

# Online Research @ Cardiff

This is an Open Access document downloaded from ORCA, Cardiff University's institutional repository: <http://orca.cf.ac.uk/124764/>

This is the author's version of a work that was submitted to / accepted for publication.

Citation for final published version:

Elsherbini, Mohamed, Allemann, Rudolf K. and Wirth, Thomas 2019. 'Dark' singlet oxygen made easy. *Chemistry - A European Journal* 25 (54) , pp. 12486-12490. 10.1002/chem.201903505 file

Publishers page: <http://dx.doi.org/10.1002/chem.201903505>  
<<http://dx.doi.org/10.1002/chem.201903505>>

Please note:

Changes made as a result of publishing processes such as copy-editing, formatting and page numbers may not be reflected in this version. For the definitive version of this publication, please refer to the published source. You are advised to consult the publisher's version if you wish to cite this paper.

This version is being made available in accordance with publisher policies. See <http://orca.cf.ac.uk/policies.html> for usage policies. Copyright and moral rights for publications made available in ORCA are retained by the copyright holders.

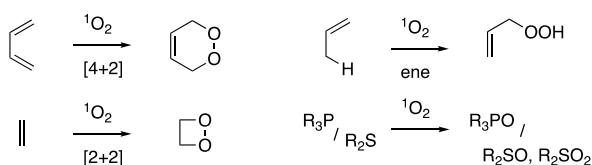


# 'Dark' Singlet Oxygen Made Easy

Mohamed Elsherbini, Rudolf K. Allemann\* and Thomas Wirth\*[a]

**Abstract:** An operationally simple continuous flow generator of 'dark' singlet oxygen has been developed. The singlet oxygen was efficiently reacted with several chemical traps to give the corresponding oxygenated products in high yields. The developed 'dark' singlet oxygen generator has been successfully applied in the synthesis of the antimalarial drug artemisinin.

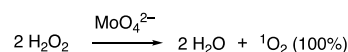
Oxidation reactions are one of the most fundamental chemical transformations in nature, industry and chemical laboratories.<sup>[1,2]</sup> Molecular oxygen is a highly appealing oxidizing agent due to its abundance in nature, low cost, chemical inertness and inherent green nature.<sup>[1,3,4]</sup> However, the drastic conditions (high pressure and/or temperature) usually associated with the utilization of oxygen in its ground state (triplet oxygen,  $^3\text{O}_2$ ) limits its applications in oxidation reactions due to safety issues, especially at large scales.<sup>[4,5,6]</sup> Molecular oxygen in its singlet state (singlet oxygen,  $^1\text{O}_2$ ) on the other hand is highly reactive with organic molecules under very mild conditions.<sup>[7]</sup> The lifetime of singlet oxygen in solutions is in the microsecond range due to its fast deactivation through electronic-to-vibrational coupling with solvent molecules but its high reactivity allows practical applications in organic synthesis. Synthetically useful applications of singlet oxygen fall into four fundamental categories (Scheme 1):<sup>[7]</sup> [4+2] cycloadditions, [2+2] cycloadditions, 'ene' reactions and oxidations of heteroatoms.



**Scheme 1.** Typical reactions of singlet oxygen.

Conventionally, singlet oxygen is generated photochemically from triplet oxygen in the presence of a photosensitizer.<sup>[7]</sup> However, generation of singlet oxygen *via* photosensitization entails many practical and technical challenges, especially when used on a large scale such as the need of specialized equipment, light penetration of the reaction media, low solubility of oxygen in solution and slow rate of oxygen mass transfer into solution, in addition to light-induced side reactions. Although some of the inherent limitations of photochemical reactions could be alleviated using photochemistry under continuous-flow conditions<sup>[6,8]</sup> and vortex reactors,<sup>[9]</sup> developing efficient non-photochemical methods for the generation of singlet oxygen ('dark' singlet oxygen)<sup>[10,11]</sup> are of great importance for boosting utilization of singlet oxygen in synthetic organic chemistry. Generation of 'dark' singlet oxygen *via* molybdate-catalysed disproportionation of

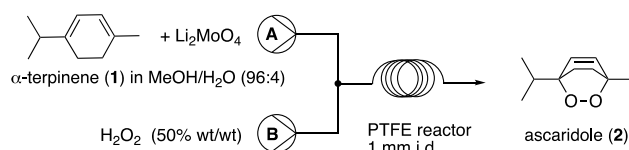
hydrogen peroxide (Scheme 2)<sup>[12]</sup> is a promising alternative to photochemical methods.



**Scheme 2.** Generation of 'dark'  $^1\text{O}_2$ .

Although, the above process is well-studied<sup>[10,12,13]</sup> and relies on cheap reagents and yields singlet oxygen quantitatively, its applications in organic synthesis are limited. The unpopularity of the  $\text{H}_2\text{O}_2 / \text{MoO}_4^{2-}$  system as a source of  $^1\text{O}_2$ , although efficient, could be attributed to the difficulty of keeping the critical balance between hydrogen peroxide and the molybdate catalyst, necessary to generate sufficient amounts of the more reactive species, oxotriperoxomolybdate ( $[\text{MoO}(\text{O}_2)_3]^{2-}$ ) as proven by  $^{95}\text{Mo}$  NMR and kinetic studies.<sup>[10]</sup> Practically, the addition of  $\text{H}_2\text{O}_2$  to the reaction mixture must be performed in small amounts with intervals over a long period of time.<sup>[12, 14, 15]</sup> In addition, the formation of dioxodiperoxomolybdate ( $[\text{MoO}_2(\text{O}_2)_2]^{2-}$ ) and tetraperoxomolybdate ( $[\text{Mo}(\text{O}_2)_4]^{2-}$ ) which disproportionate slowly (20 times slower than  $[\text{MoO}(\text{O}_2)_3]^{2-}$ ),<sup>[10]</sup> cannot be avoided and leads to long reaction times. In addition, the method is practically limited to methanol and ethanol as solvents, where the lifetime of  $^1\text{O}_2$  is relatively short, 10 and 14  $\mu\text{s}$ , respectively.<sup>[12]</sup> This limits its applicability to substrates of high relative rate of reaction with  $^1\text{O}_2$ . Using solvents where the lifetime of  $^1\text{O}_2$  is longer, such as  $\text{CHCl}_3$  (220  $\mu\text{s}$ ),  $\text{CH}_2\text{Cl}_2$  (97  $\mu\text{s}$ ) and MeCN (67  $\mu\text{s}$ ) leads to poor yields due to the formation of heterogeneous mixtures upon addition of aqueous hydrogen peroxide.<sup>[12, 16]</sup> Microemulsions have been used but large amounts of surfactants are usually required for their stabilisation.<sup>[17]</sup> These limitations could be alleviated partially or even completely using flow chemistry techniques.<sup>[18]</sup> Herein, we report a simple, efficient, and reliable continuous flow generator of 'dark' singlet oxygen and its applications in oxygenation of organic molecules of various classes.

Generation of 'dark' singlet oxygen using  $\text{H}_2\text{O}_2 / \text{MoO}_4^{2-}$  system under flow conditions was investigated in depth. The efficiency of the  $^1\text{O}_2$  generator was assessed by trapping the generated  $^1\text{O}_2$  with  $\alpha$ -terpinene (**1**) and the yield of the product ascaridole (**2**) was determined by  $^1\text{H}$  NMR using 1,3,5-trimethoxybenzene as internal standard. The concentration of the molybdate catalyst, the chemical trap ( $\alpha$ -terpinene) and the amount of hydrogen peroxide were investigated in detail in addition to the residence time and the reaction temperature using a simple flow setup shown in Figure 1.



**Figure 1.** Flow setup for generation/trapping of 'dark' singlet oxygen.

Using a fixed concentration of  $\text{Li}_2\text{MoO}_4$  (0.025 M), the concentration and flow rate of  $\alpha$ -terpinene (**1**) were initially changed while adding 4.4 equivalents  $\text{H}_2\text{O}_2$  at room temperature (Table 1, entries 1-3). Ascaridole (**2**) was formed in 10%, 11%, and 19%, respectively. Reducing the amount of  $\text{H}_2\text{O}_2$  resulted in

[a] Dr. M. Elsherbini, Prof. R. K. Allemann, Prof. Dr. T. Wirth  
School of Chemistry, Cardiff University  
Main Building, Park Place, Cardiff, CF10 3AT (UK)  
E-mail: wirth@cf.ac.uk

Supporting information for this article is given via a link at the end of the document.

a similar yield (20%, entry 4). However, when changing the temperature (Table 1, entries 5-7), a significant increase in the reaction yield (32%) was observed at 40 °C.<sup>[12]</sup> Increasing the residence time by decreasing the flow rate (Table 1, entry 8) led to a slight increase of the yield to 36%. Another significant increase of the yield (51%) was observed when the reactor volume increased from 2 mL to 4 mL (Table 1, entry 9). Although the residence time did not change compared to entry 8, the increase of reaction yield was attributed to the more efficient mixing in the reactor at higher flow rates. Increasing the reactor volume to 6 mL did not lead to any further improvement of the reaction outcome (Table 1, entry 10). Varying the amount of H<sub>2</sub>O<sub>2</sub> above and below 2.2 equivalent lead to a decrease of the yield (Table 1, entries 11,12). Reducing the concentration of **1** from 0.25 M to 0.1 M led to a dramatic increase in the reaction yield, where ascaridole (**2**) was formed in quantitative yield (Table 1, entry 13). Increasing the concentration of **1** above 0.1 M or decreasing the concentration of the molybdate catalyst led to lower product yields (Table 1, entries 14-16).

**Table 1.** Optimisation of the generation/trapping of 'dark' <sup>1</sup>O<sub>2</sub> in flow

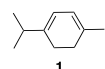
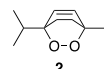
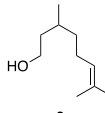
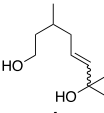
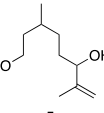
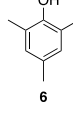
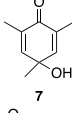





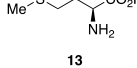
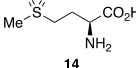
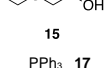
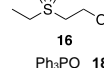


Entry	$\alpha$ -Terpinene [M]	Flow A [mL/min]	Flow B [ $\mu$ L/min]	Reactor volume [mL]	Calculated residence time [min] <sup>[a]</sup>	Temp. [°C]	Yield <b>2</b> [%] <sup>[b]</sup>
1	0.5	0.5	62.5 (4.4 eq)	2	3.56	RT	10
2	0.25	0.5	31.3 (4.4 eq)	2	3.76	RT	11
3	0.25	0.25	15.6 (4.4 eq)	2	7.53	RT	19
4	0.25	0.25	7.8 (2.2 eq)	2	7.76	RT	20
5	0.25	0.25	7.8 (2.2 eq)	2	7.76	30	24
6	0.25	0.25	7.8 (2.2 eq)	2	7.76	40	32
7	0.25	0.25	7.8 (2.2 eq)	2	7.76	50	29
8	0.25	0.125	3.9 (2.2 eq)	2	15.52	40	36
9	0.25	0.25	7.8 (2.2 eq)	4	15.52	40	51
10	0.25	0.25	7.8 (2.2 eq)	6	23.30	40	50
11	0.25	0.25	11.7 (3.3 eq)	4	15.3	40	42
12	0.25	0.25	3.7 (1.0 eq)	4	15.77	40	39
13	0.1	0.25	7.8 (5.5 eq)	4	15.5	40	100
14	0.2	0.25	7.8 (2.7 eq)	4	15.5	40	70
15	0.15	0.25	7.8 (3.6 eq)	4	15.5	40	87
16 <sup>[c]</sup>	0.1	0.25	7.8 (5.5 eq)	4	15.5	40	77

Reaction conditions: Solvent: MeOH/H<sub>2</sub>O (96:4); [Li<sub>2</sub>MoO<sub>4</sub>] = 0.025 M; <sup>[a]</sup> The actual residence time is shorter than the calculated one due to the gas evolution during the reaction. <sup>[b]</sup> Determined by <sup>1</sup>H NMR using 1,3,5-trimethoxybenzene as internal standard; <sup>[c]</sup> [Li<sub>2</sub>MoO<sub>4</sub>] = 0.015 M (15 mol%).

The optimised reaction conditions (Table 1, entry 13) were applied to other substrates and the results are summarised in Table 2. In addition to the oxidation of  $\alpha$ -terpinene (**1**), rac- $\beta$ -citronellol (**3**) was oxidised to corresponding diols **4** and **5** (1:1 mixture) in 97% yield after reduction of the initially formed hydroperoxides with sodium sulfite. Dearomatisation of mesitol (**6**) was achieved in 49% yield using the same conditions, but with the addition of 1 equiv. of NaOH to form the phenoxide ion of **6** to avoid quenching of <sup>1</sup>O<sub>2</sub> by the phenol form.<sup>[12]</sup> 2,5-Dimethyl furan (**8**) was converted into (*E*)-hex-3-ene-2,5-dione (**9**) in 73% yield upon reduction of the initially formed intermediates<sup>[19]</sup> (see supporting information). Oxidation of thioanisole (**10**) led to the formation of a mixture of the corresponding sulfoxide **11** and sulfone **12** in a 1:7 ratio.

Increasing the concentration of **10** from 0.1 M to 0.2 M lead to the formation of **11** as a major product (**11/12**, 1:0.77). Due to the insolubility of L-methionine (**13**) in methanol, an aqueous substrate solution was used. Interestingly, the corresponding sulfone **14** crushed out upon addition of methanol to the collected reaction mixture and 85% of **14** were obtained as a pure product by simple filtration. Moreover, sulfone **16** was obtained in excellent yield (98%) upon oxidation of 2-(ethylthio)ethan-1-ol (**15**). Oxidation of phosphorous was also achieved using the developed 'dark' <sup>1</sup>O<sub>2</sub> generator, where triphenylphosphine was converted quantitatively into triphenylphosphine oxide.

**Table 2.** Synthetic applications of 'dark' <sup>1</sup>O<sub>2</sub> in flow<sup>[a]</sup>

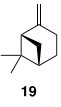
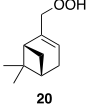


Entry	Substrate	Product(s)	Yield [%]
1			quant. <sup>[b]</sup>
2		 + 	97 <sup>[c]</sup> <b>4/5</b> (1:1)
3			49 <sup>[d]</sup>
4			73 <sup>[e]</sup>
5		 <b>11</b> +  <b>12</b>	quant. <b>11/12</b> (1:7) <b>11/12</b> (1:0.77) <sup>[f]</sup>
6			85 <sup>[g]</sup>
7			98
8			quant. <sup>[h]</sup>

<sup>[a]</sup> Reactions were performed using a 4 mL reactor (PTFE, 1 mm i.d.); solution of substrate (0.1 M) in MeOH-H<sub>2</sub>O (96:4) containing 25 mol% of Li<sub>2</sub>MoO<sub>4</sub> was pumped at 0.25 mL/min. H<sub>2</sub>O<sub>2</sub> (50% wt/wt) was pumped at 7.8  $\mu$ L/min and combined with the substrate solution using T-mixer. <sup>[b]</sup> Determined using <sup>1</sup>H NMR with 1,3,5-trimethoxybenzene as internal standard due to the volatility of **2**. <sup>[c]</sup> The initially formed hydroperoxides were reduced with sat. aq. sodium sulfite (Na<sub>2</sub>SO<sub>3</sub>) to the corresponding alcohols. <sup>[d]</sup> 1.0 equiv. of NaOH was added to the substrate solution. <sup>[e]</sup> Obtained after reduction of the initially formed intermediate using PPh<sub>3</sub> (see supporting information). <sup>[f]</sup> Using 0.2 M of **10**. <sup>[g]</sup> Aqueous L-methionine (**13**) solution was used. <sup>[h]</sup> Due to solubility problems, the PPh<sub>3</sub> concentration was reduced to 0.025 M.

Under the same conditions,  $\beta$ -pinene (**19**) and  $\alpha$ -pinene (**21**) failed to react, which could be attributed to the known low relative reaction rates of pinenes with <sup>1</sup>O<sub>2</sub>,<sup>[16]</sup> along with the relatively short lifetime of <sup>1</sup>O<sub>2</sub> in methanol (10  $\mu$ s).<sup>[11]</sup> Using solvents other than methanol and ethanol in batch led to poor yield due to the formation of a heterogeneous reaction mixture.<sup>[11]</sup> Changing the solvent from methanol to acetonitrile (lifetime of <sup>1</sup>O<sub>2</sub> = 67  $\mu$ s) led to alleviation of the problem. The addition of methanol (10%) to the acetonitrile solvent avoided the formation of a biphasic mixture in the reactor. After a quick optimization using a modified reaction setup, where the molybdate salt was separated from the substrate solution and its aqueous solution fed as a third stream (see

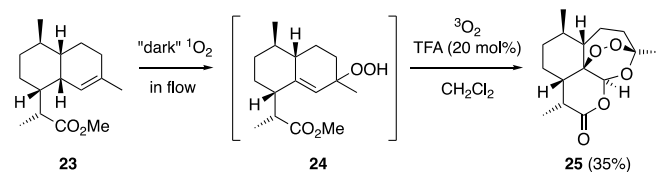
supporting information), the corresponding oxygenated products **20** and **22** were obtained in 40% and 48% yield, respectively.

**Table 3.** Oxidation of pinenes using 'dark'  $^1\text{O}_2$  in flow<sup>[a]</sup>

Entry	Substrate	Product	Yield [%]
1			40 <sup>[b]</sup>
2			48 <sup>[b,c]</sup>

<sup>[a]</sup> Reactions setup and conditions (See supporting information). <sup>[b]</sup> Performing the reaction in batch using methanol or acetonitrile led to the formation of the products in a very poor yield (< 3%). <sup>[c]</sup> Obtained after reduction of the initially formed hydroperoxide using PPH<sub>3</sub>.

Finally, the applicability of the developed 'dark'  $^1\text{O}_2$  generator was confirmed by its successful application in the synthesis of the anti-malarial drug artemisinin.<sup>[20]</sup> However, under modified reaction conditions, 60 mol% of the molybdate catalyst and adjusting the  $\text{H}_2\text{O}_2$  flow rate to 18.7  $\mu\text{L}/\text{min}$  were necessary to achieve full conversion of the dihydroartemisinic methyl ester **23**.<sup>[15]</sup> Treatment of the crude hydroperoxide **24** with trifluoroacetic acid (20 mol%) while bubbling oxygen into the reaction mixture in dichloromethane led to the formation of artemisinin **25** (Scheme 3) in 35% yield, which is comparable to established photochemical methods.<sup>[15,21]</sup>



**Scheme 3.** Application of the 'dark'  $^1\text{O}_2$  generator in the synthesis of artemisinin (**25**).

In conclusion, a simple and practical continuous-flow generator of 'dark' singlet oxygen has been developed. This method represents a reliable alternative and complementary

protocol for the well-known photochemical protocols of generating singlet oxygen. The developed generator was applied to various substrates and the expected products were obtained in good to excellent yields in sufficiently pure form so that purification was not needed in most cases. Moreover, this protocol was successfully applied to the synthesis of the anti-malarial drug artemisinin. In addition, the developed flow protocol provides a solution to some intrinsic problems of the chemical generation of  $^1\text{O}_2$  using  $\text{H}_2\text{O}_2$  /  $\text{MoO}_4^{2-}$  system in batch, such as solvent and substrate limitations.

## Experimental Section

Using the reaction setup shown in Figure 1, a solution of substrate (0.1 M) and  $\text{Li}_2\text{MoO}_4$  (0.025 M) in  $\text{MeOH}/\text{H}_2\text{O}$  (96:4) was pumped using a syringe pump (0.25 mL/min) and combined with a stream of 50% (wt/wt)  $\text{H}_2\text{O}_2$  (7.8  $\mu\text{L}/\text{min}$ ) using a T-mixer and pumped in a PTFE coil reactor (4 mL, 1 mm i.d.) at 40 °C. The first two reactor volumes (8 mL) were discarded and the next 20 mL (2.0 mmol of substrate) were collected. Quenching the reaction immediately by a reducing agent did not lead to any change in yields. Hence, the reactions were collected without quenching to simplify the workup procedure. The reaction mixture was concentrated under reduced pressure, then diluted with water (10 mL) and extracted with  $\text{CHCl}_3$  (3 x 10 mL). The combined organic layers were evaporated under reduced pressure to give the crude reaction product.

## Acknowledgements

The authors are grateful to the Bill and Melinda Gates foundation for the generous funding (Grant no: OPP1190186). We also thank Drs Alice Dunbabin and Donya Valikhani and Ms Florence Huynh, Cardiff University, for helpful discussions and assistance.

**Keywords:** Artemisinin • Flow Chemistry • Hydroperoxides • Oxidation • Singlet Oxygen

- [1] Z. Guo, B. Liu, Q. Zhang, W. Deng, Y. Wang, Y. Yang, *Chem. Soc. Rev.* **2014**, *43*, 3480–3524.
- [2] *Modern Oxidation Methods*, Ed. J.-E. Bäckvall, Wiley-VCH, Weinheim, **2010**.
- [3] a) Y.-F. Liang, N. Jiao, *Acc. Chem. Res.* **2017**, *50*, 1640–1653; b) L. Vanoye, J. Wang, M. Pablos, C. de Bellefon, A. Favre-Régouillon, *Catal. Sci. Technol.* **2016**, *6*, 4724–4732.
- [4] C. A. Hone, C. O. Kappe, *Top. Curr. Chem.* **2019**, *377*, 1–44.
- [5] P. E. Correa, G. Hardy, D. P. Riley, *J. Org. Chem.* **1988**, *53*, 1695–1702.
- [6] N. Emmanuel, C. Mendoza, M. Winter, C. R. Horn, A. Vizza, L. Dreesen, B. Heinrichs, J.-C. M. Monbaliu, *Org. Process Res. Dev.* **2017**, *21*, 1435–1438.
- [7] a) A. A. Ghogare, A. Greer, *Chem. Rev.* **2016**, *116*, 9994–10034; b) H. H. Wasserman, R. W. DeSimone, K. R. X. Chia, M. G. Banwell, in *Encycl. Reag. Org. Synth.*, Wiley, Chichester, **2013**; E. L. Clennan, A. Pace, *Tetrahedron* **2005**, *61*, 6665–6691.
- [8] a) E. N. DeLaney, D. S. Lee, L. D. Elliott, J. Jin, K. I. Booker-Milburn, M. Poliakov, M. W. George, *Green Chem.* **2017**, *19*, 1431–1438; b) F. Lévesque, P. H. Seeberger, *Org. Lett.* **2011**, *13*, 5008–5011.
- [9] D. S. Lee, Z. Amara, C. A. Clark, Z. Xu, B. Kakimpa, H. P. Morvan, S. J. Pickering, M. Poliakov, M. W. George, *Org. Process Res. Dev.* **2017**, *21*, 1042–1050.
- [10] a) Y. You, *Org. Biomol. Chem.* **2018**, *16*, 4044–4060; b) V. Nardello, J. Marko, G. Vermeersch, J. M. Aubry, *Inorg. Chem.* **1995**, *34*, 4950–4957; c) R. W. Murray, M. L. Kaplan, *J. Am. Chem. Soc.* **1969**, *91*, 5358–5364.
- [11] a) W. Fudickar, T. Linker, *Angew. Chem. Int. Ed.* **2018**, *57*, 12971–12975; *Angew. Chem.* **2018**, *130*, 13153–13157; b) M. Bauch, A. Krtischka, T. Linker, *J. Phys. Org. Chem.* **2017**, *30*, e3734.
- [12] V. Nardello, S. Bogaert, P. L. Alsters, J.-M. Aubry, *Tetrahedron Lett.* **2002**, *43*, 8731–8734.
- [13] a) P. L. Alsters, W. Jary, V. Nardello-Rataj, J.-M. Aubry, *Org. Process Res. Dev.* **2010**, *14*, 259–262; b) B. F. Sels, D. E. De Vos, P. J. Grobet, P. A. Jacobs, *Chem. Eur. J.* **2001**, *7*, 2547–56; c) F. van Laar, D. De Vos, D. Vanoppen, B. Sels, P. A. Jacobs, *Chem. Commun.* **1998**, 267–268.
- [14] X. Tang, M. Demiray, T. Wirth, R. K. Allemann, *Bioorg. Med. Chem.* **2018**, *26*, 1314–1319.
- [15] C. J. Paddon, P. J. Westfall, D. J. Pitera, K. Benjamin, K. Fisher, D. McPhee, M. D. Leavell, A. Tai, A. Main, D. Eng, et al., *Nature* **2013**, *496*, 528–532.

- 
- [16] A. A. Frimer, *Singlet O<sub>2</sub>*, CRC Press, Florida, **1985**.
- [17] a) P. L. Alsters, W. Jary, V. Nardello-Rataj, J.-M. Aubry, *Org. Process Res. Develop.* **2010**, *14*, 259–262; b) V. Nardello, L. Caron, J.-M. Aubry, S. Bouttemy, T. Wirth, R. S.-M. Chantou, W. Adam, *J. Am. Chem. Soc.* **2004**, *126*, 10692–10700.
- [18] T. Glasnov, *Continuous-Flow Chemistry in the Research Laboratory*, Springer, Cham, **2016**.
- [19] a) C. S. Foote, S. Wexler, W. Ando, R. Higgins, *J. Am. Chem. Soc.* **1968**, *90*, 975–981; b) C. S. Foote, M. T. Wuesthoff, S. Wexler, I. G. Burstain, R. Denny, G. O. Schenck, K.-H. Schulte-Elte, *Tetrahedron* **1967**, *23*, 2583–2599.
- [20] a) D. Singh, D. McPhee, C. J. Paddon, J. Cherry, G. Maurya, G. Mahale, Y. Patel, N. Kumar, S. Singh, B. Sharma, L. Kushwaha, S. Singh, A. Kumar, *Org. Process Res. Dev.* **2017**, *21*, 551–558; b) Z. Amara, J. F. B. Bellamy, R. Horvath, S. J. Miller, A. Beeby, A. Burgard, K. Rossen, M. Poliakoff, M. W. George, *Nat. Chem.* **2015**, *7*, 489–495; c) Z. Wang, L. Yang, X. Yang, X. Zhang, *Synth. Commun.* **2014**, *44*, 1987–2003; d) D. Kopetzki, F. Lévesque, P. H. Seeberger, *Chem. Eur. J.* **2013**, *19*, 5450–5456.
- [21] a) F. Lévesque, P. H. Seeberger, *Angew. Chem. Int. Ed.* **2012**, *51*, 1706–1709; *Angew. Chem.* **2012**, *124*, 1738–1741; b) J. S. Yadav, B. Thirupathaiah, P. Srihari, *Tetrahedron* **2010**, *66*, 2005–2009.
-

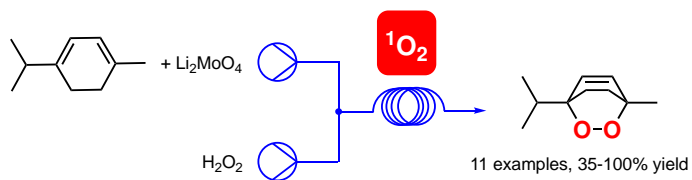
---

## COMMUNICATION

---

**An efficient and easy generation** of 'dark' singlet oxygen allows the straightforward oxygenation of various organic substrates. A simple flow setup allows the precise control of mild reaction conditions.

*Mohamed Elsherbini, Rudolf K. Allemann\*, Thomas Wirth\**



**Page No. – Page No.**

**'Dark' Singlet Oxygen Made Easy**

---