positions of ketones, and these functional groups will eventually be brought to corresponding alkynylation products.[19] Third, alkynylation products of ketone could be expediently converted to ketones, so with this deacylated alkynylation, using ketones could lead to an uncommon iterative one-carbon-increase for ketones. Fourth, this

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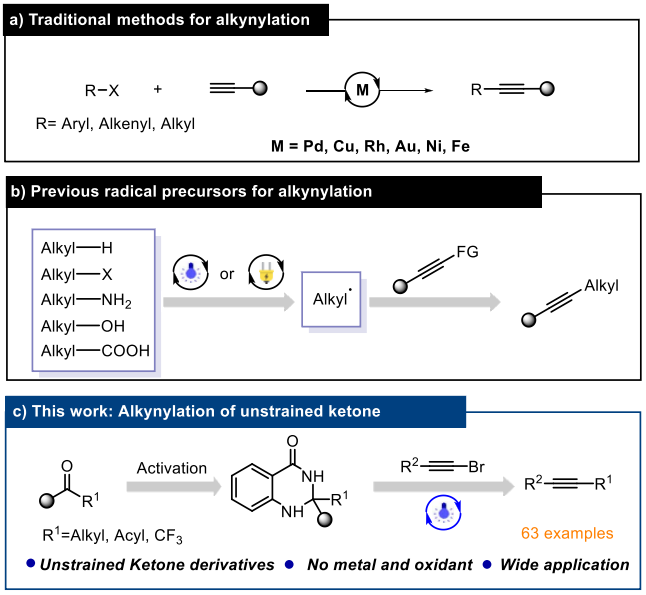
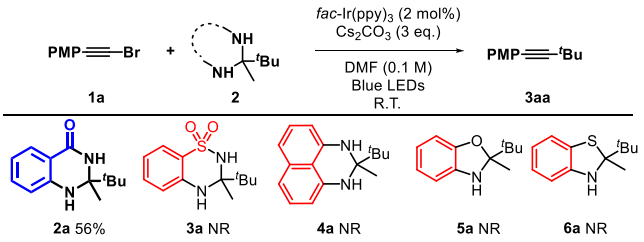
Scheme 1. Previous Work and Current Work



alkynylation could be conveniently applied to a late-stage modification of complex linear ketones. So, alkynylation of unstrained linear ketones is necessary and meaningful.

We initiated our investigation by screening five kinds of activated groups using ^{t}butyl methyl ketone as the standard substrate catalyzed by *fac*-Ir(ppy)$_3$ at room temperature with Cs_2CO_3 as the base in DMF (Scheme 2). To our delight,

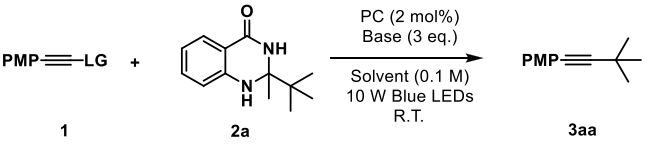
Scheme 2. Effects of the Activated Precursors[a]



[a]Conditions: **1a** (0.2 mmol), **2** (0.3 mmol), Cs_2CO_3 (0.6 mmol), 2 mol % fac-Ir(PPy)$_3$, 0.1 M, N_2, 10 W blue LEDs, 24 h. PMP = *p*-methoxyphenyl.

dihydroquinazolinone derivative **2a** could be an appropriate precursor and give product **3aa** in 56% yield. With a potential activation group in hand, analogues of **1a** alkynyl chloride and iodide were also applied to this coupling process (Table 1, Entries 1−2), and the yields of product **3aa** decreased to 30% and 27%, respectively. Then, alkynyl bromide **1a** was used to screen various solvents such as DCM, DMPU (1,3-dimethyl-perhydro-2-pyrimidinone), DMSO (dimethyl sulfone), THF, 1,4-dioxane, and $CHCl_3$ (Table 1, Entries 3−8, Table S1); DMF was the better hit for the transformation. Next, different bases were screened like Et_3N, DABCO (1,4-diazabicyclooctane), pyridine, and DBU (Table 1, Entries 9−12, Figure S2), and DBU as the most suitable base could give out target product in 64% yield. Photocatalysts (Table 1, Entries 13−19, Figure S3) were introduced to optimize the reaction, and 4-CzIPN was proved to be the best hit and afforded **3aa** in 79% yield.

Table 1. Optimization of Conditions[a]



Entry	PC	LG	Base	Solvent	Yield (%)[b]
1	*fac*-IrPPy$_3$	Cl	Cs_2CO_3	DMF	30
2	*fac*-IrPPy$_3$	I	Cs_2CO_3	DMF	27
3	*fac*-IrPPy$_3$	Br	Cs_2CO_3	DCE	24
4	*fac*-IrPPy$_3$	Br	Cs_2CO_3	DMPU	39
5	*fac*-IrPPy$_3$	Br	Cs_2CO_3	DMSO	44
6	*fac*-IrPPy$_3$	Br	Cs_2CO_3	THF	35
7	*fac*-IrPPy$_3$	Br	Cs_2CO_3	1,4-Dioxane	10
8	*fac*-IrPPy$_3$	Br	Cs_2CO_3	$CHCl_3$	31
9	*fac*-IrPPy$_3$	Br	Et_3N	DMF	ND
10	*fac*-IrPPy$_3$	Br	DABCO	DMF	trace
11	*fac*-IrPPy$_3$	Br	Pyridine	DMF	trace
12	*fac*-IrPPy$_3$	Br	DBU	DMF	64
13	3DPAFIPN	Br	DBU	DMF	51
14	4CzIPN	Br	DBU	DMF	79
15	Rhodamine B	Br	DBU	DMF	37
16	Ru(bpy)$_2$Cl$_2$	Br	DBU	DMF	N.R.
17	Mes-Acr$^+$BF$_4^-$	Br	DBU	DMF	N.R.
18	Rose Bengal	Br	DBU	DMF	N.R.
19	Perylene	Br	DBU	DMF	N.R.

[a]Conditions: **1** (0.2 mmol), **2a** (0.3 mmol), Base (0.6 mmol), 2 mol % PC, 0.1 M, N_2, 10 W blue LEDs, 24 h. [b]NMR yield with CH_2Br_2 as internal standard. PMP = *p*-methoxyphenyl.

With the optimized conditions in hand, we started to evaluate the substrate scope of the alkynylation process, and our catalytic deacylatedation alkynylation platform could be widely applied to a series of aryl alkynyl bromides no matter their electronic and steric environment (Scheme 3). The aromatic alkynyl bromides **1a**−**1e** with an electron-donating group like OMe, Et, N(Me)$_2$, SMe, and *n*-Bu in the *para* positon of the aryl ring showed excellent reactivity and supplied **3aa**−**3ea** in 79%−91% yield. Gram scale-up reaction of **1a** (4.18 g) also worked well and supplied **3aa** with 72% yield. Alkynyl bromides **1f**−**1j** with electron withdrawing groups COOMe, COMe, NO_2, SO_2Me, and SOMe all could be tolerated well by these mild conditions and gave corresponding products **3fa**−**3ja** in 69%−81% yield. Bromide and Bpin (pinacolboryl) substituted substrates **1k** and **1l** which could be conveniently utilized to undergo further transformation via transitional metal catalyzed cross-coupling also afforded desired products **3ka** and **3la** with 91% and 86% yields, respectively. The EtO group in the aryl *meta* position performs a little better than the CN group and supplied corresponding products in 84% and 73% yields. *meta*-Me, OH, NO_2, and COPh substituted aryl alkynyl bromides **1o**−**1r** all could be tolerated well to afford **3oa**−**3ra** with medium to good yields (59%−84%), and α and β substituted naphthyl alkynyl bromide **1s** and **1t** showed similar reactivity. Coupling products were obtained with similar yields (83%, 81%). Polycyclic aromatic substrate **1u** worked smoothly, and product **3ua** could be obtained in 71% yield. 3,5- and 3,4-Disubstituted alkynyl bromides **1v**−**1y** all could produce the target coupling disubstituted alkynes **3va**−**3ya** in 69%−87% yield. 1,3,5-Trisubstituted **1z** and D_5-phenyl alkynyl bromide **1aa** also could undergo the alkynylation process well and gave

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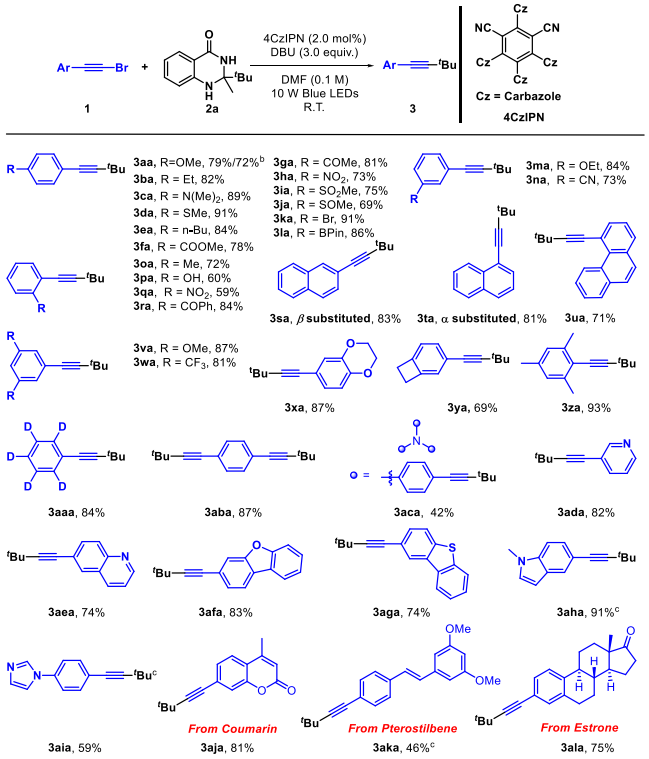
Scheme 3. Scope of Alkynyl Bromides[a]

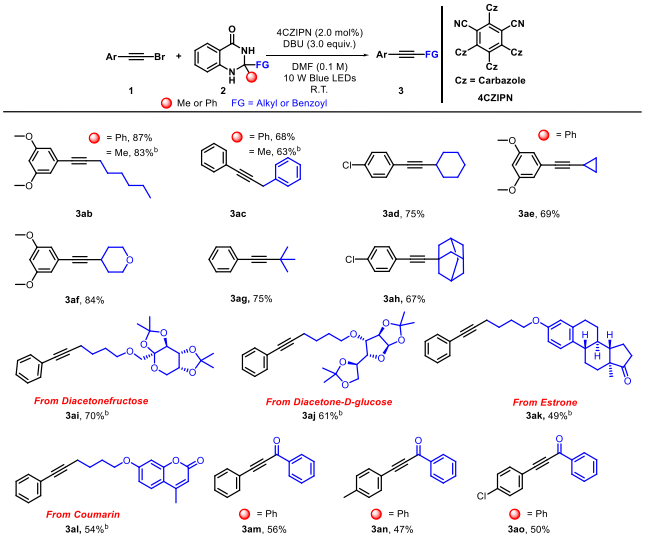


[a]Reaction conditions: **1** (0.2 mmol), **2a** (0.3 mmol), DBU (0.6 mmol), 2 mol % 4CzIPN, 0.1 M in dry DMF, N_2, 10 W blue LEDs, rt, 24 h. [b]Gram scale for **1a** (4.18 g). [c]Alkyne (0.2 mmol), NBS (0.22 mmol), DBU (0.22 mmol), 0.2 M in CH_3CN 0 °C to rt, 1−10 min; **2a** (0.3 mmol), DBU (0.6 mmol), 2 mol % 4CzIPN, 0.1 M in dry DMF, N_2, 10 W blue LEDs, rt, 24 h.

out **3za** and **3aaa** in 93% and 84% yields. Bisalkynyl and trialkynyl bromides **1ab** and **1ac** could afford corresponding products **3aba** and **3aca** in 87% and 42% yields with improving the loading of **2a** to 4.5 and 8 equiv, respectively. Alkynyl bromide containing electron-deficient pyridine and quinoline rings **1ad** and **1ae** both could undergo the alkynylation transformation and produced products **3ada** and **3aea** in 82% and 74% yields; electron-rich heteroaromatic alkynyl bromides **1ae**−**1ai** all could afford alkynylation products **3aea**−**3aia** mediated by this photoredox catalytic process. More complex alkynyl bromides derived from 4-methylcoumarin **1aj**, 3,5-dimethoxystilbene **1ak**, and estrone **1al** all were befitting coupling partners and supplied target products **3aja**−**3ala** with 46%−81% yields.

Next, we turned our attention to explore the generality of unstrained linear ketone dihydroquinazolinones, and it was worth noting that, regardless of dihydroquinazolinones being derived from primary, secondary, or tertiary alkyl methyl ketone, all could be tolerated by our catalytic system (Scheme 4); primary alkyl methyl ketones **2b** and **2c** could supply the alkynylation products **3ab** and **3ac** in 83% and 63% yields, and similar results also could be obtained when corresponding primary alkyl phenyl ketones were adopted. Secondary ketones **2d**, **2e**, and **2f** also are suitable substrates for this alkynylation transformation and afforded products **3ad**, **3ae**, and **3af** in 69%−84% yields. ^{t}Butyl methyl ketone and adamantyl methyl ketone both could be tolerated by our mild catalytic system, and alkynylation products **3ag** and **3ah** could be obtained in

Scheme 4. Scope of Unstrained Ketones[a]



[a]Except for special notes, all ketones are methyl ketones. Reaction condition: **1** (0.2 mmol), **2** (0.3 mmol), DBU (0.6 mmol), 2 mol % 4CzIPN, 0.1 M in dry DMF, N_2, 10 W blue LEDs, rt, 24 h. [b]Ketone (0.2 mmol), 2-aminobenzamide (0.2 mmol), **1** (5% mol), 0.2 M in dry DMF, 0−70 °C, 48−72 h; **1** (0.3 mmol), DBU (0.6 mmol), **2** mol % 4CzIPN, 0.1 M in dry DMF, N_2, 10 W blue LEDs, rt, 24 h.

75% and 67% yields. In order to prove the practicality of this alkynyltion process in late-stage functionalization, drug intermediate and drug-like methyl ketone derivatives were prepared from more complex substrates: diacetonefructose, α-D-allofuranose, estrone, and 4-methylumbelliferone (antitumor activity). Diacetonefructose, α-D-allofuranose, and estrone methyl ketone derivatives bearing multiple stereogenic centers **2i**, **2j**, and **2k** could undergo the alkynylation transformation smoothly to give the corresponding coupling products **3ai**−**3ak** with moderate to good (49%−78%) yields as a single isomer. For estrone derivatives, **2k** with two carbonyl groups could afford product **3ak** via regioselective elimination of the linear carbonyl. 4-Methylumbellifer methyl ketone derivative **2l** also was a suitable coupling substrate and supplied alkynylation product **3al** in 54% yield. These results preliminarily proved the potential possibility of applying this reaction to rapidly access complex structural motifs. In addition, the coupling partner also could be expanded to the acyl-type radical and afforded corresponding phenyl alkynyl ketones **3am**, **3an**, and **3ao** in 47%−56% yields.

Fluoroalkylated alkynes, widely applied to prepare complex bioactive organofluorine target molecules, are also in high demand, but as we know, only two examples reported using alkynyl halide to prepare the corresponding fluoroalkylated alkynes: Eun Jin Cho's group reported trifluoromethyl alkynylation using CF_3I as the trifluoromethyl source with photocatalyst in 2019,[15a] and David A. Vicic's group reported trifluoromethyl alkynylation using an equivalent trifluoromethyl nickel complex with alkynyl iodonium reagent in 2021.[20] However, as CF_3I is a light sensitive gas, it was not convenient to use, transport, and store, and trifluoromethyl nickel complex was costly apply in industry, so development of a novel trifluoromethyl reagent to overcome the drawbacks mentioned above is meaningful and necessary.

With this desire, we prepared dihydroquinazolinone derivatives adopting trifluoroacetophenone which was cheaper

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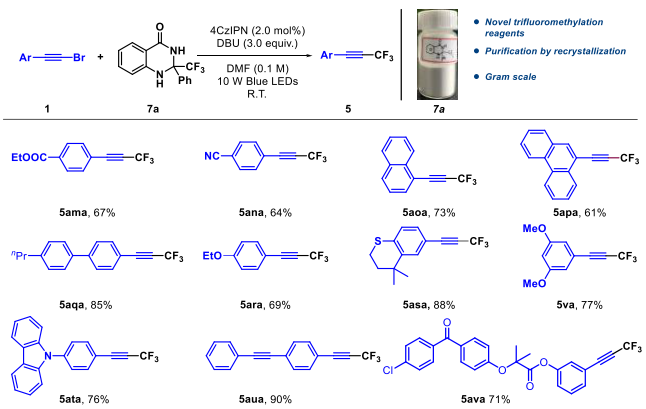
than CF_3I, and to our delight, various aryl alkynyl bromides could work well with this novel trifluoromethyl derivative (Scheme 5). Aryl ring substrates **1am** and **1an** with an electron

Scheme 5. Scope of Alkynyl Bromides for Trifluoromethylation Reactions

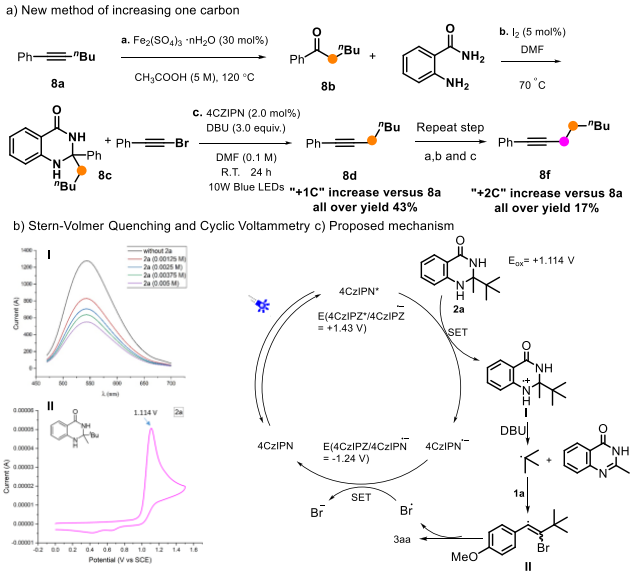


[a]Reaction conditions: **1** (0.2 mmol), **7a** (0.3 mmol), DBU (0.6 mmol), 2 mol % 4CzIPN, 0.1 M in dry DMF, N_2, 10 W blue LEDs, rt, 24 h.

withdrawing group could afford target products in 67% and 64% yields, respectively. Polycyclic aromatic ring alkynyl bromides **1ao**, **1ap**, and **1aq** all were suitable coupling partners, and **5aoa**, **5apa**, and **5aqa** could be obtained in 61%−85% yields. The aryl ring with electron-donating groups **1ar**, **1as**, **1v**, and **1at** also performed well and supplied **5ara**, **5asa**, **5va**, and **5ata** in 69%−88% yields. Alkynyl substituted substrate **1au** could be tolerated by our mild conditions and afforded **5aua** in 90% yield. Alkyne bromide **1av** derived from small molecule fenofibric acid also could go through this trifluoromethylation process and afford product **5ava** in 71% yield. These results proved that this trifluoromethyl dihydroquinazolinone which could be prepared on a gram scale by recrystallization had the potential to become a novel trifluoromethyl reagent, and further study about applications of this new trifluoromethyl reagent is going on in our lab.

Homologation by one carbon like the Arndt−Eistert−Wolff rearrangement had been applied widely in organic and medicinal chemistry, which can strongly prove the importance of the one-carbon homologation method; here, we utilized a combination of oxidation, ketalation, and our deacylatedation alkynylation method to realize one-carbon homologation of alkyne **8a**, and a "+2C" increase product **8f** could be obtained via 2 *controlled iterative* one carbon homologations in 17% whole yield. Control experiments also have been carried out to investigate the mechanism; 1.5 equiv of TEMPO as radical trapping agent could depress the alkynylation process totally (Figure S7). The switch light experiment verified the necessity of visible light in the catalytic cycle. Cyclic voltammetry analysis showed that the oxidation potential of **2a** is $E_{1/2}^{ox}$ = +1.114 V vs SCE in DMF and was shown to be within the oxidizing power of 4CzIPN (+1.43 V vs SCE) (Figure S5). Stern−Volmer fluorescence quenching experiments proved that the excited state of 4CzIPN was effectively quenched by pro-prearomatic **2a** (Scheme 6b, Figure S6). These results indicated that a single electron could transfer from dihydroquinazolinone to photoexcited 4CzIPN. DFT calculations showed that the precursor **2a** has the lowest bond

Scheme 6. Carbon Increase Reaction and Proposed Mechanism



dissociation Gibbs free energy (−7.4 kcal/mol), which indicates that after single electron transfer (Figure S9), **2a** would be the most probable to undergo homocleavage and then form the ^{t}butyl radical compared with **3a**−**6a**. Based on the above obeservations and literature reports,[12d,15c] a plausible mechanism was proposed (Scheme 6c). Excited photocatalyst 4CzIPN* was generated by irradiating the 4CzIPN with blue light, and 4CzIPN* (+1.43 V vs SCE) was quenched by precursor **2a** (E_{ox} = +1.114 V vs SCE) to generate the radical cation intermediate **I**. The ^{t}butyl radical was obtained by homocleavage of the intermediate generated from the deprotonation of intermediate **I** by DBU. Then, the ^{t}butyl radical attacked the bromide **1a** to supply vinyl radical **II** which could undergo β-elimination to afford the bromine radical and the final alkynylation product **3aa**. The bromide radical then oxidizes $4CzIPN^{\bullet-}$ to regenerate 4CzIPN for the next photoredox cycle.

In conclusion, a novel method of deconstructive alkynylation of unstrained ketone has been developed for the first time using an organic photocatalyst under blue light irradiation at room temperature. The potential practicality had been demonstrated by broad substrate scope, splendid functional group tolerance, and gram-scale reaction. A dihydroquinazolinones derivative of trifluoroacetophenone had been applied to undergo trifluoromethylation with various alkynyl bromide species, and this proved that it might become a potential novel trifluoromethylation reagent which could be easily used, transported, and stored. Rare *controlled iterative* one carbon homologation was realized by combining oxidation, and this deacylated alkynylation process further provided a novel homologation method for organic and medicinal chemistry.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its online Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.3c00145.

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FAIR data, including the primary NMR FID files, for compounds **1a−1z**, **1aa−1av**, **3aa−3za**, **3aaa−3ala**, **3ab−3ao**, **2b−2l**, **5ama−5asa**, **5va**, **5ata−5ava**, **2a**, **3a**, **4a**, **5a**, **6a**, **8a-8f**, **4** (ZIP)

Experimental procedures and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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