Intermolecular [2+2] Photocycloaddition of β-Nitrostyrenes to Olefins upon Irradiation with Visible Light

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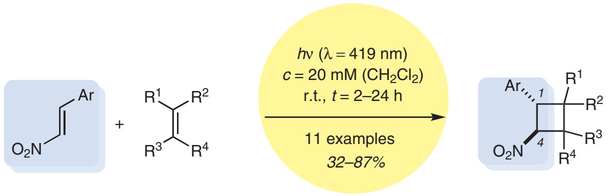
Dedicated to Victor Snieckus, a dear colleague and friend, on the occasion of his 80th birthday



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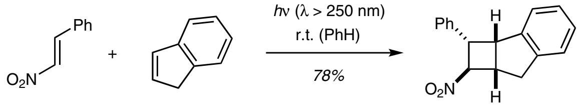
Abstract The title compounds were found to undergo a [2+2] photocycloaddition with olefins at λ = 419 nm in CH_2Cl_2 as the solvent. The resulting cyclobutanes were isolated in yields of 32–87% (11 examples) and showed a defined relative configuration at C1/C4 in the major diastereoisomer (nitro and aryl *trans*). The analysis of side products and triplet sensitization experiments support a mechanistic scenario in which a 1,4-diradical is formed as a key intermediate.

Key words cycloaddition, cyclobutanes, diastereoselectivity, nitro compounds, photochemistry, stereoselective synthesis, umpolung, visible light

Although [2+2] photocycloaddition chemistry[1] originates historically[2] from experiments performed with visible light, the advent of artificial UV light sources led – starting in the middle of the 20th century – to the almost exclusive use of short-wavelength (λ = 250–380 nm) irradiation in all areas of photochemistry. Interest in reactions that were promoted by long-wavelength (λ > 380 nm) irradiation was spurred in the 1970s and in the 1980s by the desire to find suitable energy storage systems mainly based on the [2+2] photocycloaddition of norbornadienes to quadricyclenes.[3] Aromatic carbonyl compounds[4] and transition-metal salts[5] were found to act as triplet sensitizers in this transformation allowing the reaction to occur with visible light. More recently, triplet energy sensitization has been employed for enantioselective[6] [2+2] photocycloaddition reactions that are promoted by visible light[7] in the presence of an appropriate sensitizer.[8] In the context of our work on the activation of chromophors by Lewis or Brønsted acids,[9] we became interested in the photochemistry of nitrostyrenes.[10] The compound class seemed amenable to undergo direct intermolecular [2+2] photocycloaddition reaction upon excitation with visible light and we report in this communication on our preliminary results on this topic.

Already in the 19th century, the [2+2] photodimerization of *trans*-β-nitrostyrene was observed to occur upon exposure to sunlight.[11] However, reactions with olefins in the spirit of an intermolecular [2+2] photocycloaddition have remained rare and were performed exclusively with short-wavelength light. Chapman et al. mentioned in a review on the photochemistry of unsaturated nitro compounds the reaction with olefins but did not provide any experimental details.[12,13]



Scheme 1 [2+2] Photocycloaddition of *trans*-β-nitrostyrene (**1**) and indene (**2a**) as reported by Majima et al.[14]

Later, Majima et al. employed the reaction of *trans*-β-nitrostyrene (**1**) and indene (**2a**) to form cyclobutane **3a** (Scheme 1).[14] A high-pressure mercury lamp was employed as the light source in this transformation. In more recent work, pyrex-filtered irradiation was used to study the reaction of nitrostyrenes with silyl enol ethers.[15,16]

Inspection of the UV-Vis spectrum[17] of *trans*-β-nitrostyrene in CH_2Cl_2 (Figure 1) reveals a strong absorption centered at λ = 312 nm (ε = 16500 M^{-1} cm^{-1}). This band has been previously assigned to an allowed ππ*-transition with significant charge-transfer character.[18,19] At high concentration it is evident that the absorption continues into the visible region of the electromagnetic spectrum in line with the fact that *trans*-β-nitrostyrene (**1**) is a yellow-colored solid.

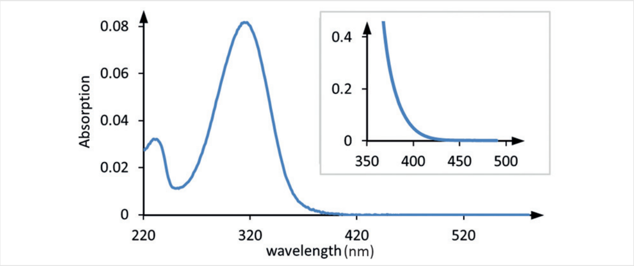
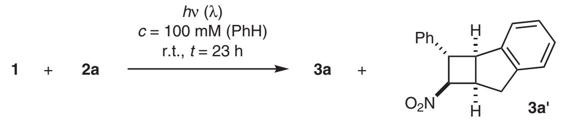


Figure 1 UV-Vis spectrum of *trans*-β-nitrostyrene in CH_2Cl_2 solution (c = 0.05 mM), the inset shows the long-wavelength absorption measured at c = 5 mM

In view of the apparent long-wavelength absorption of *trans*-β-nitrostyrene (**1**), its reaction with indene was revisited. The concentration, the solvent, and the stoichiometry (3.1 equiv indene) were taken from previous work,[14] and the reaction was run for 23 hours (Table 1). We were pleased to find that conversion was not only complete when the mixture was irradiated with fluorescent lamps[20] at λ = 300, 350, and 366 nm, but also at λ = 419 nm (Table 1, entries 1–4). In all cases, it was observed that major diastereoisomer **3a** was accompanied by a minor diastereoisomer to which structure **3a′** was assigned based on NOESY experiments. The diastereomeric ratio (d.r.) varied at around 3:1. Best yields were recorded at λ = 350 nm (Table 1, entry 2) and λ = 419 nm (Table 1, entry 4). Clearly, the [2+2] photocycloaddition was promoted by visible light as even long-wavelength light-emitting diodes (LEDs) led to a significant conversion at λ = 457 nm and at λ = 470 nm (Table 1, entries 5, 6). At λ = 517 nm, there was essentially no conversion after 23 hours (Table 1, entry 7).

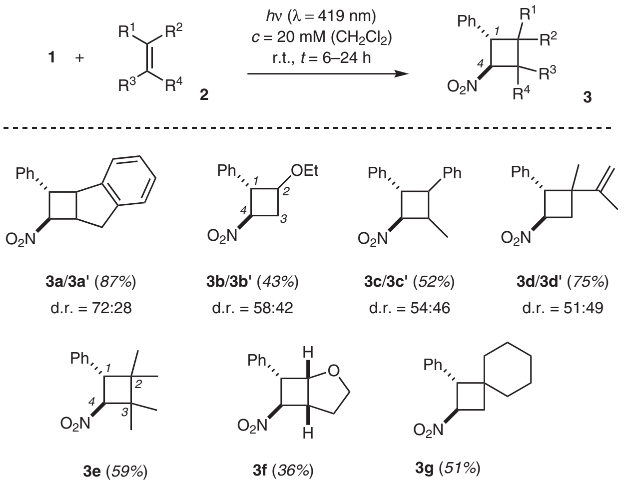
Table 1 Conversion, Yield, and Diastereomeric Ratio in the Intermolecular [2+2] Photocycloaddition Reaction to Products **3a**/**3a**′ in Correlation to the Irradiation Wavelength



Entry	λ (nm)[a]	Conv. (%)	Yield (%)[b]	d.r. (**3a**/**3a**′)[c]
1	300	100	49	77:23
2	350	100	83	80:20
3	366	100	64	77:23
4	419	100	75	75:25
5	457	71	50	75:25
6	470	42	18	73:27
7	517	<5	–[d]	–

[a] For the emission spectra of the light sources, see ref.[20]
[b] Yield of isolated products **3a** and **3a**′ as a mixture of diastereoisomers.
[c] The diastereomeric ratio (d.r.) was determined by integration of appropriate ^1H NMR signals.
[d] No significant amounts of the respective products were isolated.

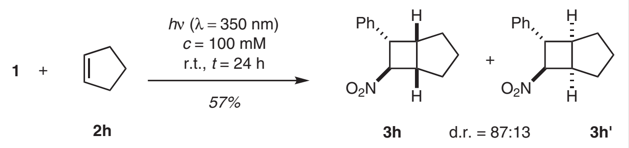
Further experiments were undertaken to identify a less problematic solvent but benzene and to optimize the reaction conditions at λ = 419 nm. While toluene was found less suited to substitute benzene, dichloromethane turned out to be an excellent solvent. A larger excess of the olefin led to higher product yields and the concentration was lowered to 20 mM in order to allow for small-scale reactions with more precious, not commercially available nitrostyrenes (vide infra). At optimized conditions[21] the [2+2] photocycloaddition products **3a**/**3a′** were obtained in a yield of 87% after 24 hours of irradiation at λ = 419 nm. A variety of other olefins was employed in the reaction, and the results are summarized in Scheme 2.



Scheme 2 Visible-light-induced [2+2] photocycloaddition of various olefins **2** to *trans*-β-nitrostyrene (**1**)

It should be noted that the reactions were not always complete and that in some cases substantial amounts (up to 22%) of starting material were recovered, mostly as *cis*-β-nitrostyrene. Yields refer to isolated products, however, and are not corrected for conversion. With olefins **2b**,**d**,**f**,**g**, the fact that the polarity of the excited state is opposite to the ground state polarity (photochemical *umpolung*) becomes particularly apparent. C–C bond formation occurs formally between two – in the ground state – electrophilic centers (C1–C2) and between two nucleophilic centers (C3–C4). The reactions with olefins **2b**–**d** led to a mixture of diastereoisomers the relative configuration of which could be in most cases elucidated by NOESY experiments (see Supporting Information for further details). Cyclobutanes **3e**–**g** were obtained as single products. For the reaction of the electron rich olefin **2b**, it was checked that there was no reaction in the absence of irradiation.[22]

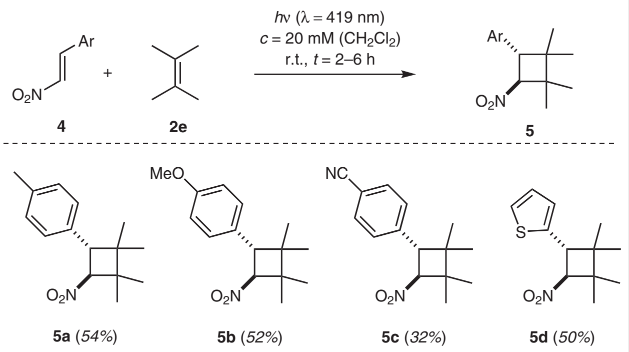
Contrary to unsaturated hydrocarbons **2e** and **2g**, cyclopentene **2h** did not react with a sufficient rate at λ = 419 nm. The [2+2] photocycloaddition could, however, be successively conducted if nitrostyrene **1** was irradiated in a



Scheme 3 Intermolecular [2+2] photocycloaddition of cyclopentene (**2h**) to *trans*-β-nitrostyrene (**1**)

solution of cyclopentene at $\lambda = 350$ nm (Scheme 3). The products were found to be a mixture of diastereoisomers in which product **3h** with the nitro group in *exo* position to the cyclopentyl ring prevailed (d.r. = 87:13).

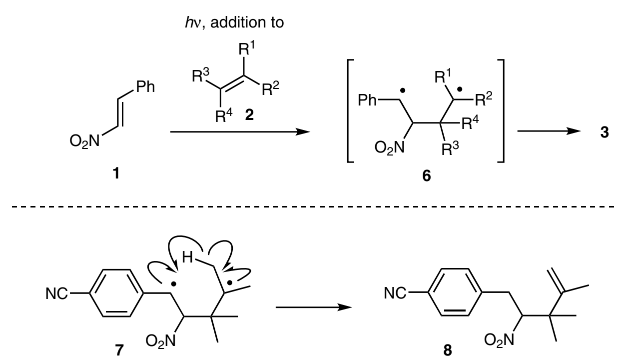
Some preliminary experiments were conducted with other aromatic nitroolefins **4** (Scheme 4). 2,3-Dimethyl-2-butene (**2e**) was employed as the reaction partner since its use avoids the formation of regio- or diastereomeric cyclobutane products. It was found that electron-rich aryl groups (*para*-tolyl, *para*-anisyl, 2-thiophenyl) in 2-position of the respective nitroethenes (**4a**,[23] **4b**,[23] **4d**[24]) led in their [2+2] photocycloaddition to results similar to those of *trans*-β-nitrostyrene. Reaction times were short (2–4 h) and cyclobutanes **5a**, **5b**, and **5d** were obtained in yields of 50–54%. The reaction with the *para*-cyano-substituted nitrostyrene **4c**[25] was less chemoselective and gave product **5c** in a yield of only 32% after a longer reaction time (6 h). A side product could be isolated (vide infra).



Scheme 4 Visible-light-induced [2+2] photocycloaddition of some 2-aryl-substituted nitroethenes **4** and 2,3-dimethyl-2-butene (**2e**)

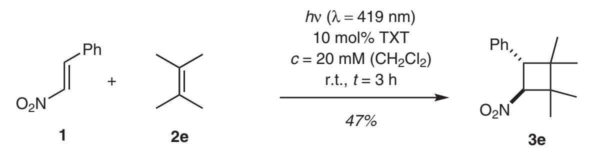
If 2,3-dimethyl-2-butene was subjected to [2+2] photocycloaddition with *cis*-β-nitrostyrene instead of *trans*-β-nitrostyrene the reaction was slower. The reaction product was exclusively the *trans*-substituted cyclobutane **3e** that was isolated in 43% yield. Irradiation of *trans*-β-nitrostyrene at $\lambda = 419$ nm in the absence of an olefin established an equilibrium[26] between the *cis* and the *trans* diastereoisomer in a ratio of 86:14.[27] This finding is in accord with the higher extinction coefficient of the *trans* diastereoisomer within the wavelength range of the light source.[20c] The absorption maximum of *cis*-β-nitrostyrene is centered at $\lambda = 309$ nm ($\varepsilon = 5200\ M^{-1}\ cm^{-1}$) in CH_2Cl_2 solution.[26b]

Mechanistically, there is no indication for a reaction course which would deviate from the pathway of typical [2+2] photocycloaddition reactions.[1] In this regard, it seems likely that olefin **2** adds to the excited substrate, for example, *trans*-β-nitrostyrene (**1**), most likely on the triplet hypersurface (Scheme 5). A 1,4-diradical **6** is formed as intermediate which collapses after intersystem crossing to product **3**. Evidence for the postulated structure of diradical **6** is based on the constitution of the products and side products. Indeed, olefins such as **8** were isolated in a few instances and their formation is readily explained by a hydrogen abstraction in the intermediate 1,4-diradical. In the reaction of olefin **2e** with styrene **4c**, byproduct **8** was obtained in 5% yield and is putatively formed via intermediate **7**.



Scheme 5 Mechanistic suggestion for the reaction of *trans*-β-nitrostyrene (**1**) with olefins **2** via triplet 1,4-diradical **6** and formation of side product **8** in the reaction between **4c** and **2e** via 1,4-diradical **7**

Further support for the hypothesis that the reaction proceeds via a triplet intermediate was obtained from the reaction of styrene **1** and olefin **2e**. In the absence of an additive the reaction was complete after 12 hours (Scheme 2), while a significant rate increase was noted upon addition of the triplet sensitizer 9*H*-thioxanthen-9-one (thioxanthone).[28] No β-nitrostyrene was detected after three hours and product **3e** was obtained in 47% yield (Scheme 6).



Scheme 6 Rate increase of the reaction between *trans*-β-nitrostyrene (**1**) and **2e** in the presence of a triplet sensitizer (TXT = thioxanthone)

In summary, we have shown that nitro-substituted cyclobutanes can be accessed by a visible-light-induced [2+2] photocycloaddition of various 2-arylnitroethenes and olefins. The yields are moderate to good (32–87%) and can possibly be further improved by adjusting the wavelength and the reaction temperature. Given the straightforward reduction of nitro compounds to amines,[11c,14,29] the method offers also access to various aminocyclobutanes. Mechanistically, it remains open to what degree a charge transfer[30] occurs upon encounter of the photoexcited nitro compound and the olefin. In addition, it might be worth to study whether other nitroethenes but nitrostyrenes are equally suited for [2+2] photocycloaddition reactions. Work along these lines is in progress in our laboratories and will be reported in due course.

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Supporting Information

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Primary Data

for this article are available online at http://www.thieme-connect.com/products/ejournals/journal/10.1055/s-00000083 and can be cited using the following DOI: 10.4125/pd0095th.

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(21) **Representative Procedure**
29.8 mg of nitrostyrene **1** (199 µmol, 1.00 equiv) and 10.0 equiv of olefin **2e** (168 mg, 2.00 mmol) were dissolved in degassed, dry CH_2Cl_2 (c = 20 mM). The reaction solution was irradiated at

λ = 419 nm in a Duran tube at r.t., and the reaction progress was monitored by TLC. When no further conversion was observed by TLC (t = 12 h), the reaction was stopped and all volatiles were removed. Purification by column chromatography (pentane/Et$_2$O = 20:1) gave product **3e** as a yellow oil (27.5 mg, 118 µmol, 59%). When performed on a mmol scale (150 mg **1**), product **3e** was obtained in 56% yield (132 mg). ^{1}H NMR (500 MHz, CDCl$_3$, 300 K): δ = 0.71 (s, 3 H, CH$_3$-2), 1.15 (s, 3 H, CH$_3$-3), 1.19 (s, 3 H, CH$_3$-2), 1.24 (s, 3 H, CH$_3$-3), 3.97 (d, ^3J = 10.1 Hz, 1 H, H-1), 4.91 (d, ^3J = 10.1 Hz, 1 H, H-4), 7.08–7.13 (m, 2 H, *ortho*-H$_{Ar}$), 7.23–7.28 (m, 1 H, *para*-H$_{Ar}$), 7.30–7.37 (m, 2 H, *meta*-H$_{Ar}$) ppm. ^{13}C NMR (101 MHz, CDCl$_3$, 300 K): δ = 19.5 (q, CH$_3$-3), 21.5 (q, CH$_3$-2), 22.8 (q, CH$_3$-3), 24.3 (q, CH$_3$-2), 39.3 (s, C-2), 44.9 (s, C-3), 49.4 (d, C-1), 84.9 (d, C-4), 127.0 (*ortho*-C$_{Ar}$H). 127.1 (d, *para*-C$_{Ar}$H), 128.6 (d, *meta*-C$_{Ar}$H), 136.4 (s, C$_{Ar}$) ppm.

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