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ARTICLE

Visible-light Mediated Oxidative Ring Expansion of Anellated Cyclopropanes to Fused Endoperoxides with Antimalarial Activity

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A visible light mediated ring expansion of readily available carbo- and heterocyclic anellated cyclopropanes by molecular oxygen at ambient pressure has been developed. Tolerating a variety of functional groups, the reaction yields fused 1,2-dioxolanes, which were tested for antimalarial activity given their close analogy to the active principle of approved drugs such as artemisinin.

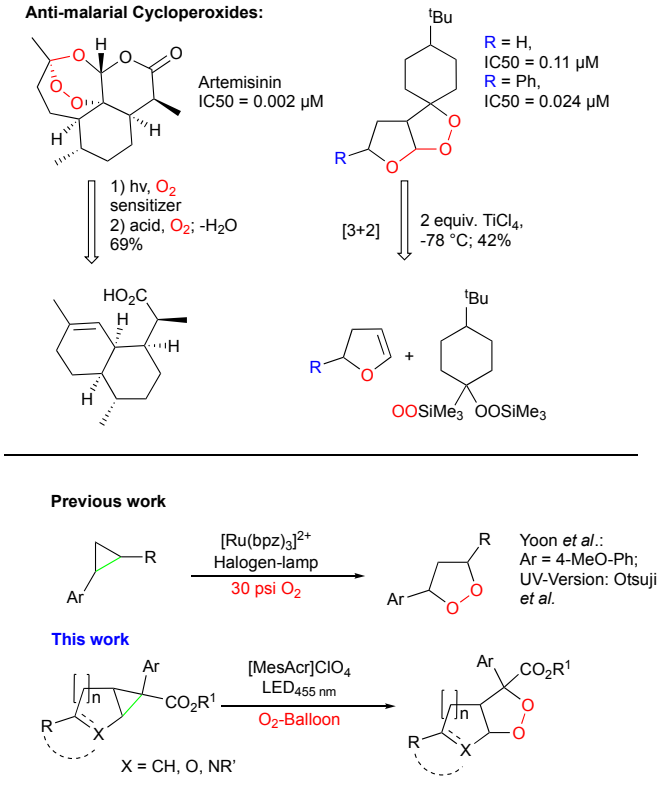
Introduction

Polycyclic cycloperoxides are prominent structural motifs in drugs with antimalarial activity, being found in the approved drug artesunate or in simpler analogues (Scheme 1).[1] Different strategies[2] for the installment of this moiety are available such as the [4+2]-cycloaddition of singlet oxygen to a 1,3-diene[3,4],the [3+2]-cycloaddition of alkenes with peroxocarbenium ions[5] derived from peroxyketals, or cyclization-peroxidation cascades employing 1,5- and 1,6-dienes[6]. The photooxygenation of donor-aryl substituted cyclopropanes to give rise to the corresponding monocyclic cyclo-peroxides was previously described under UV[7] or visible light conditions[8] using $Ru(bpz)_3^{2+}$ as photocatalyst. Drawing inspiration from this work as well as pioneering non-photocatalytic examples[9-11] we here report an operationally simple visible light mediated synthesis of complex cycloperoxides from carbo- and heterocyclic anellated cyclopropanes using Fukuzumi's catalyst. The obtained polycyclic *endo*peroxides represent lead structures for drugs approved for antimalarial[12,] treatment and, currently in clinical trials,[13] for anti-cancer agents.[14, 15]

The inherent strain of a carbocyclic three-membered ring leads to the ultrafast opening if a radical species is formed in its α-position. Utilizing the power of visible-light photoredox catalysis, not only radicals[16], but also radical cations in α-position of the cyclopropyl ring can be generated by single-electron oxidation[17,18]. The subsequent ring opening leads to a separation of radical and cationic site, allowing for cyclizations[19, 20] or their separate trapping to give rise to oxo-chlorination[17] and oxo-amination[18] products.

Rhodium catalyzed[21] or visible-light mediated[22] cyclopropanation of hetero- and carbocycles using readily available aryl diazoacetates gives scalable access to bicyclo[x.1.0] structures exhibiting a donor-acceptor substitution pattern on the cyclopropyl group. While different approaches for the selective activation of each bond in the three-membered ring have been described[23-25], the current method allows for the direct photooxygenation of the activated, i.e. donor-acceptor substituted *exo*-cyclic bond.

Scheme 1: Synthetic strategies[7, 8, 26] for and Biological Activity of Selected Cycloperoxides[27, 28].



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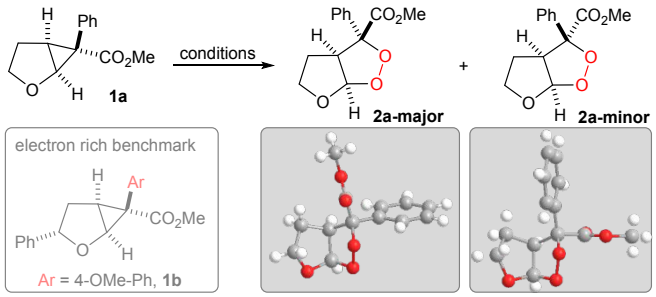
Results and Discussion

Representing the state of the art for visible light induced photo-oxygenations, the incorporation of molecular oxygen was demonstrated for electron rich (Ar = 4-OMe-Ph), monocyclic arylcyclopropanes by Yoon et al.[7], giving rise to endoperoxides in excellent yields (Scheme 1). Bringing together our continuous interest in cyclopropanated heterocycles[29] and photochemical transformations[30] we envisioned a polar-radical crossover reaction[31] of cyclopropanated 2,3-dihydrofuran **1b** with oxygen to trigger the cyclopropane ring-opening to endoperoxide **2b** (Table 1).

Table 1: Conditions Screening.



#	catalyst	sub.	solvent	yield
1[1)]	$[Ru(bpz)_3](PF_6)_2$	**1b**	$MeNO_2$/tol	decomp.
2	$[MesAcr]ClO_4$	**1b**	MeCN	15%, d.r. 3:1
3[1)]	$[Ru(bpz)_3](PF_6)_2$	**1a**	$MeNO_2$/tol	-
4[2)]	$Ir[dF(CF_3)ppy]_2(dtbpy)PF_6$	**1a**	MeCN	<5%
5	$[MesAcr]ClO_4$	**1a**	MeCN	47%, d.r. 4:1[5]
6	$[MesAcr]ClO_4$	**1a**	$CHCl_3$	6% d.r. 1:1
7	$[MesAcr]ClO_4$	**1a**	HFIP	10% d.r. 1:1
8[3)]	$[MesAcr]ClO_4$	**1a**	MeCN	49%, d.r. 4:1
9[4)]	$[Ru(bpy)_3]Cl_2$	**1a**	MeCN	-
10	Rose Bengal	**1a**	MeCN	-
11	no catalyst	**1a**	MeCN	-
12	$[MesAcr]ClO_4$, no light	**1a**	MeCN	-
13	$[MesAcr]ClO_4$, no O_2	**1a**	MeCN	-

NMR-Yields determined using 1,4-diacetylbenzene as internal standard. Reaction conditions: 10 mol% catalyst, 0.2 mmol substrate 2 mL solvent, blue LED (455 nm), O_2-Balloon, 16 h, rt. [1)]0.5 mol% catalyst, 0.2 mmol substrate, 2 mL $MeNO_2$/toluene 1:1, 30 psi O_2, 16h, rt; [2)]2 mol% catalyst; [3)] 30 psi O_2, 10 h. [4)] 5 mol% Catalyst. [5)] Combined isolated yield of separated diastereomers.

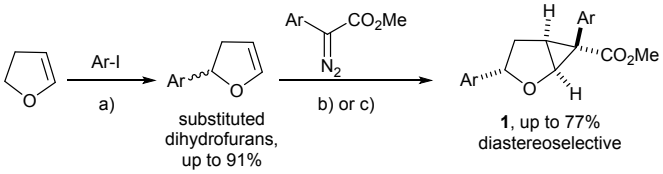
Following the precedent set by Yoon *et al.,* calling for the employment of $[Ru(bpz)_3](PF_6)_2$, ($E^*_{1/2}$ = +1.4 V vs. SCE) only decomposition of the starting material **1b** ($E_{(M/M^+)}$: +1.40 V vs. SCE) was observed (entry 1). Irradiation in presence of the highly oxidizing 9-mesityl-10-methyl-acridinium perchlorate (Fukuzumi's Catalyst; $E^*_{1/2}$ = +2.06 V vs. SCE[32]) under O_2-atmosphere in MeCN as solvent led to the formation of the two endoperoxides **2b-major** and **2b-minor** (d.r. 3:1, entry 2). Albeit complete conversion of the starting material **1b** was reached within 30 min, **2b** however was observed only in a low yield of 15%, while copious amounts of polymeric byproduct precipitated from the reaction mixture. We reasoned that **1b** was too reactive, as the initial oxidation might occur on both, the oxygen in the tetrahydrofuran-moiety and on the electron rich 4-OMe-phenyl moiety, causing the formation of undesired byproducts.

Therefore, we tested the less electron rich substrate **1a** ($E_{(M/M^+)}$: +1.95 V vs. SCE) with presumably lower reactivity towards oxidation. Little or no reaction took place under the conditions reported by Yoon *et al.* (entry 3) or using other transition metal based catalysts such as $Ir[dF(CF_3)ppy]_2(dtbpy)PF_6$ ($E^*_{1/2}$ = +1.69 V vs. SCE, entry 4). However, employing Fukuzumi's catalyst gave rise to the diastereomers **2a-major** and **2a-minor**, which were separated by column chromatography and characterized by X-ray crystallography (entry 5). Notably, the orientation of the phenyl and ester group was reversed for the major diastereomer compared to the starting material.

A short screening for optimum conditions (Table 1) showed that the reaction is strongly dependent on the solvent (entries 5-8), with acetonitrile giving the best yield and diastereomeric ratio. While the yield was by and large constant, the reaction time decreased when instead of air (ambient pressure, 20 h) an O_2-balloon (16 h, entry 5) or oxygen overpressure (30 psi, 10 h, entry 8) were applied. Control experiments revealed that singlet oxygen (produced by $Ru(bpy)_3^{2+}$ or Rose Bengal, entries 9 & 10) did not facilitate the reaction, and that light, oxygen as well as catalyst were necessary for the reaction to proceed (entries 11-13).

Since endoperoxides comprising the core structure of **2a** with a 5-aryl substitution are reported to have especially promising anti-malarial activity[28] (*cf.* Scheme 1), we were delighted to find that cyclopropanated 5-aryl-dihydrofurans **1b-d** and **1g-1n** were readily available via Heck-arylation of 2,3-dihydrofuran[33] followed by cyclopropanation with 2-aryl 2-diazoacetates (Scheme 2). For the latter either the traditional, transition metal catalyzed pathway using $Rh_2(OAc)_4$ was applied, or the recently reported, visible-light driven process[22] which allows for an environmentally friendly, metal free approach. Both conditions gave cyclopropanes **1** in 32-77% yield with complete diastereoselectivity, in which the cyclopropanation occurs opposite of the aryl moiety and the ester group orients on the convex phase of the bicycle (for details see the SI).

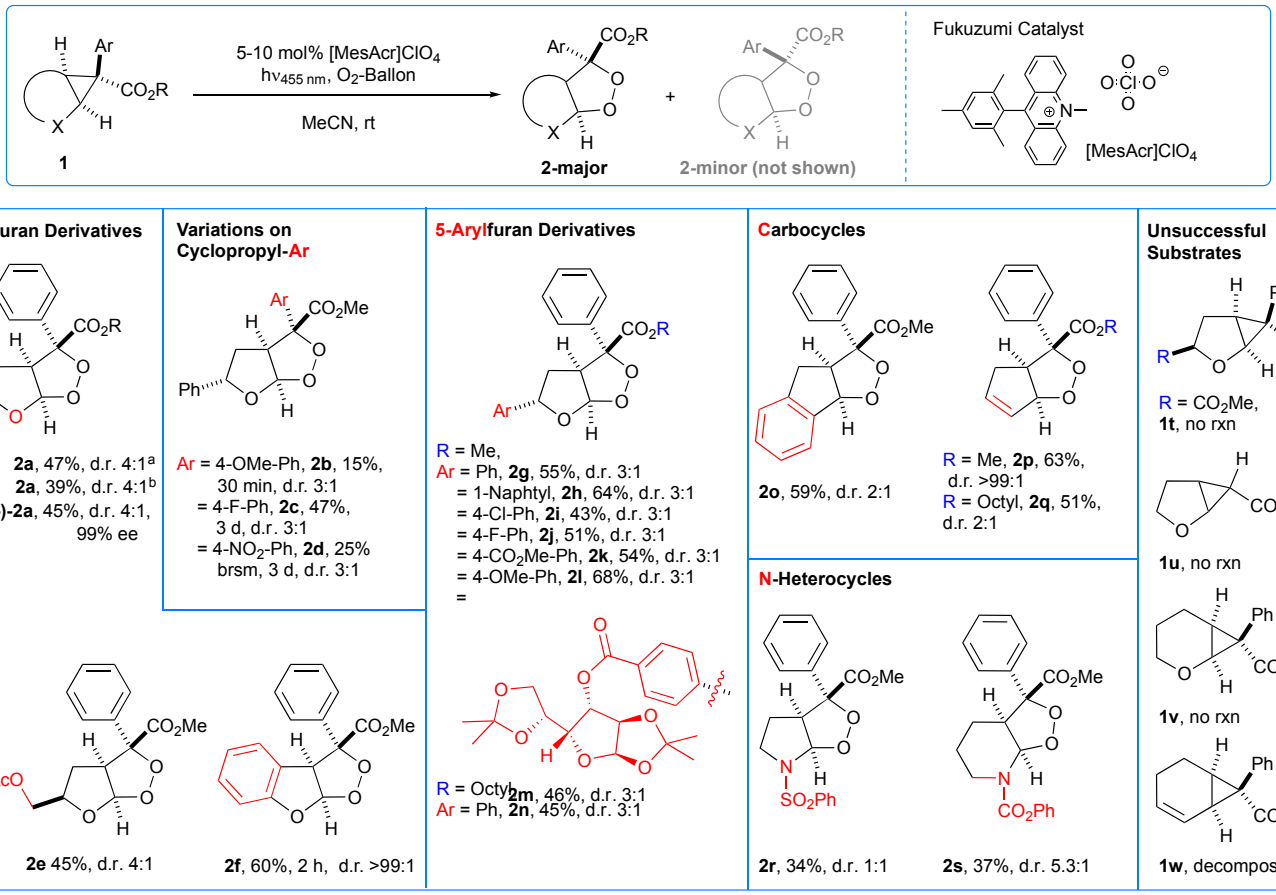
Scheme 2: Cyclopropanation of 5-aryl-2,3-dihydrofurans.



a) 5-10 mol% $Pd(OAc)_2$, $^nBu_4NCl$, KOAc, molecular sieves, DMF, 24 h.
b) $h\nu_{455\ nm}$, DCM, 24 h.
c) 0.8 mol% $Rh_2(OAc)_4$, DCM, 3 h.

Next we explored the scope of the photo-oxidation (Scheme 3):

Scheme 3: Substrate Scope.

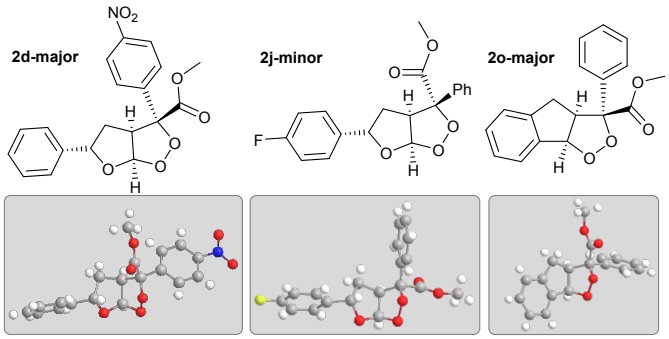


Reaction conditions: substrate 1, 5-10 mol% $[MesAcr]ClO_4$, 1 mL MeCN/0.1 mmol substrate, O_2-balloon, $h\nu_{455nm}$, rt, 10-20 h. See SI for details.[a] 1.5 mmol scale. [b] 15 mmol scale.

Switching to enantiomerically enriched (-)-**1a** (see SI) gave rise to the corresponding **(-)-2a** without erosion of enantiopurity. Scaling the reaction from employing 1.5 mmol (±)-**1a** to 15 mmol (±)-**1a** was accompanied by a loss in yield from 47% to 39% but allowed the production of 1.46 g **2a** (1.19 g **2a**-major, 0.27 g **2a**-minor). The aforementioned 5-aryl-substituted substrates (Scheme 3) were tested with variations on either aromatic group. Changes on the aryl group adjacent to the cyclopropyl group led to mixed results for **1b-1d**: The *para*-methoxyphenyl derivative **1b** was rapidly consumed (30 min) under the reaction conditions, however, the desired peroxide **2b** was obtained only in low yield (15%), while for the *para*-fluorophenyl derivative **1c** the reaction was slow, but nevertheless gave rise to **2c** in 47% yield. Even electron deficient **1d**, comprising a *para*-nitrophenyl group, was slowly converted to its corresponding peroxide **2d**. In contrast, changes on the 5-aryl-substituent were tolerated well and derivatives **2g-2n** were obtained in medium to good yields with consistent diastereoselectivity of about 3:1. However, more drastic changes of the electronic nature of the 5-position significantly altered the reactivity. Substrate 1t, comprising an electron withdrawing ester, showed no conversion, while upon reduction of this ester and protection of the resulting alcohol (**1e**) the corresponding peroxide **2e** was again obtained in moderate yield (45%).

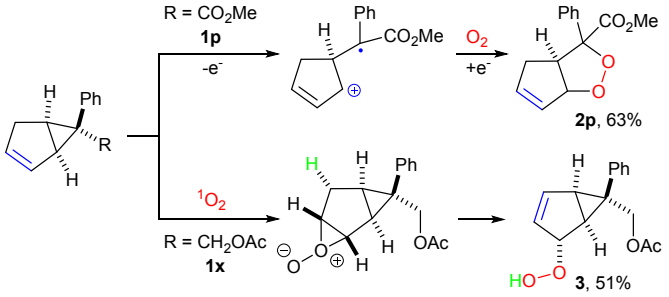
Cyclopropanated benzofuran **1f** was cleanly converted and **2f** was formed as a single diastereomer, contrasting the derivatives described above that were typically formed with a diastereoselectivity of 3-4:1. To our delight also cyclopropanes **1o-1q** derived from carbocycles such as indene and cyclopentadiene could be transformed to the carbocyclic endoperoxides **2o-2q**. Planarization of the bicycle through the sp^2-hybridized centers adjacent to the cyclopropane moiety allows an efficient overlap with the σ*-orbital of the breaking cyclopropane C-C-bond, which appears to play a role for the improved diastereoselectivity and yield (see mechanistic discussion). The beneficial effect of such an orbital interaction might also explain why the six-membered derivatives **1v** and **1w** were not amenable substrates in the photooxidation. Switching to nitrogen heterocycles, both **2r** and **2s** could be obtained in moderate yield, the latter apparently again reflecting the benefit of sp^2-hybridization of the nitrogen center. X-ray structures obtained of **2a-major** and **2a-minor** (Table 1), **2d-major**, **2j-minor**, and **2o-major** (Figure 1) allowed an unambiguous assignment of all peroxides obtained.

Figure 1: Representative Xray-structures of peroxides 2



An aryl as well as an ester substituent on the cyclopropyl ring appear to be crucial for the endoperoxide formation as became apparent by the unsuccessful reaction of cyclopropane **1u** (no conversion) and the reaction of reduced substrate **1x**, which followed a different pathway (Scheme 4), leading mainly to hydroperoxide **3** presumably via a Schenck-ene type reaction[34].

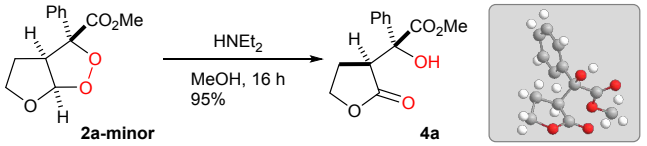
Scheme 4: Variation on the Ester Moiety.



As peroxides are generally regarded as compounds prone to spontaneous decomposition, selected compounds were subjected to thermal analysis: Carbocycle **2p** showed decomposition at 189 °C, while furan **2a** was stable up to 212 °C, nitrogen containing compound **2d** up to 290 °C and compound **2s** even up to 303 °C (see SI), ascertaining that the compounds described herein are comparably stable and safe to handle.

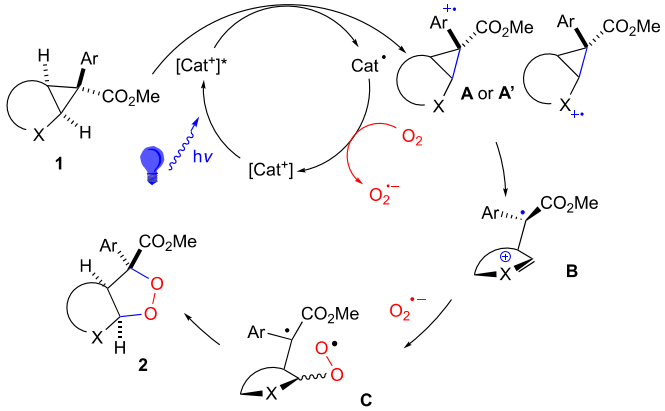
The so obtained endoperoxides can undergo a variety of transformations[28], for example disproportionative opening proceeded with excellent conservation of stereoinformation by simply stirring in MeOH in the presence of $HNEt_2$. As **2a-major** and **2a-minor** were separable by column chromatography, the respective γ-butyrolactones **4** comprising a quaternary carbon were synthesized in excellent yields (Scheme 5; transformation of **2a-major** see SI). Since enantioenriched **1a** is available using chiral rhodium-tetracarboxylates in the initial cyclopropanation[21], all four stereoisomers of otherwise challenging γ-butyrolactones are accessible.

Scheme 5: γ-Butyrolactone Synthesis.



Concerning the mechanism (Scheme 6), the dependence on a highly oxidizing catalyst such as $[MesAcr]^+$ indicates that the first step is indeed a single electron transfer (SET) from the substrate to the catalyst to give rise to **A** via oxidation of the arene moiety[35] or to **A'** via oxidation of the heteroatom/double bond[36]. Ring opening to **B** results in the separation of the radical and cationic center, the former being stabilized due to the synergistic push-pull interaction between the ester and the arene group, while the later profits from mesomeric conjugation with the neighboring heteroatom or π-system.

Scheme 6: Mechanistic Proposal.

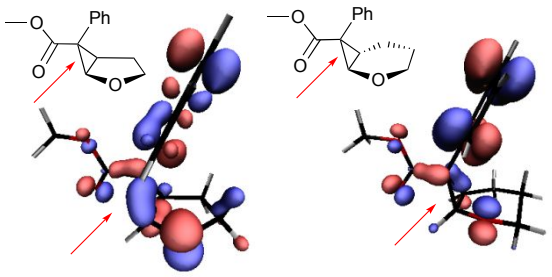


B is then trapped by superoxide radical anion[37, 38] leading to the diradical **C**, which then collapses in a productive manner to the product **2** provided that attack of $O_2^{\bullet-}$ has taken place *syn* to the neighboring group.

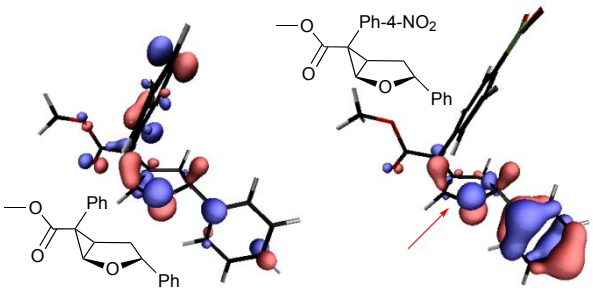
In order to elucidate the difference in reactivity between oxygen-containing five and six-membered ring systems, we examined their respective electronic structure. Therefore, calculations on a B3LYP/6-31G level were used to obtain information on the HOMO-Orbitals (Figure 2).

Comparing the electron density of furan **1a** vs. pyran **1v** (Figure 2 top), the striking difference is that in the six-membered derivative **1v** none is found on the *exo*-bond of the cyclopropyl moiety (red arrow) in stark contrast to the five-membered compound **1a**. We propose that this missing activation prevents a quick opening of the cyclopropyl ring after the initial oxidation, making the back-electron transfer more favorable and thus explaining the observed inactivity of substrate **1v**. While in previous studies the oxidation of an electron rich aryl group attached to the cyclopropyl moiety was required to trigger peroxide formation[7, 42], we found that even for an extremely electron deficient group such as a 4-NO_2-Ar (**1d**) peroxide formation was feasible. As expected, the HOMO-Orbital does not extend over this electron deficient group (Figure 2 bottom), but does include the heteroatom of the five-membered ring (red arrow). As oxidation of this ether-oxygen may lead to the same intermediate (Scheme 6, **A**) we hypothesize this process to allow for the observed slow conversion of compound **1d** to the corresponding peroxide. Oxidation of the heteroatom may be an alternative pathway to the oxidation of the aryl moiety for similar substrates, e.g. for compound **1g**. More depictions of HOMO-Orbitals (**1b**, **1c**, **1o**, **1p**) are available in the SI for comparison.

Figure 2: HOMO-Representations



Left: Substrate **1a**; right: substrate **1v**;



Left: Substrate **1g**; right: substrate **1d**;

Highest Occupied Molecular Orbital (HOMO) of selected examples as calculated with GAMESS[39, 40] on B3LYP/6-31G level, visualized with VMD[41].

The endoperoxide scaffold is of high biological interest, as it is believed to manifest the anti-malarial properties of state-of-the-art drugs against this disease such as artesunate. Malaria is a disease caused by *Plasmodium* parasites, widespread in tropical and subtropical climate and transmitted by *Anopheles* mosquitoes which expand their habitat due to climate change. A challenge for the treatment of this disease is the growing resistance against artemisinin and its derivatives, which increases the demand for new, easily accessible drugs[43]. Encouraged by the promising results for bicyclic peroxides containing a furan moiety reported by Xu *et al.*[28] (*cf.* Scheme 1), a selection of compounds **2** obtained in this study was tested against *Plasmodium Falciparum* to assess their biological activity.

Table 2: Biological activity against *P. falciparum* in vitro

#	Compound	IC_{50}	#	Compound	IC_{50}
1	**2a**	>100	5	**2h**	40
2	**2e**	>100	6	**2p**	19
3	**2f**	80	7	**2n**	14
4	**2g**	60	8	**2q**	2.5

IC50 [µmol]. For procedure, please see SI.

Compound **2a** displayed virtually no activity (IC50 >100 µmol), while for the closest literature compound, which comprises a methyl group instead of an ester, an IC50 value of 7 µmol is reported[28]. The IC50 improved from 60 µmol for phenyl-substituted compound **2g** (entry 4) to 40 µmol for naphtyl-substituted **2h** (entry 5), thus following the trend that antimalaria activity of peroxides improves with increasing lipophilicity. Notably, carbocyclic compound **2p** was amongst the best compounds tested, which we therefore wanted to enhance further. To counter the detrimental effect of its polarity we exchanged the methyl ester for an octyl ester. This led to a further improvement in both the phenyl substituted (entry 7, **2n,** compared to entry 4, **2g)** as well as the carbocyclic compound (entry 8, **2q**, compared to entry 6, **2p)** with the latter exhibiting a promising IC50 in the low micromolar range.

Conclusions

In conclusion this work expands the visible light mediated photooxygenation of arylcyclopropanes to structurally complex fused hetero- and carbocycles by using the highly oxidizing, low-cost organic dye $[MesAcr]ClO_4$ instead of transition metal catalysts. The method described herein offers a safe and scalable access to polycyclic endoperoxide structures found in state-of-the-art anti-malarial drugs while tolerating a variety of functional groups. Taking the encouraging IC50 values of **2p** and **2q** into account, a promising scaffold was identified that will be further explored towards novel antimalarial drugs.

Acknowledgements

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Conflicts of interest

There are no conflicts to declare.

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