

Vinylcyclopropane [3+2] Cycloaddition with Acetylenic Sulfones Based on Visible Light Photocatalysis

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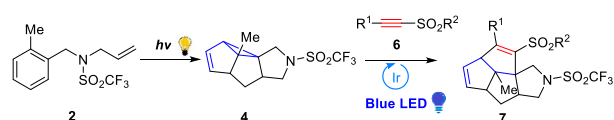
ABSTRACT: We describe the first intermolecular visible light [3+2] cycloaddition reaction being performed on a *meta* photocycloadduct employing acetylenic sulfones. The developed methodology exploits the advantages of combining UV and Visible-light in a two-step sequence that provides a photogenerated cyclopropane which, through a strain-release process, generates a new cyclopentane ring while increasing significantly the molecular complexity. This strategy could be extended to simpler vinylcyclopropanes.

Functionalized five-membered carbocyclic rings containing contiguous stereocenters are found in a wide array of natural products with diverse biological activities.¹ Therefore, simple and efficient methods to access highly substituted cyclopentanes and cyclopentenones within a polycyclic framework are particularly desirable in current organic and medicinal chemistry research.² One major general strategy to access them involves [3+2] cycloadditions, a powerful method that in a single step allows the formation of two new σ bonds and of vicinal quaternary centers.³ Vinylcyclopropanes (VCPs) represent an important class of reactive cyclopropane that can participate in this cycloaddition as three-carbon synthons, especially if they bear electron withdrawing groups on the cyclopropane ring.⁴ However, the use of non-activated VCP as a good intermolecular cycloaddition partner is still limited. In particular, the use of Rh catalysts⁵ is the most developed strategy for cycloadditions of non-activated VCPs and to find other catalyst systems and protocols that can exploit a wider range of VCP reactivity patterns remains a challenge. The merging of visible-light photocatalysis with the [3 + 2] cycloaddition involving VCPs already proved useful in strain-releasing fragmentation reactions in the assembly of larger-ring systems, but mainly using activated cyclopropanes as the substrates. Most examples reported are based on electron transfer (ET) photoredox processes,⁶ while transformations proceeding through energy transfer (EnT) are relatively underdeveloped.⁷ The broad substrate scope, often relatively independent of the electronic nature, makes the energy transfer process attractive when a broad substrate scope is desired.

Considering the lack of examples of intermolecular transition metal-catalysed visible light [3+2] cycloadditions involving nonactivated VCPs through EnT, we studied the scope of the same UV-driven strain-promoted/visible light strain-releasing sequence employed in our previous work on cyclopropyl ketones⁸ by using *meta*-photoproducts bearing a vinylcyclopropane substructure as substrates in a visible light-mediated intermolecular [3+2] cycloaddition (Scheme 1). This strategy which has gradually gained attention from the synthetic community⁹ consists of using the inherent ring-strain of the photogenerated intermediate as a thermodynamic driving force for the subsequent ring expansion. In other words, the first, UV light induced transformation provides a complex fused ring skeleton that is otherwise difficult to obtain.¹⁰ This *meta*-photoproduct is prone to undergo an irreversible ring opening due to the intrinsic strain of the three-membered ring.¹¹ This feature will

be exploited in the second, visible light induced transformation by reacting with an alkyne in a [3+2] cycloaddition reaction resulting in the formation of a new complex tetracycle.

Scheme 1. UV and visible light activation sequence

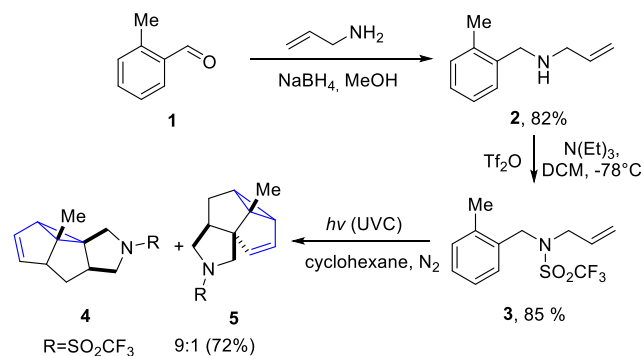


In general, non-activated alkynes display low reactivity in this type of cycloadditions, initial results between the *meta*-photoproduct **4** and simple alkynes with different catalytic systems showed no reactions. After much optimisation, we found the use of acetylenic sulfones to be an attractive alternative. The sulfone group lowers the LUMO energy of the adjacent π -bond increasing their reactivity as dienophiles while providing the means for controlling the regiochemistry of the cycloaddition.¹² Furthermore, the sulfone moiety can be removed by different methods making the acetylenic sulfones useful reagents for a variety of cycloadditions.¹³

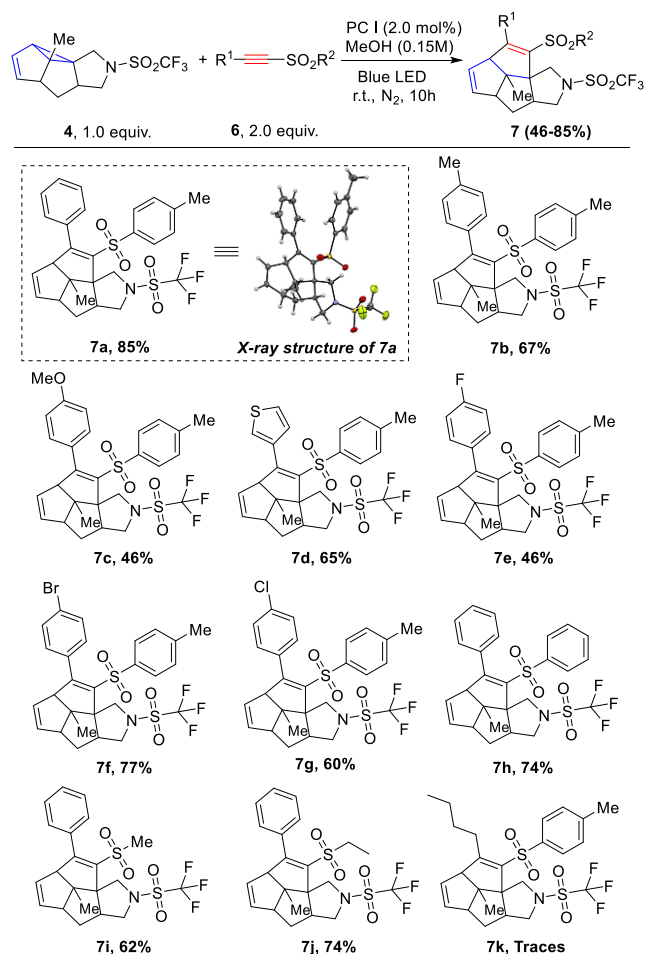
RESULTS AND DISCUSSION

Our test of the new design started with the photo-induced intramolecular arene-olefin *meta*-cycloaddition of the *N*-allyl-1,1,1-trifluoro-*N*-(2-methylbenzyl)methanesulfonamide **3** which was synthesized in two steps: a reductive amination of 2-methyl-benzaldehyde (**1**) with allylamine, followed by the reaction with trifluoromethanesulfonic anhydride. The irradiation of **3** in anhydrous cyclohexane furnished two isomeric *meta*-photocycloadducts in 72% yield (linear: angular, ratio: 9:1) (Scheme 2).

Scheme 2. Preparation of the *meta*-photoproducts **4**



Scheme 3. Substrate scope of the formal [3+2] cycloaddition.^a



^aIsolated yield.

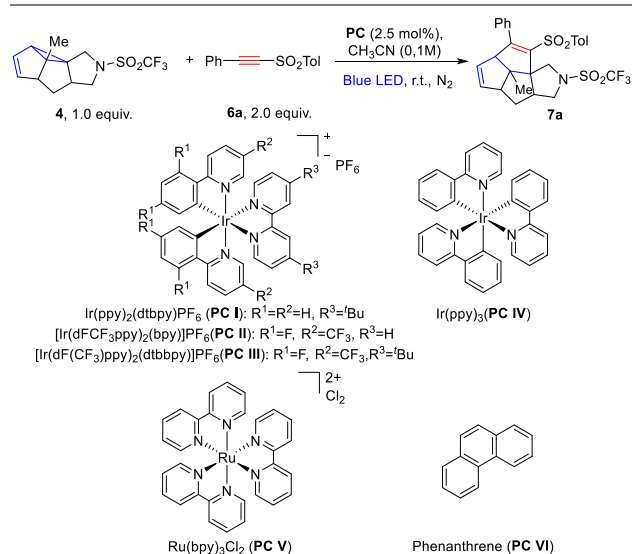
The acetylenic sulfones **6** as reaction partners were prepared in a two-step synthesis. The first step is the preparation of the Intermediates β -iodovinyl sulfones using either the cerium(IV) ammonium nitrate (CAN) mediated reaction of aryl sulfinates and sodium iodide with alkynes¹⁴ or the iodine-promoted reaction of the same substrates using water as solvent.¹⁵ The second step is the dehydroiodination of the β -iodovinyl sulfones with potassium carbonate under reflux to afford the corresponding acetylenic sulfones in relatively good yields (See Supporting information (SI)).¹⁴

The screening of various photocatalysts for the [3+2] photocycloaddition with visible-light was performed on *meta* photoproduct **4** and the acetylenic sulfone **6a** as the coupling partners (SI, Table S1). The desired product **7a** was obtained in appreciable yields (53% and 63%, respectively) when employing [Ir(ppy)₂(dtbbpy)]PF₆ (**PC I**, 2.5 mol%) and phenanthrene (**PC VI**, 100 mol%). In further optimization studies (SI, Tables S2, S3 and S4), the yield of **7a** could be increased to 85% when employing **PC I** with concomitant reduction of the catalyst loading to 2.0 mol% when using 2 equivalents of **6a**. Moreover, the cycloaddition proceeded with higher yields in polar solvents and higher concentration (0.15 M in CH₃OH).

Having optimized the reaction conditions, the scope of the synthesized alkynyl sulfones **6** (Scheme 3) was explored next. Substrates bearing electron-neutral, electron-rich, and electron-withdrawing aromatic rings were found to be suitable substrates. Alkyl groups on the sulfone moiety also provided the desired product in moderate to good yields (**7i** and **7j**). However, aromatic groups at the triple bond were required for the reaction to proceed successfully; substrate **6k** featuring a butyl-substituted alkynyl sulfone gave no reaction.

At this point, the essential factors governing the catalyst reactivity used in this reaction were investigated by analysing the results of the screening (SI, Table S1). To distinguish the two possible mechanisms, enT or ET, the redox potentials, and the calculated triplet energy of the tricyclic **4** were compared with those of the catalysts (Table 1 and SI, Table S7).

Table 1. Evaluation of photocatalysts in the [3+2] cycloaddition



Entry	PC	E _{1/2} (M ^{•+} /M ^{•-})/E _{1/2} (M [•] /M ⁻) (V vs SCE)	E _T (kcal/mol)	Yield (%) ^a
1	VI ^b	-2.10/+1.27	61.9	63
2	III	-0.89/+1.21	60.1	49
3	II	-1.00/+1.32	60.0	51
4	IV	-1.73/+0.31	55.2	49
5	I	-0.96/+0.66	49.2	53
6	V	-0.81/+0.77	46.0	traces

^a isolated yields. ^b 100 mol% of catalyst loading and UV/vis CFL bulb was used.

In the cyclic voltammograms of **4** (SI, Figure S6), oxidation and reduction features were observed with half-peak potentials of +1.96 V vs SCE and -1.65/-1.34 V vs SCE, respectively. Analyzing the reducing power of the catalyst **PC IV** (entry 4)¹⁶ and **PC VI** (entry 1)¹⁷ after excitation with that of **4** reveals that an oxidative quenching is feasible. However,

the reduction potentials of the tricycle are not sufficient to be reduced by the photoexcited states of the catalyst **PC V** (entry 6)¹⁸ or the other Iridium catalysts (entries 2-3, 5).¹⁹ Likewise, a reductive quenching could be ruled out based on the oxidation potentials of all the catalysts. On the other hand, there is no clear correlation between the triplet energies of the catalysts or photosensitizers and the reaction yield, making a Förster resonance energy transfer (FRET or sensitization) also difficult. The Gibbs free energy of each reaction intermediate was predicted using density functional theory (DFT) (Scheme 4).²⁰ While the reaction follows an overall exergonic pathway, releasing 48.9 kcal mol⁻¹ of energy, the triplet energy of **4** (59.1 kcal/mol) is considerably higher than those of **PC I** and **PC IV** (entries 4 and 5) but is low enough for the rest of iridium catalysts and for **PC VI**. Although there is no compelling evidence for an energy transfer process based on these results, the sensitization mechanism is supported by direct excitation of the VCP moiety by UV irradiation of **4**, giving rise to **7a** in 27% yield (See SI).²¹ The energy-transfer pathway was also supported by the observation that the reaction worked better in polar solvents. Charged radical ion intermediates, possibly generated through electron transfer, can be strongly stabilized in polar media.

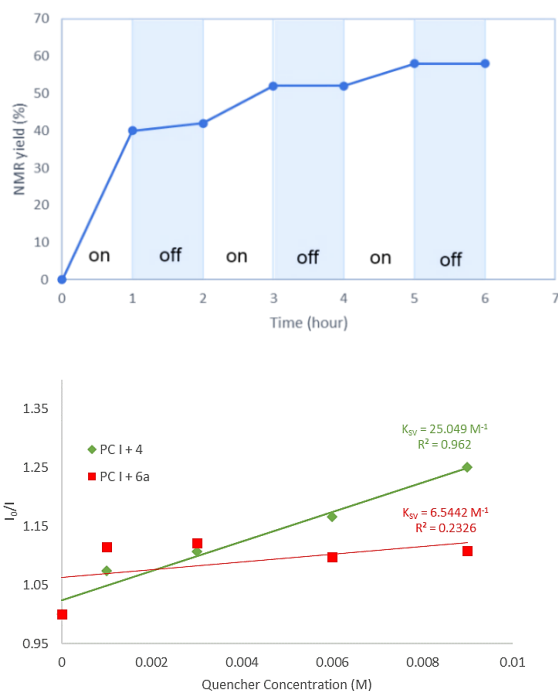


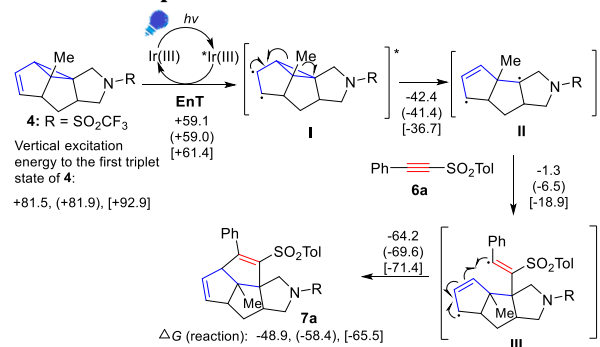
Figure 1. Mechanistic studies. (top), light on/off experiment (bottom), Stern–Volmer luminescence quenching experiments using **PC I** and variable concentrations of substrate **4** and **6a** in CH₃OH.

Several control experiments were performed to gain insight into the reaction mechanism. First, radical trapping using (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) completely inhibits the reaction, indicating it may proceed through a radical pathway. To determine whether the reaction involves an efficient²² radical chain mechanism, we

performed a light on-off experiment showing no product formation in the dark phases (Figure 1, top). Stern–Volmer quenching experiments on **PC I** revealed that the fluorescence of the catalyst could be quenched by **4**, suggesting an electron or energy transfer from the excited triplet state of the catalyst (Figure 1, bottom).

Accordingly, we propose a catalytic cycle as shown in Scheme 4. First, **PC I** acts as a sensitizer, transferring energy from its ³MLCT state to the vinylcyclopropane moiety in **4**, generating the triplet state of the latter, which undergoes a rearrangement followed by a radical addition of the acetylenic sulfone to generate the intermediate **III**. A subsequent ring-closure reaction affords the final tetracycle **7**. The occurrence of radical intermediate **III** is supported by the finding that aromatic substituents at R¹ are required for the reaction to proceed.

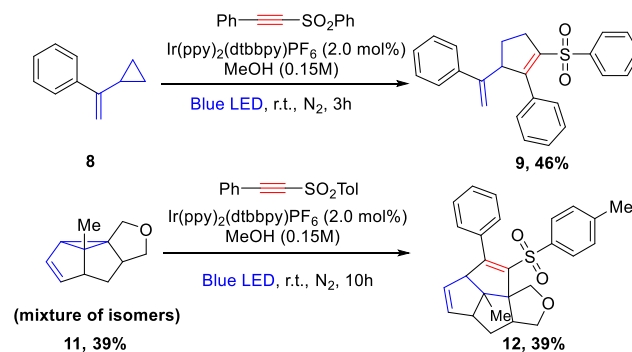
Scheme 4. Proposed mechanism



The reported adiabatic energy differences obtained with different functionals are given in kcal mol⁻¹ (no bracket: (U)B3LYP, parentheses: (U)CAM-B3LYP, square bracket: (U)M06-2X).

To further corroborate that only the vinylcyclopropane substructure of **4** is involved in the mechanism of this reaction, experiments with different substrates were performed. The [3+2] cycloaddition with the (1-cyclopropylvinyl)benzene (**8**) and the *meta* photoproduct **11** (used as an inseparable mixture of isomers without further purification) yielded the expected products in 46 and 39% yield, respectively (Scheme 5). Therefore, the procedure is likely applicable to other products of intra- or intermolecular photocycloadditions and permits the construction of complex skeletons in only two consecutive photochemical transformations.

Scheme 5. Alternative substrates in the [3+2] photocycloaddition



CONCLUSIONS

In conclusion, a visible light-mediated [3+2] cycloaddition of *meta*-photoproducts and acetylenic sulfones has been developed. Catalytic amounts of [Ir(ppy)₂(dtbbpy)]PF₆ presumably act as a triplet sensitizer. The methodology highlights the power of a consecutive UV / visible light activation sequence involving the generation of a strained intermediate and subsequent catalytic strain release.

ASSOCIATED CONTENT

Experimental procedures, detailed mechanistic studies, characterization data, X-ray crystallographic data for **7a** and NMR spectra (PDF)

Accession Codes

CCDC 2112151 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

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