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Visible light-driven cross-coupling reactions of alkyl halides with phenylacetylene derivatives for $C(sp^3)-C(sp)$ bond formation catalyzed by a B_{12} complex

The efficient coupling reaction of alkyl halides with alkynes by the dual catalysis system of the B_{12} complex and Ir complex under visible light irradiation at room temperature is reported. The useful substituted alkynes were obtained by a mild method.

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Visible light-driven cross-coupling reactions of alkyl halides with phenylacetylene derivatives for C(sp³)–C(sp) bond formation catalyzed by a B₁₂ complex[†]

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Visible light-driven cross-coupling reactions of alkyl halides with phenylacetylene and its derivatives catalyzed by the cobalamin derivative (B_{12}) with the [Ir(dtbbpy)(ppy)₂]PF₆ photocatalyst at room temperature are reported. The robust B_{12} catalyst and Ir photocatalyst provided high turnover numbers of over 33 000 for the reactions.

Substituted alkynes are important structural motifs in various areas such as medicinal chemistry, agrochemistry, and materials chemistry. Cross-coupling reactions of organic halides with terminal alkynes are useful methods of $C(sp^3)-C(sp)$ or $C(sp^2)-C(sp)$ bond formation for substituted alkynes in many relevant academic and industrial applications.¹ The most powerful and famous alkynylation of organic halides is the transition-metal, Pd and Cu, catalyzed Sonogashira reaction.² For the development of this useful reaction, various advanced protocols have been investigated such as the use of non-expensive metals, transition-metal free, room temperature, nonadditive, expansion of the substrate scope, etc.³ Among them, the coupling of terminal alkynes with unactivated alkyl halides which promote the undesired β -hydride elimination is still a challenging work.⁴ Furthermore, efficient, economical, and eco-friendly green molecular transformation is a contentious requirement in industrial synthetic organic chemistry. Light-driven molecular transformations are one of the prominent protocols in organic synthesis including the coupling reaction, and the alkynylation of aliphatic halides for the C(sp³)-C(sp) bond formation by UV or VIS light irradiation is also reported (Scheme 1).⁵ As some methods were reported in recent years, the visible light-driven, room temperature coupling reactions of non-activated aliphatic organic halides with terminal alkynes are still being explored.

Recently, we reported a visible light-driven catalytic coupling reaction of alkyl halides with styrene and its derivatives to form substituted alkenes by the cobalamin derivative, the B₁₂ complex (C1) (Fig. 1), combined with the use of a photocatalyst at room temperature.⁶ In this reaction, the supernucleophilic Co(1) species of the B_{12} complex is formed by photoinduced electron transfer from the photocatalyst, and the Co(1) complex reacted with the alkyl halide to form an alkylated cobalt complex. Subsequent photolysis of the Co–C bond produces an alkyl radical, which was utilized in the substituted alkene syntheses. As an expansion to these studies, we now disclose a visible light-driven catalytic alkynylation reaction of alkyl halides (R–X, X = Cl, Br, I) to form substituted alkynes at room temperature or 45 °C. As photoredox catalysts are utilized for various molecular transformations,⁷ great attention has been paid to the light-driven molecular transformation in recent synthetic organic chemistry. The advantage of the combined use of a photoredox catalyst and the B_{12} catalyst for the alkynylation reaction is shown in this study. Detailed mechanistic studies were also conducted.



Scheme 1 Methods of alkynylation of alkyl halides for $C(sp^3)-C(sp)$ bond formation.

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We first studied the reaction of phenethyl bromide (B1) with phenylacetylene (A1) under LED ($\lambda_{max} = 448$ nm) irradiation using the B_{12} complex (C1) as the catalyst and $[Ir(dtbbpy)(ppy)_2]PF_6$ (P1) as the photocatalyst (PC) at room temperature (Fig. 1). The coupling product, 1,4-diphenyl-1-butyne (1a), was obtained in 89% yield without any by-products (entry 1 in Table 1). Optimization of the reaction conditions is summarized in Table S1 (ESI[†]). Controlled reactions showed that both the B12 catalyst and PS are essential for the reaction (entries 2 and 3 in Table 1). Without light irradiation or a sacrificial reagent (i-Pr2NEt), the reaction did not proceed (entries 4 and 5 in Table 1). When [Ru(bpy)₃]Cl₂ (P2) or Ir(ppy)₃ (P3) was used as the PC, the yield of 1a decreased to 9% and 40%, respectively (entries 6 and 7 in Table 1). The cobalt complex (C2) having a similar Co(II)/Co(I) redox couple ($E_{1/2} = -0.65$ V vs. SCE in CH₃CN) to C1 $(E_{1/2} = -0.64 \text{ V} \text{ vs. SCE in CH}_3\text{CN})^8$ decreased the product yield to 37% (entry 8 in Table 1). Catalyst C2 decomposed due to light irradiation while the C1 catalyst survived during the reaction that was confirmed by UV-vis absorption spectroscopy and MS analysis (Fig. S25 and S26, ESI[†]). This result suggested that a higher turnover number (TON) based on the catalyst might be achieved in the present catalytic system. Actually, a high TON of 33 200 based on C1 was obtained by increasing the concentration of the substrates and reaction time (entry 9 in Table 1). The catalytic reaction was also carried out using a solar simulator to show the application of sunlight for the reaction and 1a was produced in 88% yield (entry 10 in Table 1). It should be noted that the dual catalysis strategy combined use of an efficient nonphotochemical catalyst and a suitable photocatalyst provided a useful protocol for the photochemical organic synthesis.9 Therefore, the present photocatalytic system should be applicable for the practical synthesis of the product in an eco-friendly manner.

The alkynylation reaction was applied to other alkyl halides as shown in Table 2. The yield of **1a** was 92% for phenethyl iodide while only 18% of **1a** was obtained for phenethyl chloride at room

Table 1 Photocatalytic alkynylation of phenethyl bromide (B1) under visible light irradiation at room temperature^a

	+ Br (ppy)2 PF6 (P1) hv (LED 448 nm) in MeOH under N2	la	\bigcirc
Entry	Reaction conditions	Conversion (%)	Yield of 1a (%)
1	As shown	>99	89
2	No B_{12} complex	0	0
3	No PC	0	0
4	No i-Pr ₂ NEt	0	0
5	No light	0	0
6	PC is $[Ru(bpy)_3]Cl_2$ (P2)	29	9
7	PC is $Ir(ppy)_3$ (P3)	57	40
8	C2 catalyst	69	37
9^b	[A1] = 0.4 M, $[B1] = 0.4$ M, reaction	>99	83
10 ^c	Solar simulator	> 99	88
11^d	Adding 300 equiv. mole of DMPO	>99	0

^{*a*} Light irradiation (LED, $\lambda_{max} = 448$ nm). Conditions: [C1] = 1.0×10^{-4} M, [PC] = 1×10^{-5} M, [A1] = 1.5×10^{-1} M, [B1] = 2.0×10^{-2} M, [i-Pr₂NEt] = 1.0×10^{-1} M, solvent: 10 mL of CH₃OH under N₂ at room temperature. Reaction time: 6 h. Conversions of the substrate and the product yield were based on the initial concentration of B1. ^{*b*} [C1] = 1×10^{-5} M, [i-Pr₂NEt] = 2 M. ^{*c*} Solar simulator was used as the light source. ^{*d*} [DMPO] = 6.0×10^{-1} M.

Table 2 Scope of alkyl halides^a



^{*a*} Light irradiation (LED, $\lambda_{\text{max}} = 448$ nm). Conditions: [C1] = 1.0×10^{-4} M, [PI] = 1×10^{-5} M, [A1] = 1.5×10^{-1} M, [B1–B15] = 2.0×10^{-2} M, [i-Pr₂NEt] = 1.0×10^{-1} M, solvent: 10 mL of CH₃OH in N₂ at room temperature. Reaction time: 6 h. Product yields were based on the initial concentration of the alkyl halide. ^{*b*} Reaction was carried out at 45 °C, [A1] = 3.0×10^{-1} M, [R-X] = 3.0×10^{-2} M. Reaction time: 8 h. ^{*c*} (2-Cyclohexylvinyl)benzene (*E* form) was formed in 52% yield. ^{*d*} (2-Cyclohexylvinyl)benzene (*E* form) was formed in 45% yield.

temperature. Upon increasing the reaction temperature to 45 $^{\circ}$ C, the yield of **1a** increased to 91% for phenethyl chloride. Electron withdrawing substitution on the phenyl ring of phenethyl bromide decreased the yields of the products (**1e** and **1f**) which is



^{*a*} Light irradiation (LED, $\lambda_{max} = 448$ nm). Conditions: [C1] = 1.0×10^{-4} M, [P1] = 1×10^{-5} M, [A2-A11] = 1.5×10^{-1} M, [B1] = 2.0×10^{-2} M, [i-Pr₂NEt] = 1.0×10^{-1} M, solvent: 10 mL of CH₃OH in N₂ at room temperature. Reaction time: 6 h. Product yields were based on the initial concentration of B1.

probably due to the decreasing electron density of the phenethyl radical to lower their nucleophilicities, while the yields of 1e and 1f increased to 87% and 79%, respectively, by increasing the reaction temperature to 45 °C. Benzyl halides (X = Br, Cl), (bromomethyl)cyclohexane, and bromo- or iodocyclohexane also afforded the corresponding coupling products, 1g, 1h, and 1i, respectively.‡ The scope of the alkynylation of phenethyl bromide with various substitution patterns of phenylacetylene is also shown in Table 3. No large substituent effects on the phenyl ring of the alkynes (A2-A11) were seen in the product yield, and moderate to good yields of the coupling products were obtained.§ Finally, the advantage of the present photo-catalytic system being superior to conventional radical forming reagents, n-Bu₃SnH/azobisisobutyronitrile (AIBN), was investigated. Low yields of the products (1a, 1g, and 1h) were obtained as shown in Scheme 2. Undesired homo-coupling products from organic halides were also formed by this method.

The proposed reaction mechanism is shown in Scheme 3. The UV-vis spectral change indicated the formation of the Co(1) species of the B₁₂ complex by visible light irradiation (Fig. S2, ESI†). As the $E(L/L^-)$ value of $[Ir(dtbbpy)(ppy)_2]PF_6$ (E = -1.43 V vs. SCE in CH₃CN) is negative compared to that of $[Ru(bpy)_3]Cl_2$ (E = -1.30 V vs. SCE in CH₃CN),¹⁰ the use of $[Ir(dtbbpy)(ppy)_2]PF_6$ showed a superior yield of the product as the efficient reductive formation of Co(1) species by PS (entry 6 in Table 1). We already clarified the reductive quenching of **P1** by i-Pr₂NEt followed by the electron transfer to **C1** by transient photoluminescence measurements.^{8a} ¶ The nucleophilic attack of the formed Co(1)



Scheme 2 Reactions by an *n*-Bu₃SnH/AIBN system.



Scheme 3 Proposed mechanism

species initiates the reaction.^{6,11} We hypothesized that the B_{12} complex catalyzes the alkynylation reaction *via* a radical pathway during the initial part of the reaction. To support this mechanism, some mechanistic experiments were performed. First, a radical-clock experiment with 6-bromo-1-hexene (**B16**)⁶ verified the formation of the initial phenethyl radical **G** from the alkylated cobalt complex to form the cyclic coupling product **1j** with 61% yield *via* radical **H** followed by radical **I** in the reaction with the alkyne (Scheme 4a). Next, an ESR spin-trapping experiment was conducted



Scheme 4 Mechanistic investigations of the photocatalytic alkynylation reaction.

using 5,5-dimethyl-1-pyrroline-N-oxide (DMPO) as the radical trapping reagent. The ESR signal for the carbon-centered radical trapped by DMPO (g = 2.006, $A_N = 14.7$ G, $A_H = 21.2$ G) was observed during the photocatalytic reaction (Fig. S3, ESI[†]). Under this condition, DMPO fully inhibited the product formation (entry 11 in Table 1), which implied a radical pathway for the coupling reaction. Substituent effects on the phenyl ring of the phenethyl radical for products 1e and 1f in Table 2 could be explained by the decreasing electron density of the substrate radical, which underwent a nucleophilic attack on the alkyne. To elucidate the final step for the alkyne formation from radical E in Scheme 3 or I in Scheme 4a, the formation of hydrogen gas was analyzed by GC, and no hydrogen gas was detected by GC after the reaction (Fig. S4, ESI^{\dagger}), which excludes the β -elimination of radical E. Also no deuterium isotopic effect was observed for the deuterated phenylacetylene (A1-d), and 1a was formed in 85% yield (Scheme 4b), which is similar to the standard conditions. || Therefore, C-H bond cleavage on A1 is not the rate-determining step in the reaction. Finally, on-off light experiments were conducted to explore the radical propagation mechanism. A clear light dependence was observed for the reaction and radical propagation was unlikely. Based on these experiments, the B₁₂ catalyzed coupling reaction should proceed by the mechanism as shown in Scheme 3. Radical E should be oxidized to form carbocation F by the excited state of PS $(E(L^*/L^-) = 0.70 \text{ V} \text{ vs. SCE in CH}_3\text{CN for P1})^8$ and the energetically preferred deprotonation of F to form the final product. To help understand the deprotonation of the carbocation by i-Pr2NEt, we performed DFT calculations using the B3LYP functional combined with the 6-31G** basis. All the calculated energies and optimized structures are summarized in the ESI,† and the DFT calculations support the proposed mechanism of the energetically preferred deprotonation step (Fig. S28, ESI⁺).

In summary, we have developed a visible light-driven coupling reaction of alkyl halides with phenylacetylene derivatives for $C(sp^3)$ –C(sp) bond formation. An efficient reaction system by the dual catalyst under mild conditions was conducted. The B₁₂ complex worked as an excellent catalyst with a high turnover under light irradiation. On-going work in our laboratory is focused on the application of the dual catalyst to develop various organic synthesis methods with a green procedure.

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Conflicts of interest

There are no conflicts to declare.

Notes and references

‡ Bulky *t*-butyl bromide and (1-bromoethyl)benzene provided no desired cross-coupling product with **A1**.

§ A nitro-substituent on the phenyl ring of A1 provided no desired cross-coupling product with B1.

¶ The rate constant for the electron transfer between the photoexcited P1 (P1*) and i-Pr₂NEt is 7.0×10^8 M⁻¹ s⁻¹, while the electron transfer from P1* to C1 is not observed. See ref. 8*a*.

|| Time courses of reactions are shown in Fig. S27 (ESI[†]).

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