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Methyl viologen as a catalytic acceptor for electron donor–acceptor photoinduced cyclization reactions

In our work, we develop a catalytic strategy for photocyclizations through electron-donor–acceptor complexation that bypasses the need for leaving group installation and added terminal oxidant. The simple organic catalyst and substrate associate and generate a coloured solution allowing for green light absorption that promotes formal [4 + 2] and [2 + 2] photocycloadditions.

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Methyl viologen as a catalytic acceptor for electron donor–acceptor photoinduced cyclization reactions†

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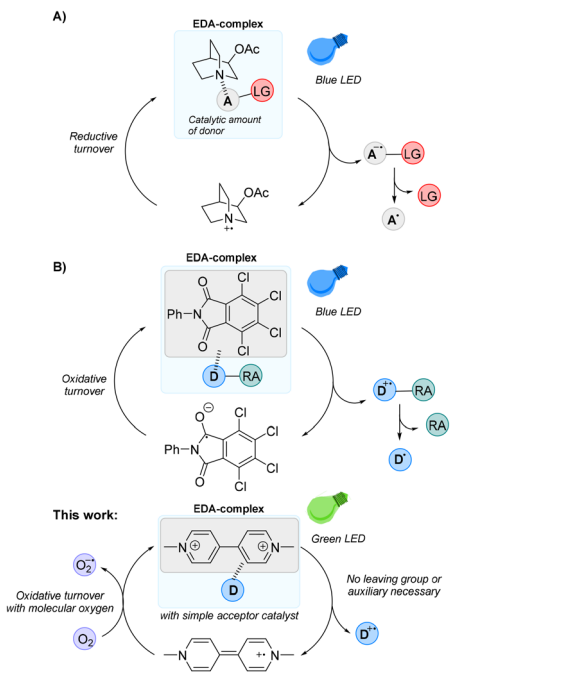
We present a new method for [2 + 2] and [4 + 2] cyclizations *via* a radical cation formation driven by methyl viologen mediated electron donor–acceptor complexes. This approach enables the synthesis of cyclobutane and cyclohexene derivatives using a catalytic amount of methyl viologen enabled by oxygen as the terminal oxidant.

The concept of electron donor–acceptor (EDA) complexation, also known as charge-transfer complexation, has been explored by scientists since the 1970s.[1–6] Initially investigated from a quantum-mechanical perspective by Mulliken and co-workers in the 1950s,[7,8] an EDA complex is formed when an electron-rich molecule (the donor) interacts non-covalently with an electron-deficient molecule (the acceptor). Unlike the individual donor or acceptor, the resulting complex typically absorbs visible light through the newly formed charge transfer band. Upon irradiation a single electron transfer (SET) process between the donor and acceptor occurs. The formed radical ion pair can undergo one of two competing pathways: it can either continue to generate the desired intermediate, or it can undergo back electron transfer (BET), which suppresses the formation of the intended product. Early research attempted to overcome BET by incorporating leaving groups to facilitate the generation of new radicals, thus promoting the desired reaction pathway.

Since 2013, the concept of EDA complexation witnessed its renaissance and many combinations of various electron-rich donors and electron-poor acceptors were investigated.[9,10] These EDA pairs required the use of both donor and acceptor in stoichiometric amounts in order to achieve the desired product in sufficient yields.[11–15] In 2019, Bosque, Bach and co-workers reported an EDA complex using 3-acetoxyquinuclidine as a catalytic electron donor with a tetrachlorophthalamide ester as the electron-poor acceptor (Scheme 1A).[16] In 2022, Melchiorre and co-workers applied tetrachlorophthalimides as a catalytic acceptor (Scheme 1B).[17] A Giese-type reaction was performed after irradiation of the EDA complex. The phthalimide radical anion was oxidized by the secondary radical, formed the Giese-type product and regenerated the catalytic donor.

In previous studies, leaving groups are usually essential when applying EDA complexes to synthesis practice,[18] and the reactions often required stoichiometric amounts of both elec-



Scheme 1 Catalytic donor (A) and acceptor (B) for EDA-complexations. This work on methyl viologen as a catalytic acceptor, oxygen as the terminal oxidant and no use of a leaving group. A = acceptor, D = donor, LG = leaving group, RA = redox auxiliary.

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tron donors and acceptors. Methyl viologen, which is known as an antimicrobial agent and herbicide, offers a promising alternative to generate EDA complexes and improve atom economy by avoiding the use of leaving groups. It was found to have three thermodynamically stable oxidation states (Scheme 2).[19] These three oxidation states are the di-cation MV^{2+}, radical cation $MV^{\bullet+}$, and neutral methyl viologen MV. The MV^{2+} can be reduced to the radical cation state $MV^{\bullet+}$, and the reduction potential of MV^{2+} to $MV^{\bullet+}$ is more feasible, which reveals the capability of being a single electron-acceptor.[20] Furthermore, previous studies have also demonstrated that methyl viologen can act as an electron acceptor for many substrate classes to form EDA complexes,[21–44] but, to the best of our knowledge, synthetic protocols have not been demonstrated. Although, pyridinium salts have been used for radical formations in EDA-complex based strategies.[45,46]

We set out to investigate methyl viologen as a suitable electron-poor acceptor for EDA complexation with different electron donors for application in synthesis.[47] Herein, we explore methyl viologen in catalytic amounts for the photoinduction of formal [2 + 2] and [4 + 2] photocycloadditions *via* EDA complexes.

As our target reaction we selected the radical cationic cyclization reaction between anethole and isoprene to form the desired cyclohexenes.[48] In order to enable the desired reactivity, we propose the formation of a charge transfer complex between the electron-rich anethole and the electron-poor methyl viologen, followed by radical addition of the anethole radical cation to isoprene. Therefore, we conducted UV/Vis-studies of this pair in different solvents. In these studies (Fig. 1), we observed the formation of charge transfer bands in trifluoroethanol (TFE), aqueous sodium dodecyl sulfate (SDS) solution and methanol. The formation of the EDA complex was more pronounced in the aqueous micellar solution compared to the organic solvents. This is likely due to the increased local concentration in the aqueous micellar solution leading to a stronger signal for the EDA complexation. Preliminary studies show that no product formation was observed in the aqueous SDS solution (details available in ESI†). However, in TFE the desired product was observed, allowing us to investigate the formal [4 + 2] cycloaddition.

All UV/Vis spectra exhibited absorption around λ_{max} = 450 nm which could relate to the predicted absorption of the methyl viologen radical cation $MV^{\bullet+}$.[20] To confirm this hypothesis, a spectroelectrochemical measurement of methyl viologen in TFE was conducted (Fig. 2) and as the reduction potential decreased, an absorption band emerged around λ_{max} = 450 nm. The single reduced methyl viologen correlates to the signal observed in the UV/vis spectra of the mixture of anethole and methyl viologen. Consequently, the presence of this absorption band correlates with the formation of the $MV^{\bullet+}$.

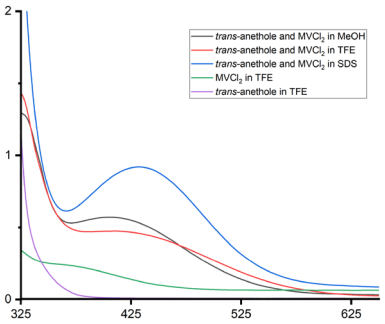


Fig. 1 UV/Vis spectroscopy of *trans*-anethole and methyl viologen in different solvents.

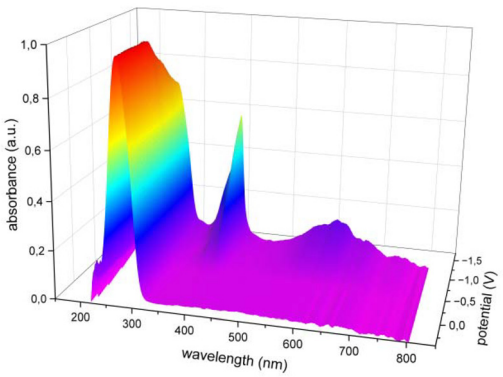
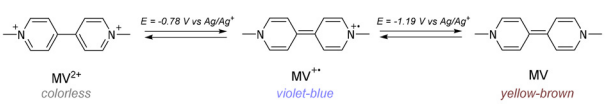


Fig. 2 Spectroelectrometric measurements of $MVCl_2$ illustrating the appearance of $MV^{\bullet+}$ in TFE.

Our optimization starts with an equimolar amount of $MVCl_2$, 3 equivalents of isoprene in 1 mL TFE (dried over molecular sieves overnight), irradiated with 520 nm green light for 24 h, under these conditions, the expected [4 + 2] cycloadduct was formed in 60% NMR yield (Table 1, entry 1). After successful product formation, we gradually reduced the amount of $MVCl_2$ to 5 mol% (entries 2 and 3), the NMR yield remained constant (entry 3, 60% NMR yield). After decreasing the amount of solvent (entry 4) and reaction time (entry 5), the desired product was isolated in a good yield (entry 6, 72%). We tested various solvents that also exhibit potential ability to stabilize formed radical cation intermediates such as $MeNO_2$ and MeOH (entries 7 and 8), but the desired product was not observed.[49] Control reactions (entries 9–11) showed that methyl viologen and light are crucial to form the desired product and oxygen was found to play a vital role in the reaction cycle, likely to regenerate the methyl viologen acceptor. Oxygen has been previously reported to react fast with the methyl viologen radical cation ($MV^{\bullet+}$).[50–52]

The radical cation cyclization reaction Initiated by the methyl viologen mediated EDA complex formation demonstrates a relatively broad generality for this type of radical



Scheme 2 Three oxidation states of methyl viologen.

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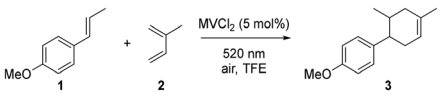
Table 1 Optimization of the EDA photoinduced formal cycloaddition[a]

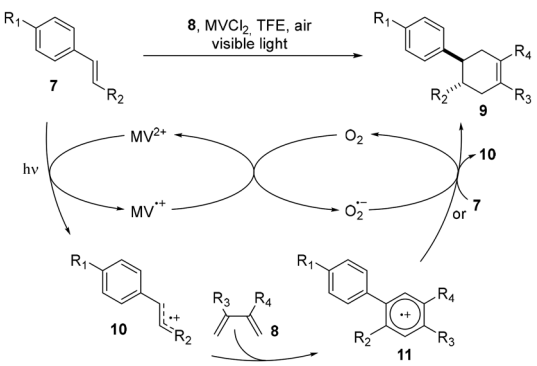


Entry	$MVCl_2$	Solvent	Time	Yield[b]
1	100 mol%	TFE (2 mL)	24 h	60%
2	50 mol%	TFE (2 mL)	24 h	56%
3	5 mol%	TFE (2 mL)	24 h	60%
4	5 mol%	TFE (1 mL)	24 h	64%
5	5 mol%	TFE (1 mL)	16 h	66% (72%)
6	5 mol%	MeOH (1 mL)	16 h	0%
7	5 mol%	$MeNO_2$ (1 mL)	16 h	0%
8	5 mol%	DCE : TFE (4 : 1) (1 mL)	16 h	3%
9[c]	5 mol%	TFE (1 mL)	16 h	0%
10[d]	—	TFE (1 mL)	16 h	1%
11[e]	5 mol%	TFE (1 mL)	16 h	14%

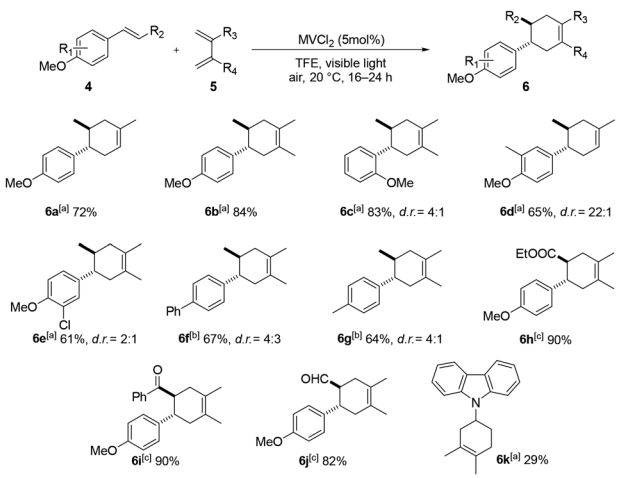
Reactions were performed with *trans*-anethole (0.2 mmol), methyl viologen and isoprene (3.0 eq.) in solvent irradiated with a 520 nm LED (10 W) at 20 °C. [a] Full optimization table is available in the ESI.† [b] NMR yield (isolated yield). [c] Dark. [d] Without $MVCl_2$. [e] Degassed solvent.

chain reaction (Scheme 3). Anethole and compounds with similar structures efficiently formed the [4 + 2] cycloadduct as anticipated (**6a–6e**). Previous studies have exhibited the crucial role of the alkoxy group on the benzene ring in visible light induced radical cation-based cyclization reactions.[53–59] The methyl viologen mediated EDA complexes demonstrate an improved tolerance to other *para* substituents compared to most strategies and substrates substituted with *para*-phenyl and *para*-methyl groups could be converted to the desired products in good yields (**6f–6g**). Electron-deficient olefins typically favor thermal or acid-mediated [4 + 2] cycloadditions and their exploration in photochemical reactions has been limited.[60] In this context, electron-deficient olefins generally do not function well as electron donors in EDA complex formations. However, in this study, we found that these electron withdrawing group (EWG)-conjugated olefins exhibited yields of up to 90% (**6h–6j**), with aldehyde groups being well-tolerated. *N*-Vinylcarbazole could also be successfully employed in the [4 + 2] cyclization as an electron-rich olefin (**6k**), broadening the scope of potential electron donors to be paired with methyl viologen as the acceptor.

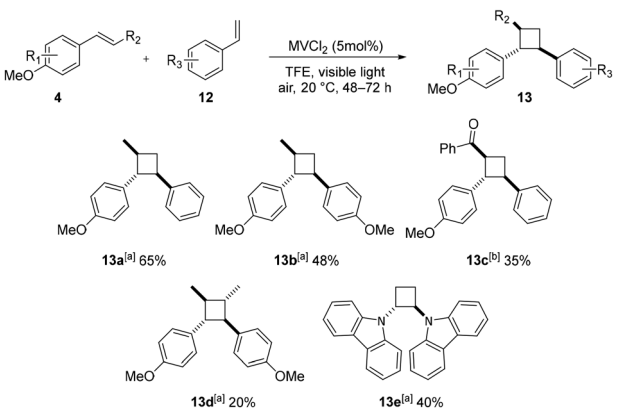
We propose that the mechanism of the electron rich olefin–$MVCl_2$ EDA complex induced oxidative cycloaddition begins with a charge transfer complex formation with the olefin and methyl viologen, followed by visible light irradiation, which initiates single electron transfer generating a radical ion pair. In the presence of oxygen, the radical cation state of methyl viologen is rapidly oxidized back to its di-cation state, effectively suppressing back electron transfer. The formed radical cation **10** then undergoes radical cyclization to afford the product radical cation **11**. This product radical cation can be further oxidized by $O_2^{\bullet-}$ or another equivalent of neutral **7**, initiating another round of the radical chain reaction and generating the product **9** (Scheme 4).



Scheme 4 Proposed mechanism.



Scheme 3 Scope of the radical cation formal Diels–Alder reaction. Reactions were performed with methyl viologen (5 mol%) and diene (3.0 eq.) in dry TFE irradiated with LED light (10 W) at 20 °C. [a]520 nm LED light (10 W) for 16 h. [b]520 nm LED light (10 W) for 72 h. [c]445 nm LED light (10 W) for 24 h.



Scheme 5 Scope of the radical cation [2 + 2] cycloaddition. Reactions were performed with methyl viologen (5 mol%) and diene (3.0 eq.) in dry TFE irradiated with LED light (10 W) at 20 °C. [a]520 nm LED light (10 W) for 48 h. [b]445 nm LED light (10 W) for 72 h.

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After successfully exploring the radical cation-based [4 + 2] cyclization, we propose that the radical cation **10** can also be applied in the radical cation-based [2 + 2] cyclization (Scheme 5). We started with anethole and styrene, resulting in a moderate yield with regioselectivity being strictly controlled (**13a**). Substituting styrene with *para*-methoxy group led to a decline in yield (**13b**). When using an electron-deficient ketone, the yield was modest after prolonged irradiation (**13c**). We found that dimerization is also feasible, **13d** was isolated after 48 h irradiation. To inhibit oxidative cleavage of the substrates, we tested degassed solvent, but this only resulted in trace amounts of the product, supporting the proposed role of oxygen in the reaction mechanism. Another dimer **13e** was also isolated in a modest yield, which was suppressed by competitive polymerization.

Conclusions

In summary, methyl viologen mediated EDA complexes provide an easily available and atom economical method for synthesizing cyclobutane and cyclohexene molecules under very mild conditions. This approach requires a catalytic amount of methyl viologen, which can be regenerated using air as the terminal oxidant. The process effectively inhibits back electron transfer without the need for leaving groups, further improving atom economy. Additionally, the reaction is tolerant to atmospheric conditions and utilizes environmentally friendly visible light for irradiation, making it both efficient and sustainable.

Author contributions

R. J., W. L. and L. N. contributed to writing the manuscript. Experiments were performed by R. J., W. L. and J. Z. The project was guided by L. N.

Data availability

The data supporting this article have been included as part of the ESI.†

Conflicts of interest

There are no conflicts to declare.

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