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# One-Pot Synthesis of Functionalized Fused Furans via a BODIPY-Catalyzed Domino Photooxygenation

Audrey Mauger,[a] Jonathan Farjon,[a] Pierrick Nun,[a] and Vincent Coeffard*[a]

**Abstract:** Six-membered ring fused furans containing a tetrasubstituted tertiary carbon were prepared *via* an unprecedented one-pot BODIPY-catalyzed domino photooxygenation/reduction process. A series of functionalized furans was synthesized from readily available 2-alkenylphenols and mechanistic studies were performed to account for the domino photosensitized oxygenation.

Photosensitized oxygenation is a convenient process to introduce oxygen atoms into organic architectures. This strategy requires the combination of light, oxygen and a photosensitizer to produce highly reactive oxygen species (ROS) such as singlet oxygen ($^1O_2$).[1] Singlet oxygen is an excited state of molecular oxygen and its high reactivity towards electron-rich substrates has been harnessed in various domains of science such as medicine (photodynamic therapy), materials science and wastewater treatment.[2] From a synthetic standpoint,[3] reactions of singlet oxygen include Schenck-ene reactions,[4] [2+2]- and [4+2]-cycloadditions,[5] heteroatom oxidation[6] and C-H functionalization of inert bonds.[7] Over the past decades, there has been a growing interest in domino reactions which can produce an important increase of molecular complexity *via* one-pot reactions without isolation of intermediates, work-up and purification.[8] Within this context, multiple oxyfunctionalization by means of singlet oxygen has enabled the straightforward synthesis of oxygenated products. For instance, the ene/[4+2]-cycloaddition cascade photooxygenation strategy has been applied to acyclic polyenes and cyclohexa-1,4-dienes for the preparation of functionalized oxygenated architectures.[9] Aromatic substrates such as styrene derivatives,[10] dihydronaphthalenes,[11] and furans[12] also underwent singlet oxygen-mediated multiple oxyfunctionalization.[13] Despite significant contributions, domino photooxygenation remains limited to a scant number of substrates and reaction combinations. In addition, to the best of our knowledge, singlet oxygenation of phenol derivatives have never been embedded in multiple domino oxyfunctionalization while *para*-substituted phenols are known to react with singlet oxygen.[14] As part of our ongoing research into the implementation of dearomative processes,[15] we report herein an unprecedented domino photooxygenation process towards fused furans from readily available 2-alkenylphenols (Scheme 1).

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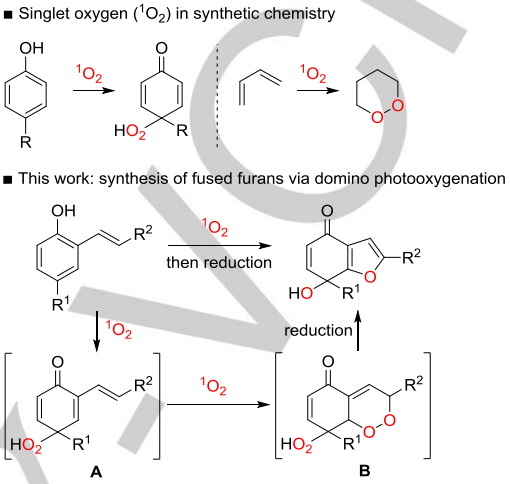


**Scheme 1.** Domino photooxygenation strategy.

Starting from readily available 2-alkenylphenols, we envisioned that electrophilic singlet oxygen would first react with the electron-rich phenol moiety leading to the hydroperoxide **A**. This intermediate would react through a [4+2]-cycloaddition with another molecule of singlet oxygen to afford **B**, which would be further reduced to the targeted furans. Challenges to this strategy includes chemoselectivity issues (phenol dearomatization versus [2+2]-cycloaddition between $^1O_2$ and the alkene or Schenck-ene reaction if $R^2$ is an alkyl group), further undesired photooxygenation of the product **B** and implementation of a one-pot protocol. Nevertheless, the finding of suitable conditions would pave the way to an untrodden route towards functionalized six-membered ring fused furans found in natural products such as Evodone,[16] Eupachinin A[17] and Icacinlactone F.[18]

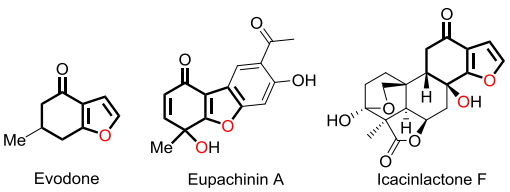


**Figure 1.** Natural compounds with cycloalka[*b*]furan moiety.

At the outset of our studies, we focused on the optimization of the domino photooxygenation process. Our investigations began with the reaction of phenol **1a** in the presence of 2 mol% of photosensitizer under oxygen atmosphere and light irradiation (Table 1).

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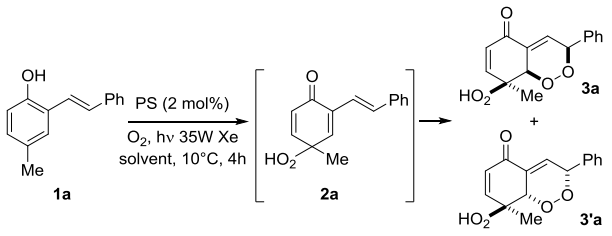
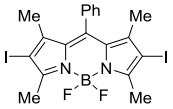
**Table 1.** Optimization of the reaction conditions.[a]




| Entry | PS | Solvent | **2a:3a:3'a**[b] | Yield [%][c] |
|---|---|---|---|---|
| 1 | MB | $CDCl_3$ | - | n.r. |
| 2 | TPP | $CDCl_3$ | 0:77:23 | 15 |
| 3 | RB | MeOH | 100:0:0 | 5 |
| 4[d] | RB | MeOH | 100:0:0 | 10 |
| 5[e] | RB | MeOH | 100:0:0 | 16 |
| ***6*** | ***4*** | ***$CDCl_3$*** | ***0:75:25*** | ***65*** |
| 7[f] | **4** | $CDCl_3$ | 0:65:35 | 46 |
| 8 | **4** | $CHCl_3$ | 0:68:32 | 48 |
| 9 | **4** | MeOH | - | n.r |
| 10 | **4** | MeCN | 0:60:40 | 23 |
| 11 | **4** | DMF | - | <5% |
| 12 | **4** | Toluene | 0:70:30 | 8 |

[a] Reaction conditions unless otherwise noted: **1a** (0.25 mmol), PS (0.005 mmol), $O_2$, hv (Xe), solvent (4.8 mL), 10°C. n.r.: no reaction. [b] Determined by $^1$H NMR analysis on the crude reaction mixture. [c] Combined isolated yields. [d] 4 mol% of RB was used. [e] 8 mol% of RB was used. [f] The reaction was performed at 25°C.

Commercially available photosensitizers were first tested in the domino photooxygenation process. The reactions were run in a typical singlet oxygenation solvent, *i.e.* $CDCl_3$, for which $^1O_2$ lifetime will be high enough to ensure an optimal reaction rate.[19] While methylene blue (MB) did not promote the reaction, tetraphenylporphine (TPP) afforded the products **3a:3'a** in 15% combined isolated yields along with several unidentified by-products (entries 1 and 2). Two diastereomers were obtained and full analyses were carried out to unambiguously confirm their structure (see supporting information for full details). The reaction using rose Bengal (RB) as a photosensitizer was then investigated in methanol due to its insolubility in chloroform. Regardless of the catalyst loading, the hydroperoxide **2a** was obtained in very low yields from 5% to 16% (entries 3-5). We then turned our attention to the iodo-bodipy photosensitizer **4** which has been successfully applied to singlet oxygen-mediated transformations such as photooxidation of naphthols (Figure 2).[20] Formation of the desired targets **3a:3'a** was seen with **4** (65% yield) at 10°C, while the hydroperoxide could not be detected in the crude reaction mixture (entry 6). While similar results were obtained at 0°C, running the reaction at



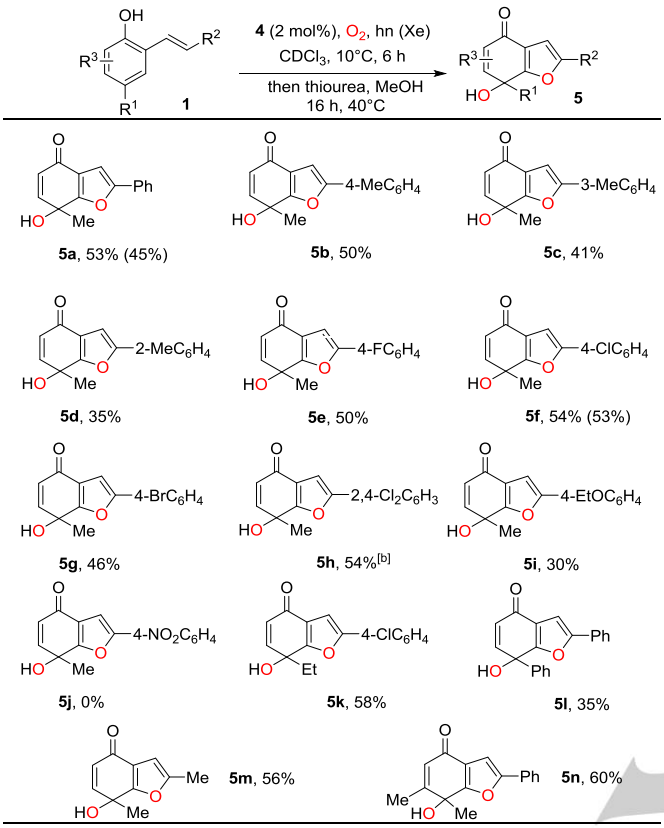

**4**
$\lambda_{(max)abs}$ = 529 nm
$\varepsilon$ = 85000 $M^{-1}cm^{-1}$
$^1O_2$ quantum yield : $\Phi_\Delta$ = 0.79

**Figure 2.** Photosensitizer **4**.[20]

25°C had a negative impact both on the yield and diastereoselectivity (entry 7). The influence of the reaction medium was then investigated by screening various solvents (entries 8-12). When $CDCl_3$ was replaced by its C-H isotopomer, a lower yield was obtained. While acetonitrile enabled the domino photooxygenation process (23% yield), switching to methanol, DMF or toluene was detrimental to the oxygenation reaction. It is worthwhile noting that peroxide products **3a** and **3'a** turned out to be quite unstable and this prompted us to investigate a one-pot reduction step to form table products such as furans. Having established the best reaction conditions for the domino photooxygenation step (Table 1, entry 6) we next turned our focus toward the reduction step. Based on literature data,[9b] a rapid screening of reducing agents ($n$$Bu_2S$, Co(salen), $Ph_3P$) showed that thiourea enabled both reduction of the hydroperoxide and the endoperoxide moiety to afford furan **5a** (Table 2). From a practical point of view, a methanolic solution of thiourea was added after the photooxygenation step owing to the limited solubility of thiourea in $CDCl_3$. A series of 2-alkenyl phenols was prepared to test the scope of our protocol. The photooxygenation reaction time was extended to 6 h to ensure full conversion of the starting materials before addition of thiourea.

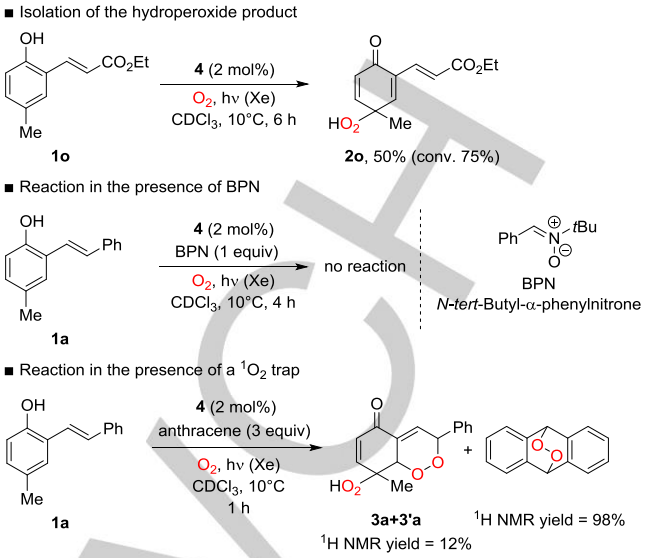
Under optimized conditions, the reaction of **1a** produced furan **5a** in 53% isolated yield. The introduction of a *para*-tolyl substituent ($R^2$) on the substrate did not impinge on the yield producing **5b** in 50% yield. Changing the methyl group on the aromatic ring from the *para*-position to the *meta*- or *ortho*-position led to lower levels of yields. As a result, **5c** was produced in 41% yield while **5d** was isolated in 35% yield. The presence of halogen substituents on the substrate was well tolerated producing the corresponding furans **5e-h** in 46-54% yields. Nevertheless, an increase of the photosensitizer **4** loading (4 mol%) was required for the formation of **5h** in order to ensure full conversion of the starting material after 6 h of reaction time. Under these conditions, furan **5h** was obtained in 54% yield. Electron-donating group such as the ethoxy group on **1i** was tolerated affording **5i** in 30% yield. In contrast, substrate **1j** did not undergo the desired transformation. Under the photooxygenation conditions, *E-Z* isomerization of **1j** was observed in crude $^1$H NMR while no trace of the desired product was detected. From a synthetic standpoint, it is interesting to note that the reaction proceeded with similar levels of yields when the reaction was performed in $CHCl_3$ for 6 h. For instance, furan **5a** was prepared in 45% yield (53% in $CDCl_3$) and the product **5f** was isolated in 53% yield (54% in $CDCl_3$). In addition, scaling up the reaction in $CHCl_3$ to 3 mmol scale provided **5a** in 42% yield after 13 h reaction time.

**Table 2.** Substrate scope.[a]




[a] Reaction conditions unless otherwise noted: **1** (0.25 mmol), **4** (0.005 mmol), $O_2$, hv (Xe), $CDCl_3$ (4.8 mL), 10°C, 6 h followed by addition of thiourea (1 mmol) in MeOH (2 mL), 40°C, 16 h. The yields in brackets were obtained for reactions performed in $CHCl_3$ for the photooxygenation step. [b] 4 mol% of **4** was used.

Variations to the $R^1$ substituent on the phenol ring were next investigated. Ethyl-derived phenol **1k** was also amenable to the photooxygenation reaction providing access to **5k** in 58% yield. The yield decreased when a phenyl-substituted phenol **1l** was used in the reaction and product **5l** was isolated in 35% yield. We then turned our attention to the challenging substrate **1m** bearing a methyl group on the alkene. Similar substrates are known to undergo singlet oxygen-promoted ene reaction or oxidative cleavage of the double bond under photosensitized oxygenation.[21] We were pleased to find that the conditions enabled the selective formation of furan **5m** in 56% yield. The phenol **1n** bearing an additional methyl group on the aromatic ring is a suitable substrate for the photooxygenation process. Under optimized conditions, **5n** was obtained in 60% yield. In order to get some insights about the reaction mechanism, a series of experiments was carried out on the photooxygenation of **1** (Scheme 2). With reference to our domino strategy depicted in Scheme 1 and the results gathered in Table 1, the first singlet oxygen molecule should react with the phenol moiety to give the corresponding hydroperoxide. This hypothesis was fully confirmed by performing the photooxygenation of the phenol **1o** bearing an electron-withdrawing substituent on the alkene which hampers the [4+2] cycloaddition due to a lower reactivity of the diene towards electrophilic singlet oxygen.[9b] Iodo-bodipy **4** is




**Scheme 2.** Control experiments.

known to produce singlet oxygen $^1O_2$[20] and superoxide anion radical $O_2^{\bullet-}$[22] depending on the reaction conditions. No reaction occurred by running the photooxygenation of **1a** with 1 equivalent of BPN, a quencher of both $^1O_2$ and $O_2^{\bullet-}$,[23] which confirms the involvement of these species in the domino photooxygenation process. The formation of $^1O_2$ is supported by the observation that addition of a chemical $^1O_2$ trap such as anthracene has an important impact on the reaction kinetics. While a mixture of diastereomers **3a/3'a** was obtained in 36% yield without anthracene, the addition of 3 equivalents of anthracene led to the formation of **3a/3'a** in only 12% yield along with anthracene-9,10-endoperoxide (98% yield). To further shed the light on the mechanism, the kinetic profile of the photooxygenation of **1a** was investigated (Figure 3, see supporting information for full details).

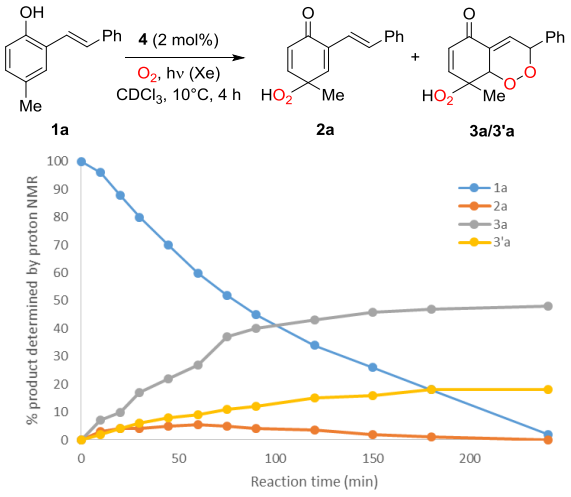



**Figure 3.** Photooxygenation kinetic profile.

The yield of the double oxygenated products **3a/3'a** increases as the reaction proceeds while the diastereomeric ratio remains constant throughout the reaction (d.r., 75/25). Interestingly, the hydroperoxide intermediate **2a** was detected in the reaction mixture from the very start of the reaction and it reaches a maximum concentration after 1 h. In line with results of Scheme 2, this observation indicates that photooxygenation of **1a** would first lead to the intermediate **2a** which would react with a second equivalent of singlet oxygen to produce **3a** and **3'a**. The diastereomers were obtained in 66% NMR yield (**3a/3'a**, 73/27) and these results were in complete agreement with the results depicted in Table 1 (entry 6). In addition, careful analyses of the crude revealed the presence of unidentified aldehydic side-products at the end of the photooxygenation protocol which could explain the moderate yields of the process.

In summary, an unprecedented synthesis of six-membered ring fused furans under mild conditions has been described. Central to the implementation of the one-pot strategy is the photosensitized singlet oxygen-mediated phenol dearomatization followed by a [4+2]-cycloaddition. A reductive work-up enabled the synthesis of diversely functionalized furans containing a tetrasubstituted tertiary carbon center. Detailed mechanistic studies were carried out to get a better understanding of the photosensitized domino oxygenation process.

## Acknowledgements

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**Keywords:** heterocycles • photochemistry • homogeneous catalysis • oxidation • synthetic methods.

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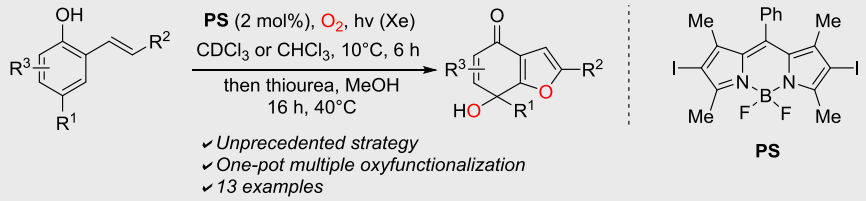


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**One-Pot Synthesis of Functionalized Fused Furans via a BODIPY-Catalyzed Domino Photooxygenation**

**Enlightening domin$^1O_2$:** In this report, a one-pot photosensitized double oxygenation/reduction process was developed. This strategy provided access to six-membered ring fused furans containing a tetrasubstituted tertiary center.