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Chemo- and Regioselective Synthesis of Alkynyl Cyclobutanes by Visible Light Photocatalysis

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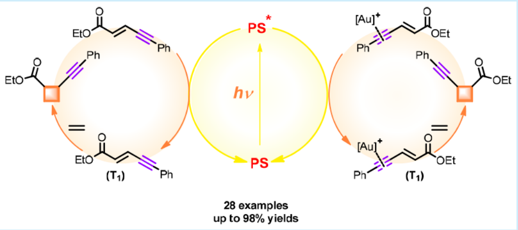
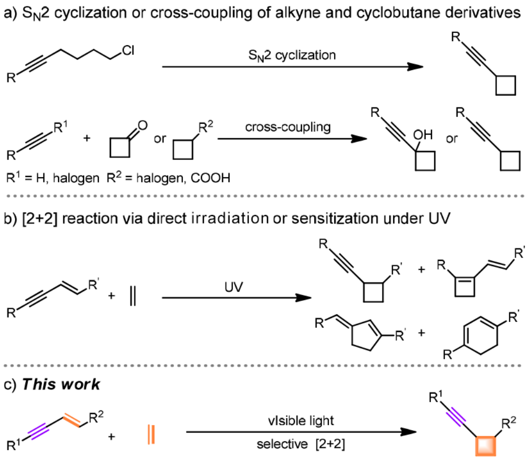
Supporting Information

ABSTRACT: Here is the first visible light catalytic intermolecular cross [2 + 2] cycloaddition of enynes with alkenes to alkynyl cyclobutanes established with good functional group tolerance and high reaction efficiency and selectivity. Detailed studies reveal that enynes, including nonaromatic ones, can be sensitized by *fac*-Ir(ppy)$_3$ via an energy transfer pathway. Addition of the Lewis acid PPh_3AuNTf_2 enables the cross photo[2 + 2] cycloaddition reaction to take place under both direct visible light irradiation or sensitization by $Ru(bpy)_3(PF_6)_2$.



Alkynyl cyclobutanes, structures in which a strained cyclobutane ring is connected to a potentially reactive acetylene unit, occupy an important place in organic chemistry because these structures can be readily transformed to many other useful and reactive molecular skeletons.[1] As illustrated in Scheme 1a, conventional syntheses of 1-alkynyl cyclobutanes involve transition-metal-catalyzed cross-coupling,[2] nucleophilic addition reactions,[3] and strong base-catalyzed intramolecular cyclizations of long-chain alkynyl halocarbons.[4] It is well-known that cyclobutanes can be readily constructed by light-induced [2 + 2] addition of olefins.[5] Based on this, we envisaged that irradiation of enynes in the presence of olefins would yield the above 1-alkynyl cyclobutanes (Scheme 1b). Such UV-irradiated cross addition reactions have been reported by Hopf *et al.*[6] However, these additions were often accompanied by other types of additions.[7] Only a few terminal and cyclic enynone gave [2 + 2] adducts as the sole products with moderate efficiency (Scheme 1b).[8]

Scheme 1. Synthesis of Alkynyl Cyclobutane



During the past few years, successful visible-light-induced photocycloadditions of aryl olefins, enones, and 1,3-dienes have been reported. In several of these studies, it was shown that triplet sensitization is a successful way to facilitate the reaction, even in an enantioselective fashion.[9] These studies motivated us to examine the photocycloaddition between an enyne and an olefin via visible-light-activated catalysis. We envisioned that by extending the conjugation of an alkene with an alkynyl substitution, the triplet energy of the substrate would be lowered. Complexation of the alkyne part with Lewis acids would possibly further decrease the triplet energy of the present system. Such a decrease in triplet energy would allow the use of visible-light-absorbing photosensitizers to accomplish the intermolecular cross [2 + 2] cycloaddition of an excited enyne with an olefin via an energy transfer pathway.

In the present work, we summarize our successful design for the highly efficient intermolecular cross [2 + 2] cycloaddition of enynes with olefins under visible light irradiation. To our knowledge, such a type of addition by visible light photocatalysis (VLPC) has not been reported. We have found that enynes, even the ones substituted with an aliphatic group, could be sensitized efficiently by 1 mol % of *fac*-Ir(ppy)$_3$ without any additive to react with terminal olefins to yield alkynyl cyclobutanes with high chemo- and regioselectivity. Various functional groups, including ester, ketone, aldehyde, carboxylic acid, amide, and phenyl sulfone, were tolerated. Addition of

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Lewis acids such as PPh_3AuNTf_2 enabled the [2 + 2] reaction to take place under both direct visible light irradiation and sensitization by a photocatalyst with lower triplet energy.

Initial efforts were focused on exploring the feasibility of a visible-light-induced energy transfer pathway for the cross [2 + 2] reaction of enyne. We synthesized the ethyl (*E*)-5-phenylpent-2-en-4-ynoate **1a** as a model substrate and explored its photophysical properties (Figure 1). UV−vis absorption spectra showed that **1a** has no obvious absorption above 400 nm. Direct excitation by 330 nm light at 77 K generated a moderate phosphorescence emission with λ_{max} at 532 nm (the emission in the region less than 470 nm is attributed to fluorescence; see Figure S1). The phosphorescence corresponds to a triplet energy of 53.7 kcal/mol for **1a**. Comparing the triplet energy of **1a** with that of commercial photocatalysts *fac*-$Ir(ppy)_3$ (55.2 kcal/mol)[10] and $Ru(bpy)_3(PF_6)_2$ (48.9 kcal/mol), it is clear that *fac*-$Ir(ppy)_3$ rather than $Ru(bpy)_3(PF_6)_2$ would sensitize the photoaddition of enyne with olefins via triplet−triplet energy transfer. As expected, the emission of *fac*-$Ir(ppy)_3$ was quenched by **1a** (Figure S2), and the lifetime was shortened from 1140 to 326 ns (Figure S3). This corresponded to a quenching constant of 5.80×10^9 s^{-1} M^{-1} (Figure S4). Considering the possibility that Lewis acid coordination would further decrease the triplet energy of the substrate, PPh_3AuNTf_2 was selected due to its strong interaction with alkynyl groups. As expected, the absorption of **1a** in the presence of PPh_3AuNTf_2 was red-shifted to 450 nm in comparison to that in its absence. Upon excitation, a new phosphorescence peak up to 610 nm was detected, which matches the triplet energy of the photocatalyst $Ru(bpy)_3(PF_6)_2$. Thus, we expect $Ru(bpy)_3(PF_6)_2$ to act as a suitable photosensitizer in the presence of PPh_3AuNTf_2.

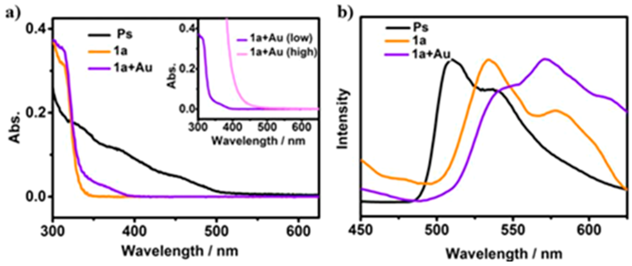
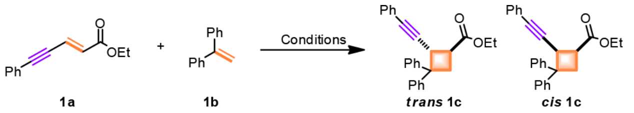


Figure 1. (a) Absorption spectra of *fac*-$Ir(ppy)_3$ (**Ps**), **1a**, PPh_3AuNTf_2, and **1a** + PPh_3AuNTf_2. $[Ir(ppy)_3] = 2.0 \times 10^{-5}$M; $[\mathbf{1a}] = 2.0 \times 10^{-5}$ M, $[PPh_3AuNTf_2]$ =2.0×10^{-5} M (high concentration: $[\mathbf{1a}] = 0.05$ M, $[PPh_3AuNTf_2] = 0.05$ M). (b) Normalized phosphorescence spectra of $Ir(ppy)_3$, **1a**, and **1a** + PPh_3AuNTf_2 at 77 K. Excitation wavelength was 330 nm for **1a**, 350 nm for **1a** + PPh_3AuNTf_2, and 450 nm for *fac*-$Ir(ppy)_3$.

With the information in mind, we first attempted the intermolecular cross [2 + 2] cycloaddition of ethyl (*E*)-5-phenylpent-2-en-4-ynoate **1a** with 1,1-diphenylethylene **1b** by using *fac*-$Ir(ppy)_3$ as the photocatalyst (Table 1). Irradiation of the above mixture in THF for 5 h provided alkynyl cyclobutane **1c** in 85% yield and 2:1 dr (entry 1; for more details about the optimization of solvent and dosage of olefin **1b**, see Table S1) (*trans*/*cis*, identified by the NOEDS spectra, Figures S13 and S14), accompanied by the homodimer formation of enyne **1a** as a byproduct. The experiments with pure (*E*)-**1a** and a mixture of (*E*)- and (*Z*)-**1a** (2:1) gave identical products (entry 2), suggesting that the geometry around the ene part of enyne does not control the product distribution. Control experiments established that light and photocatalyst were necessary; omitting any one of these components did not result in the product (entries 6 and 7). If the triplet energy is above that of **1a**, the reaction worked independent of the electrochemical potentials of the catalysts. In addition to *fac*-$Ir(ppy)_3$ ($E_{1/2}^{IV/*III} = -1.73$ V vs SCE), two other iridium photocatalysts, $Ir(ppy)_2(dtbbpy)(PF_6)$ ($E_{1/2}^{IV/*III} = -0.96$ V vs SCE) and $Ir[dF(CF_3)ppy]_2(dtbbpy)(PF_6)$ ($E_{1/2}^{IV/*III} = -0.89$ V vs SCE), having lower redox ability and similar triplet energy, performed well as sensitizers. In the presence of these two photocatalysts, the reaction proceeded smoothly to yield the product in 76 and 74% yields, respectively (entries 3 and 4). Consistent with the conclusion that the catalyst used in this study functions as a triplet sensitizer, no reaction occurred when $Ru(bpy)_3(PF_6)_2$ ($E_{1/2}^{III/*II} = -0.81$ V vs SCE) with a lower triplet energy but similar redox potential as $Ir(ppy)_2(dtbbpy)(PF_6)$ and $Ir[dF(CF_3)ppy]_2(dtbbpy)(PF_6)$ were used as the catalyst (entry 5).

Table 1. Optimization of Conditions[a,b]

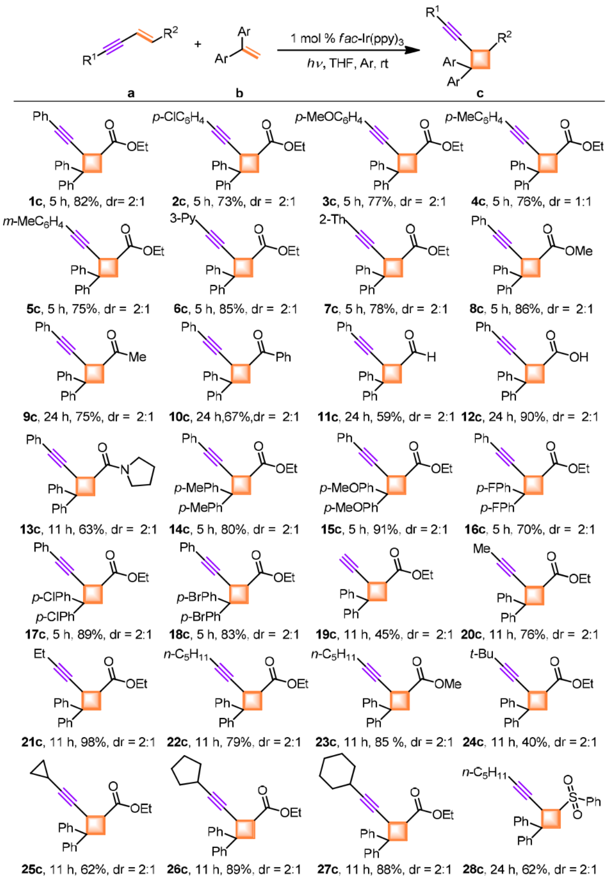


entry	photocatalyst	solvent	yield (%)	dr
1	*fac*-$Ir(ppy)_3$	THF	85	2:1
2[c]	*fac*-$Ir(ppy)_3$	THF	83	2:1
3	$Ir(ppy)_2(dtbbpy)(PF_6)$	THF	76	2:1
4	$Ir[dF(CF_3)ppy]_2(dtbbpy)(PF_6)$	THF	74	2:1
5	$Ru(bpy)_3(PF_6)_2$	THF	0	
6[d]		THF	0	
7[e]	*fac*-$Ir(ppy)_3$	THF	0	

[a] Conditions: 0.2 mmol (1 equiv) **1a** (*E*/*Z* = 2:1), **1b**, 1 mol % Photocatalyst, 2 mL solvent, Ar, blue LEDs, room temperature. [b] Yield and dr (*trans*/*cis*) was determined by ^1H NMR analysis of the unpurified reaction mixture using 1,1-diphenylacetonitrile as the internal standard, and the *trans* and *cis* diastereomers were identified on the basis of the NOEDS spectrum. [c] The absolute *trans*-**1a** (*E*/*Z* > 19:1) was used. [d] No *fac*-$Ir(ppy)_3$. [e] No light.

The generality of the above visible-light-induced energy transfer strategy was established by exploring the substrate scope of cycloaddition with *fac*-$Ir(ppy)_3$ as the photosensitizer. Examination of the reactivity of numerous enynes and alkenes (Scheme 2) led to the following observations: (a) Good yields of products were obtained regardless of the substituents on the yne part of the enyne. Alteration of the para substituent on the phenyl group present on the yne part (**2c**−**5c**) changed neither the reactivity nor the yield of the product. (b) Similar to aryl-substituted enynes, heteroaryl-substituted ones such as ethyl-(*E*)-5-(pyridine-3-yl)pent-2-en-4-ynoate and ethyl-(*E*)-5-(thiophene-2-yl)pent-2-en-4-ynoate also readily afforded the corresponding products with 85 and 78% yields (**6c**−**7c**). (c) On the ene side of enynes, a variety of substituents are tolerated. For example, the ester group of **1a** can be readily replaced by a ketone, aldehyde, amide, and carboxylic acid group without losing reactivity (**8c**−**13c**). The carboxylic acid derivative was converted into the [2 + 2] adduct in 90% yield (**12c**). (d) The above photoaddition also tolerated a number of diarylethylene derivatives (**14c**−**18c**) as reaction partners; both electron-donating and electron-withdrawing groups showed excellent reactivity. (e) An even more important observation relates to the fact that the addition works even with nonaromatic enynes (**19c**−**28c**). Although an unsubstituted enyne (**19c**) gave a reduced yield of the addition product with diphenylethylene

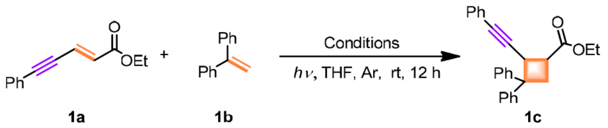
Scheme 2. Scope of Substrates



(45%), introduction of an alkyl group at the terminal position generally increased the yield to well above 70% (**20c**–**23c**). The only exception was the *tert*-butyl-substituted enyne **24c**. Both aliphatic and alicyclic substituents were tolerated at the yne end. Overall, the above VLPC cycloaddition was found to be general, and the yields of the alkynyl cyclobutanes were good.

As argued above, anticipating that addition of PPh_3AuNTf_2 would further decrease the triplet energy of **1a**, we irradiated a mixture of **1a**, diphenylethylene, $Ru(bpy)_3(PF_6)_2$, and PPh_3AuNTf_2. The cycloadducts were obtained in 53% yield and 2:1 dr, as shown in Scheme 3. Neither the yield nor the dr value changed when the initial isomer ratio was changed from *E*/*Z* 19:1 to *1:19*. Interestingly, we found that the dimerization, albeit in low yield, could be achieved when a mixture of **1a**, diphenylethylene, and PPh_3AuNTf_2 were directly irradiated. In this case, the product yield was dependent upon the initial isomer (Scheme 3). We speculate that triplet generation might have been favored by the heavy Au atom.

Scheme 3. [2 + 2] Photocycloaddition of Enyne by Other Photocatalysts



Condition **A**:
1 mol % $Ru(bpy)_3(PF_6)_2$
2.5 mol % PPh_3AuNTf_2

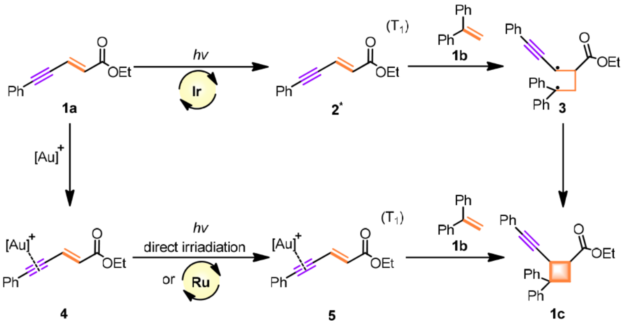
E/Z >19:1 Yield =53%, dr = 2:1
Z/E >19:1 Yield =53%, dr = 2:1

Condition **B**:
2.5 mol % PPh_3AuNTf_2

E/Z >19:1 Yield =8%, dr = 1:1
Z/E >19:1 Yield =28%, dr = 1:1

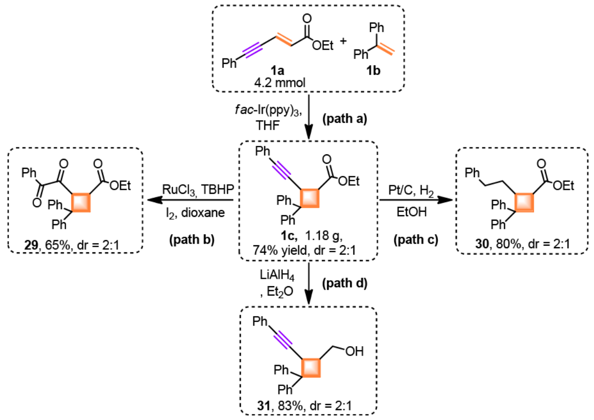
The above experimental data could be understood on the basis of the mechanism illustrated in Scheme 4. When a mixture of enyne, alkene, and *fac*-$Ir(ppy)_3$ is irradiated with blue light, the last one absorbs the light and populates the enyne to the excited triplet state via the well-known triplet–triplet energy transfer pathway.[9b] The triplet enyne reacts with the ground-state alkene to yield the diradical **3** that closes to yield the cyclobutene. This reaction also occurs in the presence of the Lewis acid PPh_3AuNTf_2. Under this condition, PPh_3AuNTf coordinates with the enyne to red-shift its absorption and lower its triplet energy. Such a complexation allows the direct irradiation with visible light and permits the use of normally inactive $Ru(bpy)_3(PF_6)_2$ to act as a triplet sensitizer.

Scheme 4. Proposed Mechanism



To illustrate the synthetic application of this reaction further, a gram-scale reaction of enyne **1a** and olefin **1b** was conducted in the presence of 1 mol % of *fac*-$Ir(ppy)_3$. The reaction proceeded smoothly to give the isolated product **1c** in 74% yield with 2:1 dr (Scheme 5, path a). Furthermore, **1c** could be converted to related 1,2-dicarbonyl cyclobutane in 65% yield via $RuCl_3$/TBHP oxidization (**29**, Scheme 5, path b).[11] The alkynyl group in **1c** could be reduced to an alkyl[12] group by Pt/C under H_2 (1 atm) in 80% yield (**30**, Scheme 5, path c). Treatment of **1c** with $LiAlH_4$[13] afforded the cyclobutylmethanol **31** in 83% yield (Scheme 5, path d).

Scheme 5. Synthetic Applications



In summary, we have established the occurrence of a highly efficient [2 + 2] reaction between an enyne and an alkene to yield alkynyl cyclobutanes with high chemo- and regioselectivity initiated by visible light. The reaction tolerated various functional groups such as ester, ketone, aldehyde, carboxylic acid, amide, and phenyl sulfone. Both aryl- and alkyl-substituted enynes showed high reactivity and gave the corresponding cyclobutanes in high yields. This simple and efficient method provides a new method for the synthesis of alkynyl cyclobutanes. Control and spectroscopic experiments established the reaction to be initiated by an energy transfer process. By lowering the triplet energy of the enyne through complexation with the Lewis acid PPh_3AuNTf_2, the utility of lower triplet energy sensitizers such as $Ru(bpy)_3(PF_6)_2$ in this reaction has been established. Further studies directed toward achieving chiral selectivity during this valuable VLPC [2 + 2] reaction are underway in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02934.

Experimental and NMR data (PDF)

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Notes

The authors declare no competing financial interest.

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