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Photochemistry Hot Paper

[2+2] Cycloaddition of 1,3-Dienes by Visible Light Photocatalysis**

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Abstract: *[2+2] Photocycloadditions of 1,3-dienes represent a powerful yet synthetically underutilized class of reactions. We report that visible light absorbing transition metal complexes enable the [2+2] cycloaddition of a diverse range of 1,3-dienes. The ability to use long-wavelength visible light is attractive because these reaction conditions tolerate the presence of sensitive functional groups that might be readily decomposed by the high-energy UVC radiation required for direct photoexcitation of 1,3-dienes. The resulting vinylcyclobutane products are poised for a variety of further diversification reactions, and this method is consequently expected to be powerfully enabling in the synthesis of complex organic targets.*

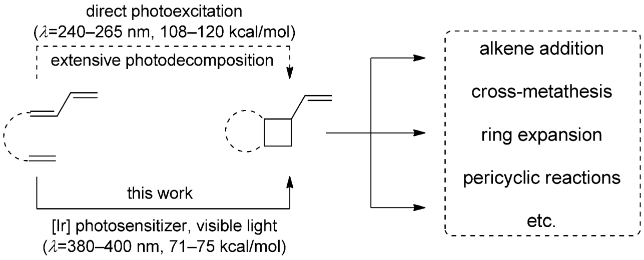

Figure 1. [2+2] Cycloadditions of 1,3-dienes provide access to synthetically versatile vinylcyclobutanes.

Photochemical reactions provide uniquely direct access to molecular structures that are often difficult to synthesize using other reaction types.[1] The utility of photochemical [2+2] cycloaddition reactions, in particular, has become widely appreciated both because of the prevalence of cyclobutanes in a diverse family of bioactive natural products[2] and because of the utility of strain-releasing fragmentation reactions in the assembly of larger-ring systems.[3] Over the past several years, our research group has taken advantage of the unique properties of transition metal chromophores to develop a variety of photocycloaddition reactions that can be accomplished with visible light.[4,5] In examining synthetic targets to demonstrate the utility of visible light induced photocycloadditions, we realized that [2+2] cycloadditions of 1,3-dienes would afford versatile vinylcyclobutanes that are ideally poised for diverse synthetic elaborations by manipulation of their alkenyl substituents (Figure 1). Notably, only a few examples of [2+2] diene–olefin photocycloadditions have been reported in the context of total synthesis.[6,7] This stands in sharp contrast to the multitude of syntheses that feature analogous [2+2] enone–olefin photocycloadditions. One important reason for this discrepancy is that the direct photoexcitation of dienes requires irradiation with very high-energy UVC light (ca. $\lambda = 240$–265 nm).[8] These high-energy photons (108–120 kcal mol^{-1}) are incompatible with the highly functionalized organic substrates generally required for late-stage synthetic applications. The ability to promote the [2+2] cycloaddition of dienes with low-energy visible light (< 75 kcal mol^{-1}) would thus greatly increase the versatility of this vastly underexploited transformation and facilitate its use in synthesis.

Most of the recent interest in visible light mediated photochemical reactions has focused on photoinduced redox activation of organic functional groups using transition metal photocatalysts such as $[Ru(bpy)_3]^{2+}$ (**1**, Table 1).[5] We have reported a complementary approach that uses iridium complex **2** to perform the [2+2] cycloaddition of a variety of electronically diverse styrenes via an energy-transfer mechanism.[9] We speculated that this strategy might also be capable of activating dienes towards [2+2] cycloaddition reactions using visible light. Although dienes are more resistant to one-electron oxidation than styrenes,[10] their lowest-lying triplet states are quite similar in energy (ca. 55–60 kcal mol^{-1}).[11] We reasoned, therefore, that the same visible light activated photocatalysts that proved to be effective for sensitization of styrenes might also activate simple 1,3-dienes and could thus provide access to a wide range of synthetically valuable vinylcyclobutane products.

Triene **3** was selected as a model substrate for our preliminary investigations (Table 1). The direct photoexcitation of this compound requires short-wavelength UVC light, and as expected, irradiation at $\lambda = 254$ nm resulted in rapid and complete decomposition after 30 min (entry 1), consistent with the destructive nature of these high-energy photons. No trace of the desired [2+2] cycloadduct could be observed even at partial conversion (entry 2). In contrast, we were pleased to find that vinylcyclobutane **4** was formed in high yield upon irradiation of **3** with a household CFL bulb in the presence of 1 mol% of iridium complex **2** (entry 3).[12] Importantly, we did not observe any products arising from competitive electrocyclization or [4+2] cycloaddition events under these conditions. The observation that **1**, which possesses a substantially lower triplet energy (47 kcal mol^{-1}),[13] fails to promote this reaction (entry 4) is consistent with the proposed role of **2** as a triplet sensitizer rather than a photoredox catalyst. Finally, no reaction occurred in the

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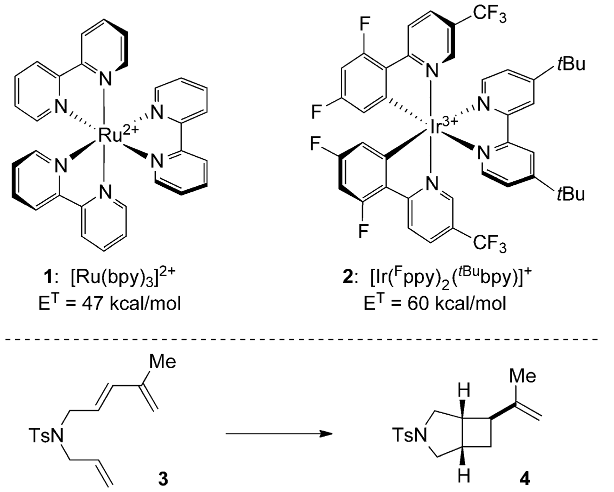
Table 1: Control studies for visible light promoted diene–olefin [2+2] cycloadditions.[a]



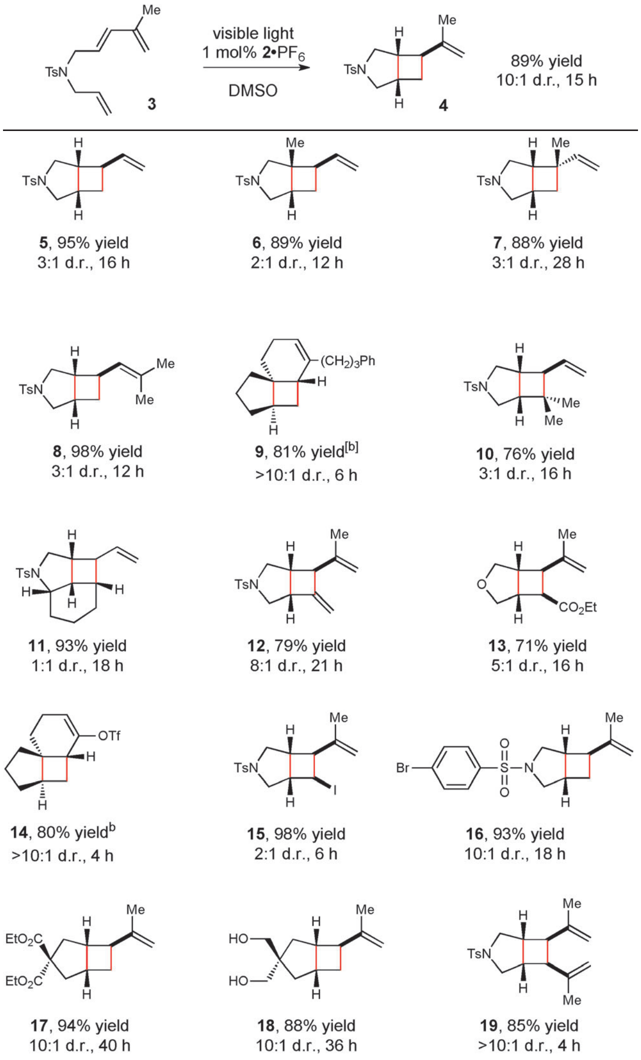
Entry	Conditions	Conversion [%]	Yield [%]
1[b]	*hν* (UVC), 30 min	100	0
2[b]	*hν* (UVC), 10 min	63	0
3	1 mol% **2**·PF_6, *hν* (visible), 15 h	100	89
4	1 mol% **1**·$(PF_6)_2$, *hν* (visible), 15 h	12	0
5	*hν* (visible), 15 h	6	0
6	1 mol% **2**·PF_6, no light, 15 h	0	0

[a] Yields determined by ^{1}H NMR spectroscopic analysis of the unpurified reaction mixtures using an internal standard. Reactions conducted in DMSO unless otherwise noted. [b] Reactions conducted in MeCN. Ts = 4-toluenesulfonyl.

absence of either light or the photocatalyst (entries 5 and 6), in line with our observations in studies of similar systems.

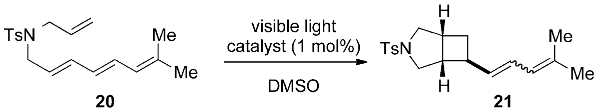
Table 2 summarizes experiments probing the effect of substrate modifications on the [2+2] cycloaddition. Collectively, these studies demonstrate that the scope of this reaction is broad. Substrates bearing substitution at each position of the diene underwent smooth reaction (**4**, **6**–**9**, and **14**), including systems that produce cyclobutanes bearing quaternary centers (**6**, **7**, **9** and **14**). Similarly, a wide range of structurally varied alkenes served as suitable partners in this cycloaddition, and their reactions proved to be relatively insensitive to their electronic and steric properties (**10**–**13**, **15**). Although we focused on sulfonamide-tethered substrates because of their ease of synthesis, ether-containing and all-carbon tethers provide good yields as well (**9**, **13**, **14**, **17**, and **18**). The reactions of cyclic dienes occurred at somewhat faster rates (**9** and **14**), which is consistent with the prevention of energy-wasting *cis*–*trans* diene isomerizations, although a small amount of an inseparable Diels–Alder side product was also produced in these reactions. Most notably, the visible light induced cycloaddition was quite tolerant of a wide range of functional groups, including vinyl iodide and aryl bromide bonds that could be sensitive to either direct photodecomposition or photoredox-induced dehalogenation[14] (**15** and **16**). Other functional groups that are easily tolerated include esters, triflates, and unprotected alcohols (**13**, **14**, **17**, **18**), all of which provide useful synthetic handles for further elaboration.

Table 2: Investigation of structural diversity in the visible light-promoted [2+2] cycloaddition of 1,3-dienes.[a]



[a] Unless otherwise noted, we report isolated yields as averaged values from two reproducible experiments. Diastereomer ratios were determined by ^{1}H NMR spectroscopic analysis of the unpurified reaction mixtures. [b] Yields of the [2+2] cycloadduct determined by ^{1}H NMR spectroscopic analysis using an internal standard.

We also investigated the sensitization of higher-order conjugated polyenes (Scheme 1). Substrate **20** underwent high-yielding cycloaddition to **21** upon irradiation in the presence of **2**·PF_6; however, the product was formed as a 1:1 mixture of *E* and *Z* isomers. The poor geometric selectivity is attributable to unproductive photosensitization and subse-



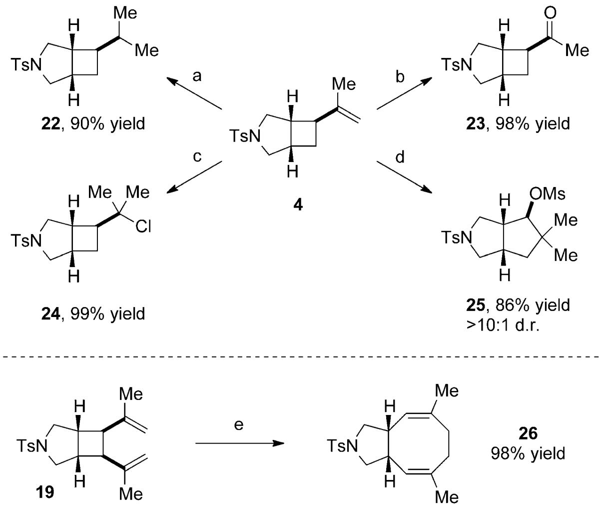
Ir conditions: 1 mol% **2**•PF_6, 18 h: 96% yield, 1:1 *E*/*Z*, 2:1 d.r.

Ru conditions: 1 mol% **1**•$(PF_6)_2$, 4 h: 93% yield, >10:1 *E*/*Z*, 2:1 d.r.

Scheme 1. [2+2] Cycloaddition of higher-order polyenes. DMSO = dimethylsulfoxide.

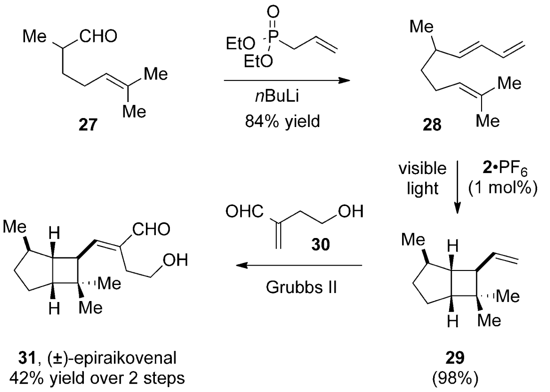
quent isomerization of the product diene. Speculating that a photocatalyst possessing a lower-energy triplet state might be able to selectively activate the more conjugated triene but not the higher-energy diene, we conducted a photocycloaddition in the presence of $[Ru(bpy)_3]^{2+}$ (**1**). Indeed, under these reaction conditions, the cycloaddition proceeds with excellent geometric selectivity. These studies highlight the versatility of energy transfer as a mode of photoactivation; the availability of a vast number of well-characterized transition-metal photocatalysts[15] with long-lived excited states spanning a wide range of triplet excited state energies is a distinct advantage of this approach.

The vinylcyclobutane motif readily accessible by this method is synthetically powerful because it is amenable to a diverse set of high-yielding functionalization and rearrangement reactions (Scheme 2). For example, cycloadduct **4** undergoes hydrogenation to afford **22** as well as ozonolysis to give cyclobutyl methyl ketone **23**. The vinylcyclobutane can be elaborated by a variety of acid-promoted processes as well. The addition of HCl across the alkene occurs in quantitative yield (**24**) without fragmentation of the cyclobutane. In contrast, methanesulfonic acid initiates a cationic ring expansion that generates the corresponding cyclopenta[c]pyrrole ring system (**25**). Finally, divinylcyclobutane **19** provides access to ring-expanded cyclooctadiene **26** in excellent yield through a facile thermal Cope rearrangement.



Scheme 2. Synthetic elaboration of vinylcyclobutane products. a) H_2, 10% Pd/C, MeOH, RT; b) 1. O_3, CH_2Cl_2, −78 °C 2. DMS; c) HCl (2 M Et_2O), CH_2Cl_2, RT; d) $MeSO_3H$, CH_2Cl_2, RT; e) Benzene, 80 °C. DMS = dimethylsulfide.

The availability of complexity-building reactions of vinylcyclobutanes suggests that the ability to perform [2+2] cycloadditions of a structurally diverse set of dienes should be an enabling strategy in the synthesis of many complex organic targets. To highlight this feature, we designed a concise and modular synthesis of the cyclobutane-containing natural product (±)-epiraikovenal[16] (Scheme 3). The diene precursor (**28**) to the key photochemical step is accessible by Horner–Wadsworth–Emmons olefination of aldehyde **27**. Subsequent photocycloaddition proceeds in high yield to generate the cyclobutane-containing carbocyclic core of the natural product (**29**). The unpurified product of the cycloaddition was then subjected to cross-metathesis with enal **30** to deliver fully functionalized (±)-epiraikovenal (**31**) in 42 % yield over these two steps.



Scheme 3. Modular synthesis of (±)-epiraikovenal.

In summary, iridium photocatalyst **2** enables the [2+2] photocycloaddition of a structurally diverse range of 1,3-diene substrates using visible light irradiation. The low-energy photons involved in this process are tolerant of a variety of common functional groups that would be prone to decomposition by the significantly higher-energy UVC wavelengths required for direct photoexcitation of 1,3-dienes. We expect that this greater functional group compatibility coupled with the range of diversification reactions available to vinylcylobutanes will facilitate the exploration of [2+2] diene–olefin cycloadditions in the context of complex target-oriented organic synthesis. Studies along these lines are underway in our laboratory.

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[12] The reaction time can be significantly reduced by irradiation with a higher-intensity purple LED light source. Under these reaction conditions, **1** is converted into **2** in 90% yield (10:1 d.r.) after 7 h. However, household CFL bulbs were generally used to represent more readily accessible consumer light sources.

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