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Visible-light-induced chemoselective reductive decarboxylative alkynylation under biomolecule-compatible conditions†

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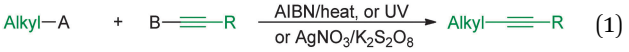
We report a visible-light-induced reductive decarboxylative C(sp^3)–C(sp) bond coupling reaction to construct aryl, alkyl and silyl substituted alkynes at room temperature in organic solvents or neutral aqueous solutions. This chemoselective alkynylation was compatible with various functional groups and biomolecules, and did not affect the protein enzyme activity.

The search for new chemoselective reactions is a consistent pursuit for organic chemists.[1] To enable modification of molecules with increasing complexity especially biomolecules with various sensitive functional groups, new chemoselective reactions with improved functional group compatibilities and milder reaction conditions are required.[2] Compared to cationic or anionic reactions, radical reactions are less sensitive to solvents, and can be performed under neutral and aqueous solutions to increase the functional group compatibility.[3] Traditionally, classical radical initiation conditions such as heating, UV light irradiations, or strong oxidants/reductants limit their functional group compatibility. Recently, it was shown that radical reactions were initiated under mild visible-light-catalysis conditions,[4] and some limited examples suggested that visible-light-induced reactions could be biomolecule-compatible.[5]

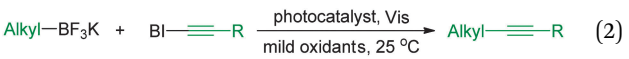
The alkyne moiety is a versatile synthetic building block[6] and chemoselective C(sp^3)–C(sp) bond coupling reactions are useful to construct alkyl substituted alkynes.[7] The transition metal-catalyzed C(sp^3)–C(sp) bond coupling reactions were successful for primary and secondary alkyl–alkyne coupling reactions when appropriate ligands were used to minimize β-hydrogen elimination, but the tertiary alkyl–alkyne coupling reaction remained elusive.[8] The radical-type C(sp^3)–C(sp) bond coupling reactions were promising, but the use of heating, UV irradiation or strong oxidants limited their chemoselectivity and functional group compatibility (eqn (1)).[9] Recently, our group reported a visible-light-induced radical deboronative alkynylation reaction under mild oxidative conditions (eqn (2)).[5c] As the visible-light-induced reductive C(sp^3)–C(sp) bond coupling reactions were unprecedented and the versatile chemical toolbox under different redox conditions was desirable, we aimed to develop a chemoselective reductive alkyl–alkyne coupling reaction and to further explore its biomolecule-compatibility under neutral aqueous conditions (eqn (3)).

A classical radical C(sp^3)–C(sp) bond coupling reaction (heat, UV, or strong oxidants)



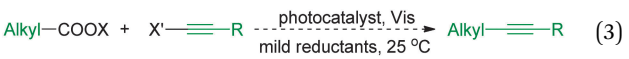
(1)

A visible-light-induced radical C(sp^3)–C(sp) bond coupling reaction (mild oxidants)



(2)

A visible-light-induced radical C(sp^3)–C(sp) bond coupling reaction (mild reductants)



(3)

The carboxylate moiety is ubiquitous in organic molecules. Recently, some carboxylate derivatives were shown to generate alkyl radicals under visible-light-catalysis conditions, but the decarboxylative alkynylation remained unknown.[10,11] We first studied various carboxylate derivatives and alkynylation reagents under blue LED (λ_{max} = 468 ± 25 nm) irradiations.[12] Using $[Ru(bpy)_3](PF_6)_2$ as the photocatalyst and diisopropylethylamine (DIPEA)/the Hantzsch ester (HE) as the reductants, we found that *N*-acyloxyphthalimide **1** coupled with alkynyl halides (X = Br) or alkynyl benziodoxoles (X = BI)[5c,9c] in low yields at room temperature (entries 1 and 2 in Table 1). The use of alkynyl sulfones (X = SO_2R)[9a,b,13] as alkynylation reagents improved the results and the alkynyl phenylsulfone (X = SO_2Ph) gave alkyne **3** in optimal 76% yield in 30 minutes (74% isolated yield, entries 3–5). The photocatalyst, light irradiation and reductants were all critical (entries 6–8). This reaction also proceeded smoothly under neutral

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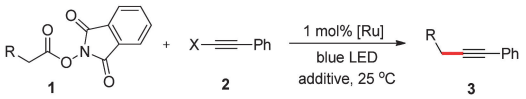
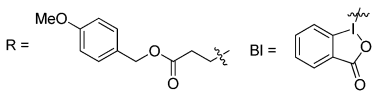
† Electronic supplementary information (ESI) available: Complete mechanistic experiments, optimization tables, experimental methods, and additional experimental data. See DOI: 10.1039/c4cc06344a

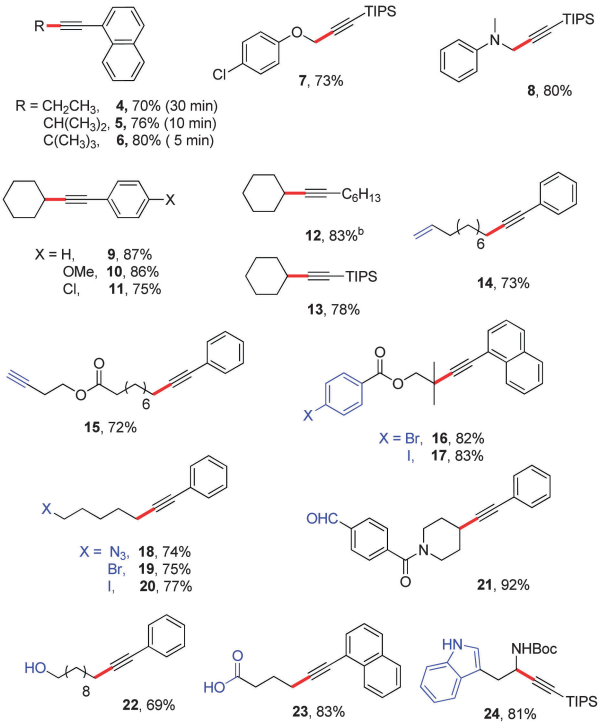
Table 1 Optimization of the decarboxylative alkynylation



Entry	Conditions[a]	Time	Conversion[b] (%)	Yield[b] (%)
1	X = Br	30 min	>95	28
2	X = Bl	30 min	>95	16
3	X = SO_2CF_3	30 min	60	29
4	X = SO_2CH_3	30 min	>95	57
5	X = SO_2Ph	30 min	>95	76 (74)
6	Entry 5, no blue LED	12 h	<5	0
7	Entry 5, no [Ru]	12 h	<5	0
8	Entry 5, no iPr_2NEt/HE	12 h	<5	0
9[c]	Entry 5, neutral condition	30 min	>95	73 (69)
10	Entry 5, air	30 min	>95	71

[a] Reaction conditions: **1** (0.10 mmol, 1.0 equiv.) **2** (0.15 mmol, 1.5 equiv.), $Ru(bpy)_3(PF_6)_2$ (0.001 mmol, 0.1 equiv.), iPr_2NEt (0.20 mmol, 2.0 equiv.), and Hantzsch ester (HE, 0.15 mmol, 1.5 equiv.) in 1.0 mL CH_2Cl_2 under nitrogen with blue LED irradiation. [b] Conversions and yields were determined by ^1H NMR analysis, isolated yields are in parentheses. [c] HCOOH (0.20 mmol, 2.0 equiv.) was added to reaction conditions.





[a]Reaction conditions: entry 5 in Table 1, unless otherwise noted. [b]3 equiv. of alkynyl sulfone was used.

Scheme 1 Substrate scope and functional group compatibility of the decarboxylative alkynylation.

conditions or in an air atmosphere (entries 9 and 10), which were friendly to base-sensitive functional groups and helpful for daily convenient operations.

We next examined the substrate scope of the reaction under the optimized reaction conditions (entry 5 in Table 1). By one-step preparation from the readily available carboxylic acids,[14] we prepared primary, secondary, and tertiary alkyl substituted *N*-acyloxyphthalimides. Alkyne products **4–6** with different alkyl substitutions were obtained in 70%, 76% and 80% yields, respectively (Scheme 1).[8] The α-heteroatom (oxygen or nitrogen) substituted alkynes **7** and **8** were rarely reported in transition-metal-catalyzed or radical-type C(sp^3)–C(sp) cross-coupling reactions, while 73–80% yields were observed by using this method.[8] Aryl alkynes unsubstituted or substituted with methoxy or chloride groups **9–11** were constructed in 75–87% yields.[15] Alkyl and silyl-substituted alkynes **12–13** were also obtained smoothly in 78–83% yields.

Functional groups prone to transition-metal-catalysis were tolerated in this reaction, where unactivated alkenes, unactivated alkynes, aryl bromides/iodides, or azides were unaffected (products **14–18**). Sensitive nucleophilic or electrophilic groups were compatible, where alkyl bromides/iodides, aldehydes, alcohols, carboxylic acids, or indoles[16] remained intact (products **19–24**). This excellent chemoselectivity and functional group compatibility would potentially enable the alkynylation of functional-group-rich molecules with a protecting-group-free synthesis.[17]

To gain mechanistic insights into this $[Ru(bpy)_3](PF_6)_2$/DIPEA/HE photocatalytic system, we performed luminescence quenching experiments: DIPEA and HE quenched the photoexcited Ru(II)* effectively, while *N*-acyloxyphthalimides and alkynyl sulfones had no effect (ESI,† Schemes S1–S5). We further recorded UV-Vis spectra of the photoexcited Ru(II)* under the DIPEA reductive conditions and observed the signature absorption band of Ru(I) at 510 nm (ESI,† Scheme S6).[18] These observations suggested the formation of the Ru(I) intermediate by the photoredox process. To show how Ru(I) interacted with the *N*-acyloxyphthalimides, we tracked the reaction mixture and found >95% yield of phthalimides as the reduction adducts (ESI†). We also synthesized *N*-acyloxyphthalimide **25** with a pendent alkene and observed 5-*exo* cyclized alkynylation product **26** in 68% yield (Scheme 2a). Taken together, a Ru(I)-mediated alkyl radical formation from reductive decarboxylation was suggested.

The radical alkynylation mechanism of alkynyl triflone(trifluoromethyl sulfone) was previously elucidated and a radical chain reaction from the reactive trifluoromethyl radical was suggested.[9a] To investigate our reaction mechanism, we used the C13-isotopic-labelled alkynyl sulfone **29** and observed alkyne **30** with C13 retention in 82% yield. The β-addition followed by an exclusive alkyl R group migration was unlikely, while an α-addition followed by a sulfonyl radical elimination was suggested (Scheme 2b). To test if the sulfonyl radical initiated a radical chain reaction, we incubated *N*-acyloxyphthalimides with the sulfonyl radical generated from the known procedure and observed no decarboxylation (ESI,† Scheme S8).[19] The exclusive light-dependence of the reaction also suggested that the radical chain mechanism was unlikely in this reaction (Scheme 2c).

On the basis of the mechanistic investigation discussed above, we proposed the reaction mechanism (Scheme 3). The photoexcited Ru(II)*[20] was reduced to Ru(I) by DIPEA/HE,[10d] and the resulting Ru(I) reduced *N*-acyloxyphthalimides by single-electron-transfer. The phthalimide was eliminated after reductive cleavage, and

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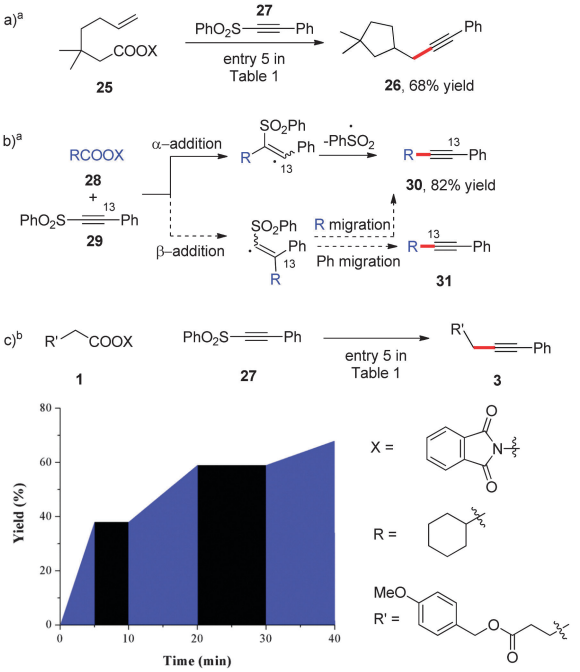
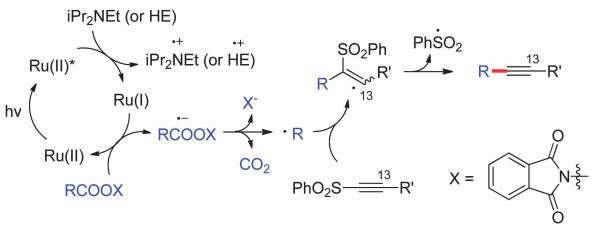


[a]Reaction conditions: entry 5 in Table 1, unless otherwise noted. [b]The blue area indicates the blue LED irradiation, while the black area indicates the dark treatment.

Scheme 2 Mechanistic investigations of the decarboxylative alkynylation reaction.

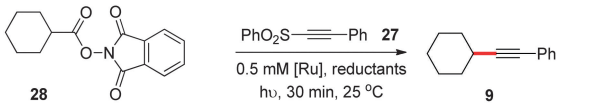


Scheme 3 Mechanistic proposal of the decarboxylative alkynylation.

the carboxyl radical released carbon dioxide to yield the alkyl radical. After α-addition to the alkynyl sulfone and the sulfonyl radical elimination, the alkyne product was obtained.

We next tested if the neutral aqueous reaction conditions and biomolecule-compatibility were possible. When water was added to the optimized reaction conditions in organic solvents (entry 5 in Table 1), the yields of alkynylation were compromised especially in water-miscible solvents (entries 1 and 2 in Table 2). The use of NADH (nicotinamide adenine dinucleotide hydrogen) as the water-soluble reducing surrogate was not found to be effective (entry 3). Gladly, the use of ascorbates as water-soluble reductants enabled the decarboxylative alkynylation in neutral aqueous solution in 76% yield, which was firstly used for visible-light-induced decarboxylative radical formation (isolated yield 76%, entry 4).[5b,21] We also tested if this reaction was affected by various endogenous or exogenous biomolecules.[22] Upon addition of stoichiometric (mole or mass) amounts of amines, amino acids, nucleosides, oligosaccharides, nucleic acids, proteins, or cell lysates to the reaction conditions, uncompromised 73–84% alkynylation

Table 2 Decarboxylative alkynylation reaction in neutral aqueous solutions



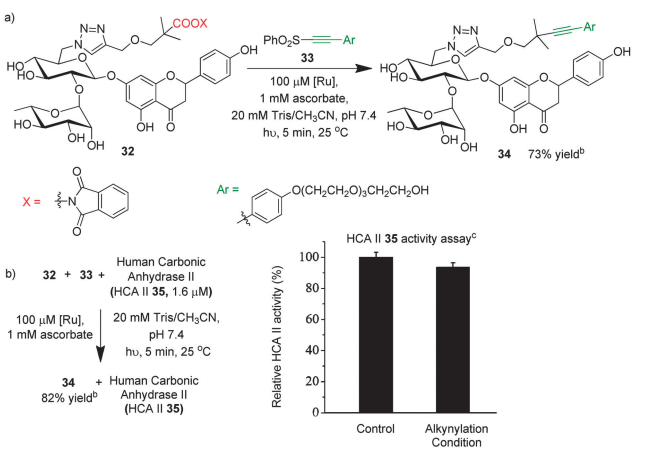
Entry	Conditions[a]	Conversion[b] (%)	Yield[b] (%)
1	Entry 5 in Table 1, CH_2Cl_2/H_2O	92	69
2	Entry 5 in Table 1, CH_3CN/H_2O	92	36
3	Entry 5 in Table 1, CH_3CN/H_2O NADH to replace HE	>95	24
4	CH_3CN/pH 7.4 Tris, ascorbates	>95	76 (76)

[a] Reaction conditions: **28** (0.10 mmol, 27.3 mg, 10 equiv.) **27** (0.15 mmol, 36.3 mg, 1.5 equiv.), $Ru(bpy)_3(PF_6)_2$ (0.005 mmol, 4.3 mg, 0.05 equiv.), and ascorbates ester (0.23 mmol, 2.3 equiv.) in 10.0 mL 1:1 CH_3CN/aqueous buffer (300 mM pH 7.4 Tris) under nitrogen with 468 nm LED irradiation for 30 min. [b] Conversions and yields were determined by ^1H NMR analysis, isolated yields are in parentheses.

yields were observed (ESI,† Tables S3 and S4). The alkynylation at low-concentrations was also tested as it was required for biomolecule studies. Using the water-soluble naringin-conjugated *N*-acyloxyphthalimide **32** (100 μM concentration),[2,3] we found that alkyne **34** was obtained smoothly within 5 minutes in 73% yield (Scheme 4a).

Finally, we tested if biomolecules were affected by the neutral aqueous reaction conditions by performing decarboxylative alkynylation in the presence of a protein enzyme.[24] We treated 100 μM of naringin-*N*-acyloxyphthalimide **32** and 1.6 μM of human carbonic anhydrase II (HCA II)[25] **35** under aqueous reaction conditions. After 5 minutes, the oligosaccharide alkynylation was completed in 82% yield, as analyzed by HPLC. We isolated HCA II from the completed reaction by ultrafiltration and subjected to enzymatic assay. Following the 4-nitrophenyl acetate hydrolysis spectrophotometrically,[26] we observed less than 10% loss of the HCA II catalytic activity after the reaction under alkynylation conditions (Scheme 4b).

In conclusion, we have developed a visible-light-induced reductive decarboxylative C(sp^3)–C(sp) bond coupling reaction within 30 minutes at room temperature in organic solvents or



[a]Reaction conditions: **32** (100 μM), **33** (5 mM), $Ru(bpy)_3Cl_2$ (100 μM), and ascorbates (1 mM) in 1:9 CH_3CN/aqueous buffer (20 mM pH 7.4 Tris) with blue LED irradiation for 2 min. [b]Conversions and yields were determined by HPLC analysis. [c]Error bars represent the standard deviation of results from three independent reaction repeats.

Scheme 4 Decarboxylative alkynylation in low concentrations and compatibility with human carbonic anhydrase II.

neutral aqueous solutions. The reaction mechanism was investigated to reveal a light-dependent radical reaction pathway, which involved a reductive Ru(I) intermediate, decarboxylative alkyl radical formation and alpha-addition to alkynyl sulfones. This chemoselective alkynylation under mild reaction conditions was compatible with various functional groups and biomolecules, and did not affect the protein enzyme activity.

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