



Visible light-promoted metal-free aerobic photooxidation of xanthenes, thioxanthenes and dihydroacridines in deep eutectic solvents

Sarah-Jayne Burlingham, Alejandro Torregrosa-Chinillach, Diego A. Alonso^{**}, Rafael Chinchilla^{*}

Departamento de Química Orgánica, Facultad de Ciencias, and Instituto de Síntesis Orgánica (ISO), Universidad de Alicante, Apdo. 99, 03080, Alicante, Spain

ARTICLE INFO

Keywords:

Photooxidation
Xanthenes
Thioxanthenes
Acridones
Deep eutectic solvents

ABSTRACT

Benzylic systems such as 9*H*-xanthenes, 9*H*-thioxanthenes and 9,10-dihydroacridines can be easily oxidized to the corresponding xanthenes, thioxanthenes or acridones, respectively, in deep eutectic solvents by a visible blue light-promoted photooxidation procedure carried out using ambient air as oxidant in the presence of riboflavin tetraacetate as a metal-free photocatalyst. The obtained yields are high or almost quantitative, and the reaction media can be recovered and reused. The environmental friendliness of the protocol is demonstrated based on several green metrics.

1. Introduction

In recent years, visible-light photocatalysis has emerged as an interesting synthetic tool compared to traditional photochemistry [1,2]. This is due to organic compounds lacking absorbance of this radiation, which reduces side reactions frequently associated with classical photochemical reactions carried out with high-energy UV light. However, when this less energetic and innocuous visible light is employed, adding catalytic amounts of a sensitizer as a photocatalyst is required, although the reaction setup is much simpler. Amongst the successful transformations under these conditions are visible light-induced photooxidation reactions [3–14], particularly those involving benzylic bonds [15–17]. When the final oxidant is the cheap and environmentally friendly molecular oxygen [18,19], this results in a direct technique to generate carbonyl systems.

The concept of visible light-promoted aerobic benzylic photooxidation can be applied to prepare compounds such as xanthenes, thioxanthenes and acridones from the appropriate precursors. Thus, xanthenes (9*H*-xanthen-9-ones) are interesting to prepare [20,21], as this moiety is present in biologically active compounds [22–25], as well as in the case of thioxanthenes [26] and acridones [acridin-9 (10*H*)-ones] [27–29].

Xanthenes can be obtained by the aerobic photocatalytic benzylic oxidation of 9*H*-xanthenes. Thus, ruthenium- [30], iron- [31–33] or copper-containing [34] species have been successfully employed as

photocatalysts (Scheme 1a), but using a metal-based catalyst has less-than-desirable environmental effects. Therefore, using metal-free photocatalysts for this transformation has also been explored [35–39] (Scheme 1b). In addition, the photooxidation of the methylene position in *N*-substituted 9,10-dihydroacridines (acridanes) leading to acridones has been less frequently investigated. Thus, *N*-methylacridane has been transformed into *N*-methylacridone by photooxidation using manganese [40] or ruthenium complexes [41] as photocatalysts in the presence of oxygen (Scheme 1c), and a metal-free procedure has also been reported for the visible light-induced oxidation of 9,10-dihydroacridines to acridones [37] (Scheme 1d).

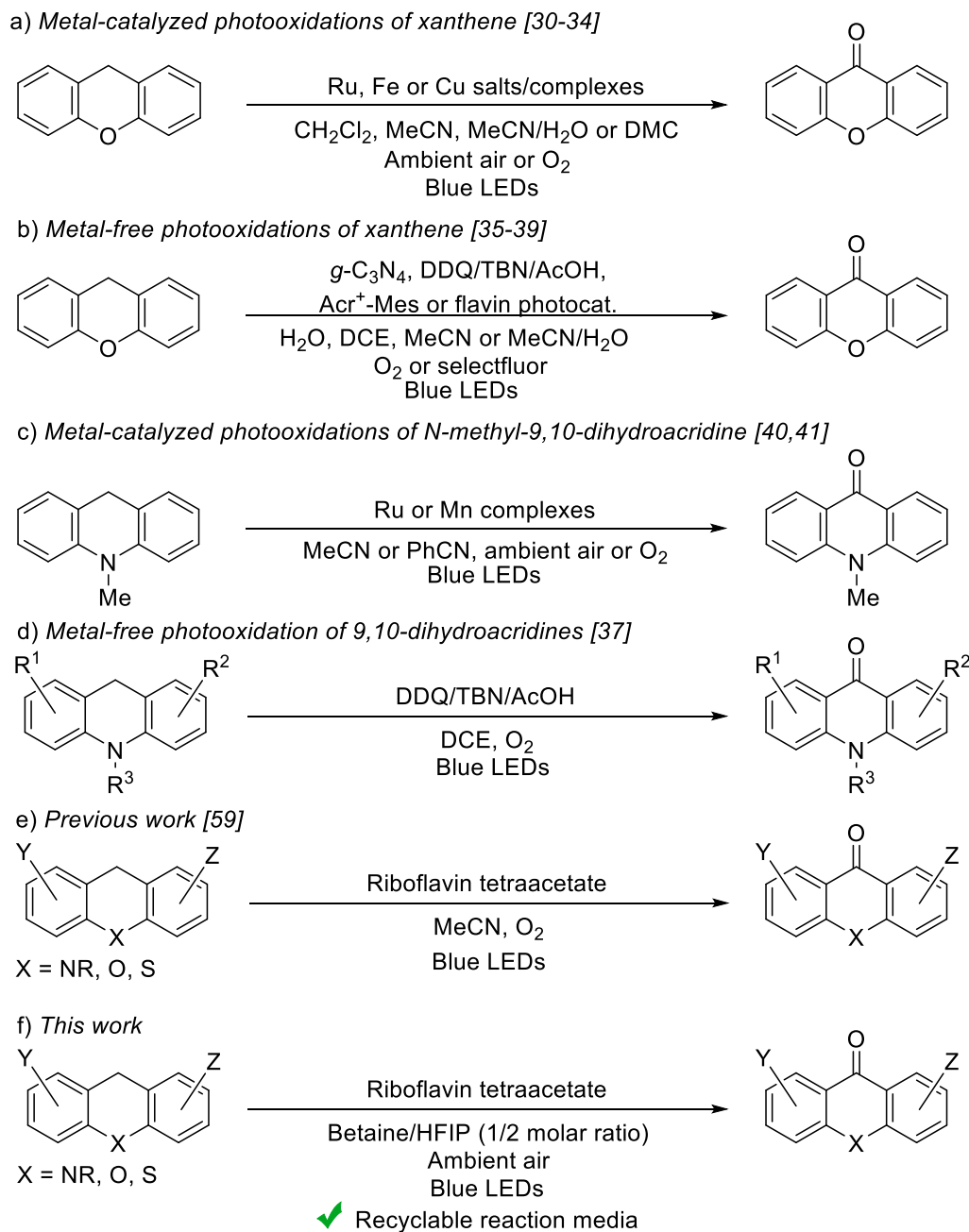
All these methodologies have been carried out using traditional volatile organic compounds (VOCs) as solvents, which are ubiquitously employed as reaction media. However, from an environmental point of view, they show intrinsic drawbacks, such as accumulation in the atmosphere, flammability, toxicity and non-biodegradability. Consequently, several alternative reaction media in organic transformations have been explored [42,43]. Among them, deep eutectic solvents (DESs) are attracting a growing interest [44–55], as DESs are non-volatile, show a low ecological footprint, are economical, essentially non-toxic and easily recyclable. However, up to date, there is only one recent report about the use of DESs in a photochemical organic reaction, although using an expensive ruthenium-based photocatalyst was necessary [56].

Moreover, some safety considerations must be remarked when using the “ideal” oxygen as an oxidant. Thus, it is tempting to take oxygen for

* Corresponding author.

** Corresponding author.

E-mail addresses: diego.alonso@ua.es (D.A. Alonso), chinchilla@ua.es (R. Chinchilla).



Scheme 1. Precedents of the visible light promoted photooxidation of xanthenes, thioxanthenes and 9,10-dihydroacridines, and this work.

granted because it is present in the air. The US CGA (Compressed Gas Association) [57], as well as the European Industrial Gases Association (EIGA) [58], defined oxygen-enriched mixtures or atmospheres as those containing more than 23.5 % oxygen by volume. In oxygen-enriched atmospheres, the reactivity of oxygen significantly increases the risk of ignition and fire. Materials that may not burn in normal air may do it vigorously in an oxygen-rich environment. Sparks considered harmless may cause fires, and materials may burn with a much hotter flame and propagate faster. All these reasons justify the convenience of using oxidation procedures carried out using oxygen in the form of much safer ambient air.

We recently reported a visible light-induced photooxidation of xanthenes, thioxanthenes and dihydroacridines carried out using a metal-free photocatalyst and pure oxygen as the final oxidant in acetonitrile as solvent [59] (Scheme 1e). We report now (Scheme 1f) a convenient, safe and environmentally benign preparation of xanthenes,

thioxanthenes and acridones, carried out by irradiation of the corresponding xanthenes, thioxanthenes and dihydroacridines **1** (Fig. 1a) in the presence of just ambient air, and using DESs formed by the combination of several hydrogen-bond acceptor and hydrogen-bond donor species, in the appropriate molar ratio, as reaction media (Fig. 1b). That means that for the first time the use of visible light, a recoverable and reusable DES as neoteric reaction medium and a low-costing metal-free photocatalyst was merged. The results obtained are excellent, allowing to isolate the oxidized compounds in very high yields just by simple filtration and reusing the DES.

2. Results and discussion

We used the photooxidation of 9H-xanthene (**1a**) to xanthone (**2a**) under visible blue light irradiation for 16 h at 30 °C as the model optimization reaction (Table 1). Riboflavin tetraacetate (**4a**, 5 mol%)

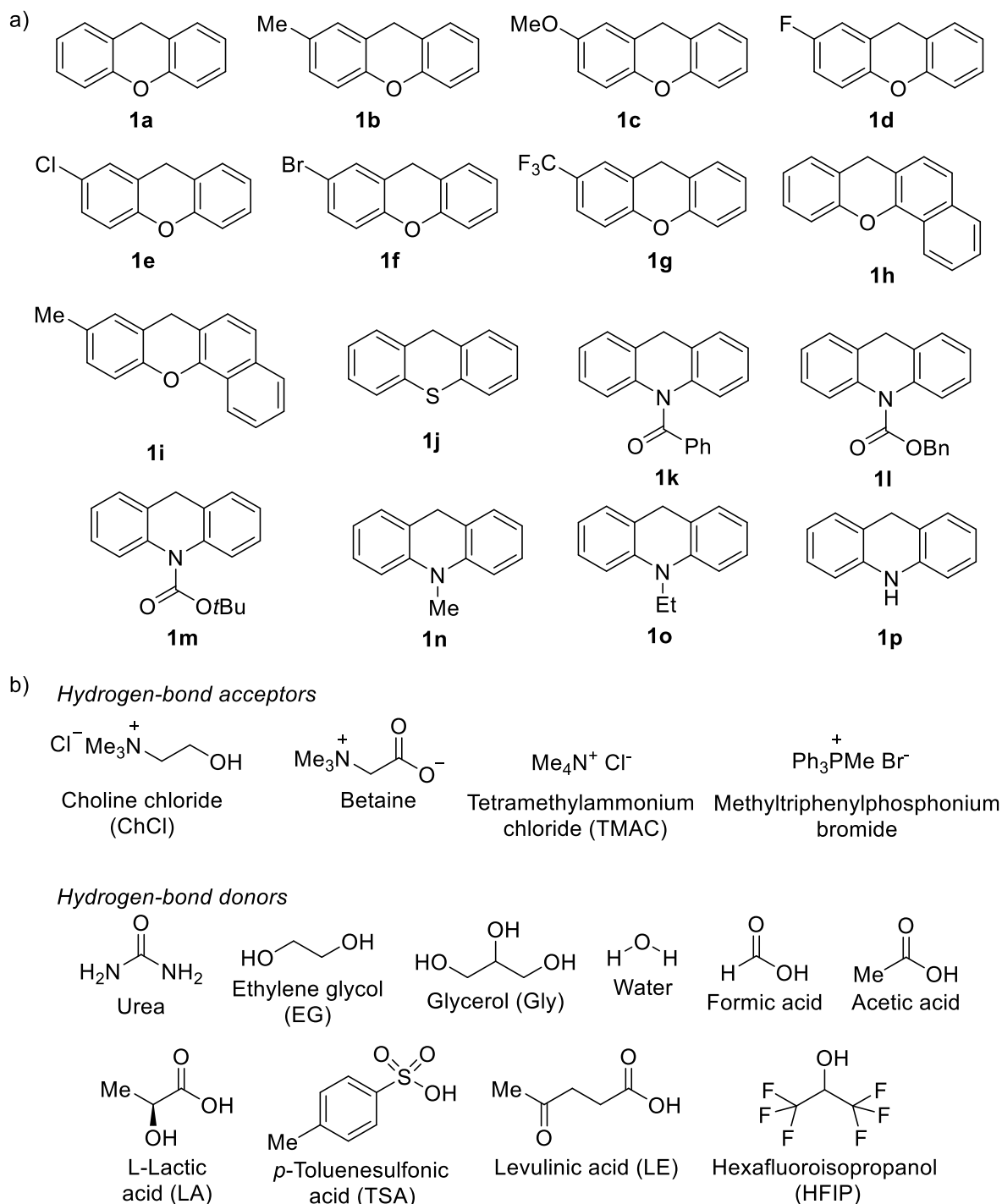


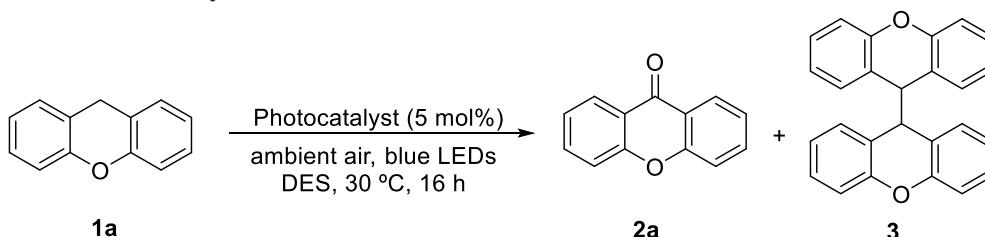
Fig. 1. Structures of the compounds employed in this study: (a) starting xanthenes, thioxanthenes and 9,10-dihydroacridines; (b) Components of the employed DESs, formed by a hydrogen-bond acceptor and a hydrogen-bond donor.

(Fig. 2), an economical dye from vitamin B2, was initially employed as metal-free photocatalyst due to its good performance previously shown [59]. Several DESs were assayed as reaction media, employing ambient air (open flask) as the oxidant. The conversion to **2a** was determined by ^1H NMR on the crude reaction mixture, obtained by adding water to the reaction mixture, extracting with ethyl acetate and evaporating the solvent. This extraction procedure employed in the search of the optimal reaction conditions assures that all possible products and/or byproducts are in the organic phase and can be analyzed by NMR.

Under these conditions, using the DES formed by choline chloride (ChCl)/urea (1/2 M ratio) as reaction media gave **2a** in a negligible

conversion (Table 1, entry 1). When the DES formed by the combination ChCl/ethylene glycol (EG) (1/2 M ratio) was employed, the conversion was just slightly higher, but the ^1H NMR analysis of the reaction crude also revealed the presence of bixanthene **3** as an undesirable homo-coupling by-product (Table 1, entry 2) [62]. Other ChCl-based DESs were used (Table 1, entries 3–10), the combination of ChCl/AcOH (1/3 M ratio) achieving the highest conversion to **2a** (Table 1, entry 7). In addition, using the DES formed by tetramethylammonium chloride (TMAC)/AcOH (1/4 M ratio) afforded an 89 % conversion (Table 1, entry 11). Moreover, several *N,N,N*-trimethylglycine (betaine)-based DESs were assayed (Table 1, entries 12–14), obtaining an excellent result

Table 1
Optimization of the reaction conditions for the photooxidation of 9H-xanthene in DESs.



Entry	Photocatalyst	DES ^a (molar ratio)	2a Conv. (%) ^b	3 Conv. (%) ^b
1	4a	ChCl/urea (1/2)	3	0
2	4a	ChCl/EG (1/2)	16	13
3	4a	ChCl/Gly (1/2)	9	9
4	4a	ChCl/H ₂ O (1/2)	50	40
5	4a	ChCl/HCO ₂ H (1/2)	38	20
6	4a	ChCl/AcOH (1/2)	41	25
7	4a	ChCl/AcOH (1/3)	88	7
8	4a	ChCl/LA (1/2)	4	0
9	4a	ChCl/TSA (1/2)	2	0
10	4a	ChCl/LE (1/2)	33	14
11	4a	TMAC/AcOH (1/4)	89	7
12	4a	Betaine/EG (1/2)	36	35
13	4a	Betaine/LA (1/2)	18	3
14	4a	Betaine/HFIP (1/2)	100	0
15	4a	Ph ₃ MePBr/EG (1/3)	30	35
16	4b	Betaine/HFIP (1/2)	98	2
17	5	Betaine/HFIP (1/2)	71	15
18	6	Betaine/HFIP (1/2)	16	24
19	7	Betaine/HFIP (1/2)	35	27
20	8	Betaine/HFIP (1/2)	6	39
21 ^c	4a	Betaine/HFIP (1/2)	98	2
22	-	Betaine/HFIP (1/2)	31	16
23 ^d	4a	Betaine/HFIP (1/2)	26	2

^a Abbreviations: ChCl: choline chloride; EG: ethylene glycol; Gly: glycerol; HFIP: hexafluoroisopropanol; LA: lactic acid; LE: ethyl lactate; TMAC: tetramethylammonium chloride; TSA; *p*-toluensulfonic acid.

^c The reaction was carried out using a 2 mol% of 4a.

^b Relative to the starting material and determined by ¹H NMR (300 MHz) on the crude reaction mixture after extraction.

^d The reaction was performed in the absence of light.

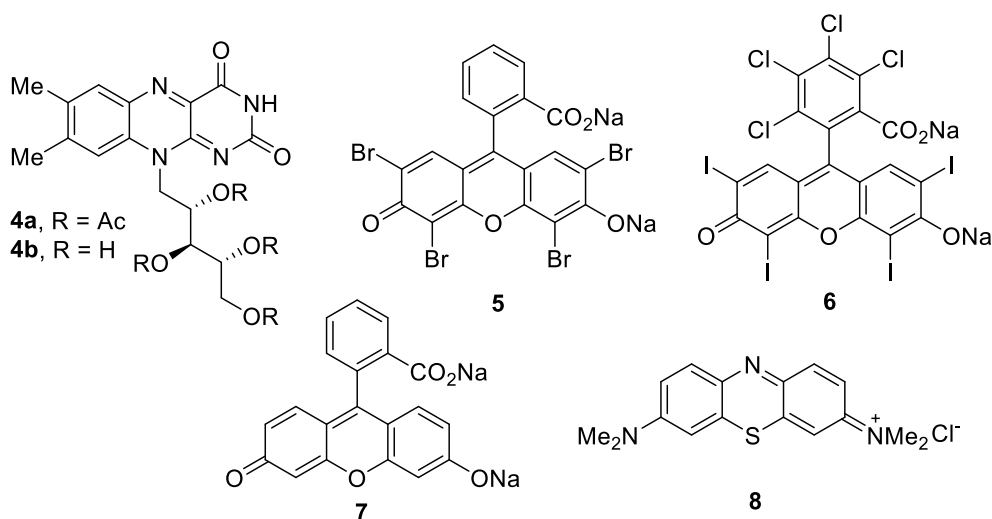
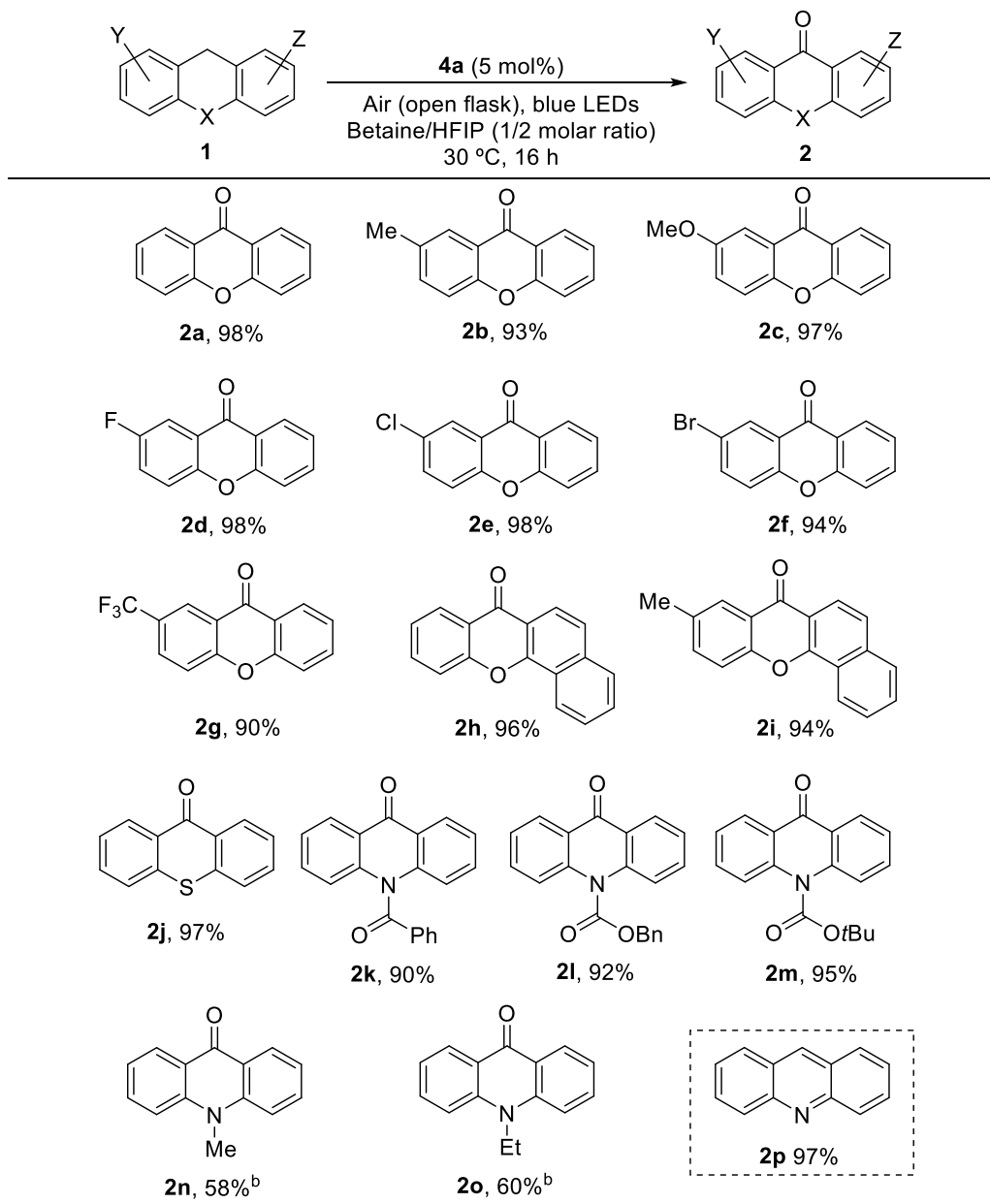


Fig. 2. Photocatalysts employed in this study.

when using the DES formed by the combination betaine/hexafluoroisopropanol (HFIP) (1/2 M ratio) [60], which gave a complete conversion to 2a and no by-product 3 (Table 1, entry 14). Furthermore, we also attempted a phosphonium-derived DES, but it proved ineffective (Table 1, entry 15).

We subsequently explored the performance of other organic dyes, previously employed in different photoredox reactions, as photocatalysts (5 mol%) [8,13,14], working in the DES betaine/HFIP (1/2 M ratio). Thus, when riboflavin (4b, Fig. 2) was employed, the conversion to 2a was slightly lower, although a small amount of the dimer 3 was

Table 2
Photocatalyzed oxidation of 9*H*-xanthenes, 9*H*-thioxanthene and 9,10-dihydroacridines.^a



^a Isolated yield after filtration.

^b Yield after purification by flash chromatography.

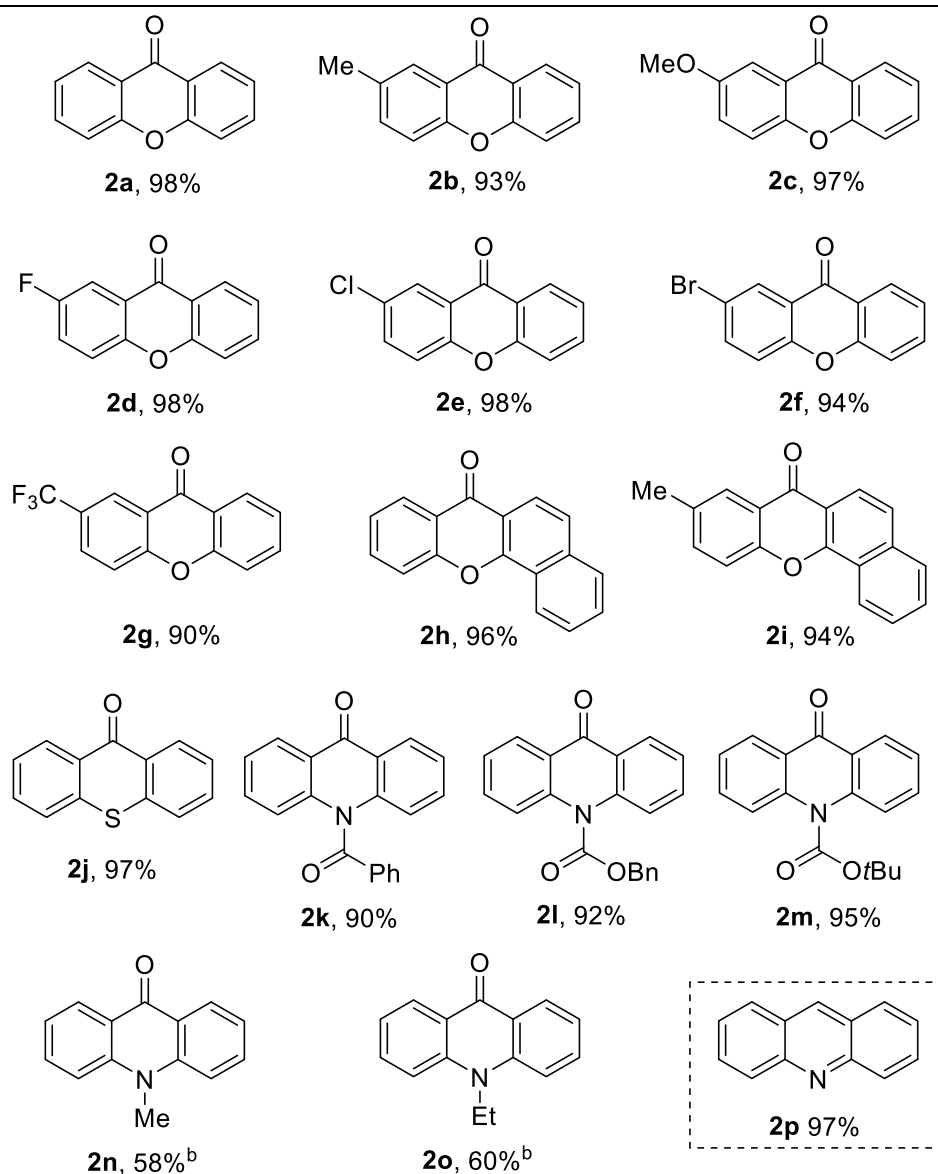
observed (Table 1, entry 16), the use of eosin Y sodium salt (5), rose bengal sodium salt (6), fluorescein sodium salt (7) or methylene blue (8) (Fig. 2) affording much lower conversions (Table 1, entries 17–20), also obtaining considerable amounts of the bixanthene by-product 3.

We lowered the loading of photocatalyst **4a** down to 2 mol% in the DES betaine/HFIP (1/2 M ratio), observing a 98 % conversion to **2a** and a small amount of undesirable bixanthene **3** (Table 1, entry 21). In addition, we carried out the reaction under the best reaction conditions but in the absence of photocatalyst and without light, obtaining low conversions (Table 1, entries 22 and 23).

Once the best reaction conditions were fixed [**4a** (5 mol%) as photocatalyst; betaine/HFIP (1/2 M ratio) as DES], finding the most convenient procedure for the isolation of the final product was crucial, as the conventional extraction used in the optimization step was

environmentally unfriendly and inconvenient for reusing the DES. Thus, after observing that, under the optimized conditions, the product precipitates from the reaction crude, a simple filtration allowed the isolation of pure xanthone **2a** in 98 % yield (Table 2) and the recovery of the DES.

With the optimal reaction conditions and isolation procedure in hand, we extended the methodology to other xanthenes (Table 2). Thus, when 2-substituted 9*H*-xanthenes with electron-releasing and electron-withdrawing groups **1b–g** were photooxidized, the corresponding xanthenes **2b–g** were obtained in high isolated yields. Moreover, benzo-condensed 9*H*-xanthenes **1h** and **1i** were employed in the oxidation reaction, affording the corresponding xanthenes **2h** and **2i** in 96 % and 94 % yield, respectively. Furthermore, 9*H*-thioxanthene **1j** was also explored for the photooxidation reaction, affording the final



^a Isolated yield after filtration.

^b Yield after purification by flash chromatography.

thioxanthone **2j** close to quantitative yield.

We also applied this photooxidation protocol to *N*-substituted 9,10-dihydroacridines, obtaining excellent results for the corresponding acridones (Table 2). Thus, when a benzoyl *N*-substituent was present in the starting 9,10-dihydroacridine **1k**, the *N*-benzoylated acridone **2k** was isolated in 90 % yield. In addition, the presence of an *N*-benzyloxycarbonyl group yielded xanthone **2l**, while an acid-sensitive *N*-substituent, such as the *tert*-butoxycarbonyl (Boc) group, was also tolerated under these neutral oxidation conditions, allowing to isolate the *N*-Boc-acridone **2m** in 95 % yield. Furthermore, an *N*-alkylated 9,10-dihydroacridine, such as *N*-methyl-9,10-dihydroacridine (**1n**), was attempted, but the oxidized compound **2n** was obtained in only 58 % isolated yield after purification by column chromatography (Table 2). The reaction was also attempted with the *N*-ethyl derivative **1o**, obtaining **2o** in 60 % isolated yield (Table 2), confirming the lower reactivity of dihydroacridines bearing *N*-electron releasing substituents.

We also explored this photooxidation reaction using the *N*-unsubstituted 9,10-dihydroacridine **1p**, but instead of the corresponding *N*-

unsubstituted acridone, fully aromatized acridine **2p** was isolated in a 97 % yield (Table 2), an aromatization process previously observed [62].

The possibility of reusing the DES is crucial in a synthetic methodology performed using these neoteric solvents. Therefore, we explored the reusability of the DES by carrying out different reaction cycles of the model photooxidation reaction performed under the best reaction conditions. Thus, we carried out the oxidation reaction of xanthene (**1a**), and once xanthone (**2a**) was filtered off, the recovered DES was employed as solvent for a subsequent run after adding additional **1a**. However, a dramatic decrease in the formation of **2a** was observed, suggesting a possible degradation of photocatalyst **4a**. Therefore, fresh **4a** (5 mol%) was added to the DES after each run, together with **1a**. In this way, a consistent 98 % isolated yield of **2a** was obtained after five consecutive cycles, always using the recovered DES (Fig. 3).

Due to the high yield of the procedure and the absence of any work-up or the need for the purification of the final product, we supposed that its efficiency in its environmental impact should be excellent. A measure

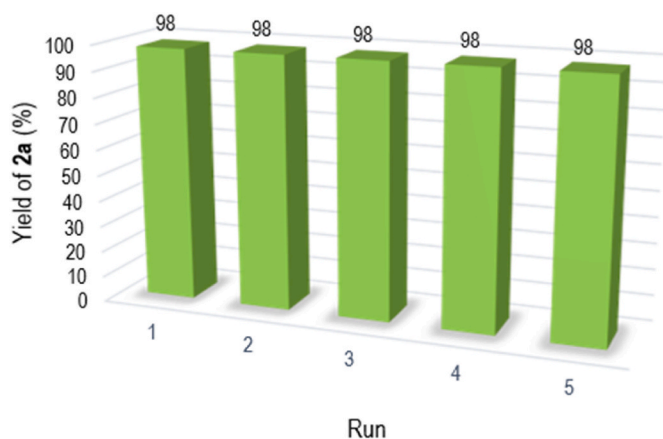


Fig. 3. Recyclability of the DES betaine/HFIP (1/2 M ratio) in several consecutive photooxidations of **1a**.

Table 3

Green metrics for the photooxidation of **1a** to **2a** catalyzed by **4a** in the DES betaine/HFIP (1/2 M ratio).

Parameter	Value	(%) ^{a,b}
EcoScale	86	86
Reaction Yield (Rxn Yield)	0.980	98
Atom Economy (AE)	0.916	92
Stoichiometric Factor (SF)	1.000	
1/SF	1.000	
Reaction Mass Efficiency (RME)	0.853	85
Material Recovery Parameter (MRP)	0.950	95
E-factor		
	Total	0.172
	Kernel	0.030
	Excess	0.000
	Catalyst	0.142
	Solvent	0.000 ^c
	Work-up	0.000
	Purification	0.000

^a Some parameters are expressed as percentages.

^b The value has been rounded off to the nearest whole number.

^c Solvent is recovered.

Table 4

Reactions conditions and yields using previously reported visible light-promoted aerobic photooxidation of **1a** to **2a**.

Entry	Reaction conditions	Yield (%)	Ref.
1	1 (0.02 mmol), 4a (10 mol%), Fe complex (8 mol%), air (open flask), blue LEDs, MeCN, rt, 1.5 h	96	[31]
2	1 (0.1 mmol), DPZ (0.5 mol%), NHI (20 mol%), Fe ₂ O ₄ ·2H ₂ O (10 mol%), O ₂ atmosphere, blue LEDs, CH ₂ Cl ₂ , 25 °C, 19 h	93	[32]
3	1 (0.2 mmol), FeCl ₃ ·6H ₂ O (5 mol%), LiBr (5 mol%), air (open flask), blue LEDs, MeCN, 25 °C, 48 h	99	[33]
4	1 (1 mmol), DDQ (1 mol%), TBN (5 mol%), AcOH (0.2 equiv.), O ₂ (balloon), blue LEDs, DCE, 25 °C, 12 h	99	[37]
5	1 (0.3 mmol), Acr ⁺ -Mes (5 mol%), Selectfluor (2 equiv.), Ar, blue LEDs, MeCN/H ₂ O (1:1), 25 °C, 12 h	93	[38]
6	1 (1 mmol), flavin-based catalyst (5 mol%), TFA (0.7 equiv.), O ₂ (balloon), MS 4 Å, blue LEDs, MeCN, 45 °C, 24 h	99	[39]
7	1 (0.2 mmol), 4a (5 mol%), O ₂ (balloon), blue LEDs, MeCN, 25 °C, 8 h	99	[59]

of this is the EcoScale [61], a semi-quantitative scale that considers the yield, cost of the materials, safety reaction conditions, and ease of work-up/purification to evaluate an organic synthesis, with a maximum value of 100 points. Thus, the value of EcoScale for the photooxidation of **1a** to **2a** under the optimized reaction conditions is 86 (Table 3),

which means, according to the established definitions, that reaction conditions can be ranked as “excellent” (EcoScale >75).

In addition, different green metrics, such as atom economy (AE), stoichiometric factor (SF), reaction mass efficiency (RME), materials recovery parameter (MRP), reaction yield (Rxn Yield), and environmental factor profile (E-factor referring to kernel, excess, solvent, catalyst, work-up, and purification), have been calculated (Table 3) [62]. The E-factor of the whole process (0.172) results quite low, as there is no contribution of the solvent (the DES can be reused), and excellent values for AE (92 %), SF (1.000), and RME (85 %) are shown (Table 3).

All these green metrics are sufficiently near to optimum to consider that this protocol is excellent from an environmental point of view. However, it is important to compare it with some other methodologies. Therefore, reaction conditions and yields of representative reported procedures are summarized in Table 4.

In addition, radial-pentagon diagrams (Fig. 4) with all the efficiency parameters presented in Table 3 have been also drawn for the oxidation of **1a** to **2a** using the reported metal-based- and metal-free-photocatalyzed procedures shown in Table 4, proving the higher sustainability of the presented method. Thus, results using metal-photocatalyzed methodologies such as the oxidation promoted by **4a** and a Fe(III) complex [31] (Table 4, entry 1), the combination of dicyanopyrazine (DPZ) + *N*-hydroxyimide (NHI) and a Fe(II) salt [32] (Table 4, entry 2) or a Fe(III) salt combined with a Li salt [33] (Table 4, entry 3) were represented (Fig. 4a). In addition, results employing non-metal-photocatalyzed methodologies such as the use of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) + *tert*-butyl nitrite (TBN) + AcOH [37] (Table 4, entry 4), the use of 9-mesityl-10-methylacrydinium tetrafluoroborate (Acr⁺-Mes) as photocatalyst [38] (Table 4, entry 5), the use of the combination flavin + trifluoroacetic acid (TFA) [39] (Table 4, entry 6) or the use of **4a** in MeCN [59] (Table 4, entry 7) were also depicted (Fig. 4b). In all cases, the protocol presented in this work resulted much more efficient from an environmental point of view.

We were also interested in the applicability of this methodology to the oxidation of the benzylic position of other non-heteroatom-containing systems, such as 9*H*-fluorene (**9**) anthrone (**11**) and even diphenylmethane (**13**). Thus, the photooxidation of these systems under the optimized reaction conditions allowed us to obtain the corresponding carbonyl compounds **10**, **12** and **14** in moderate yields, although increasing the loading of **4a** up to 15 mol% was necessary (Scheme 2). Interestingly, these photooxidation reactions were unsuccessful when performing the reaction in acetonitrile as solvent instead of the DES, even using pure oxygen as the oxidant [59].

3. Conclusions

Deep eutectic solvents have been used as suitable media in a photocatalyzed reaction, such as the visible light-promoted benzylic oxidation of 9*H*-xanthenes, 9*H*-thioxanthenes and 9,10-dihydroacridines to xanthenes, thioxanthenes or acridones, respectively. The procedure employs ambient air as oxidant in the presence of an economical metal-free photocatalyst. Other related benzylic systems have also been oxidized under these conditions, although less efficiently. This simple and environmentally convenient metal-free photooxidation procedure allows the easy isolation of interesting products in high to quantitative yields, allowing the recovery and reuse of the eutectic solvent. Green metrics prove the higher sustainability of this methodology compared to others previously reported.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

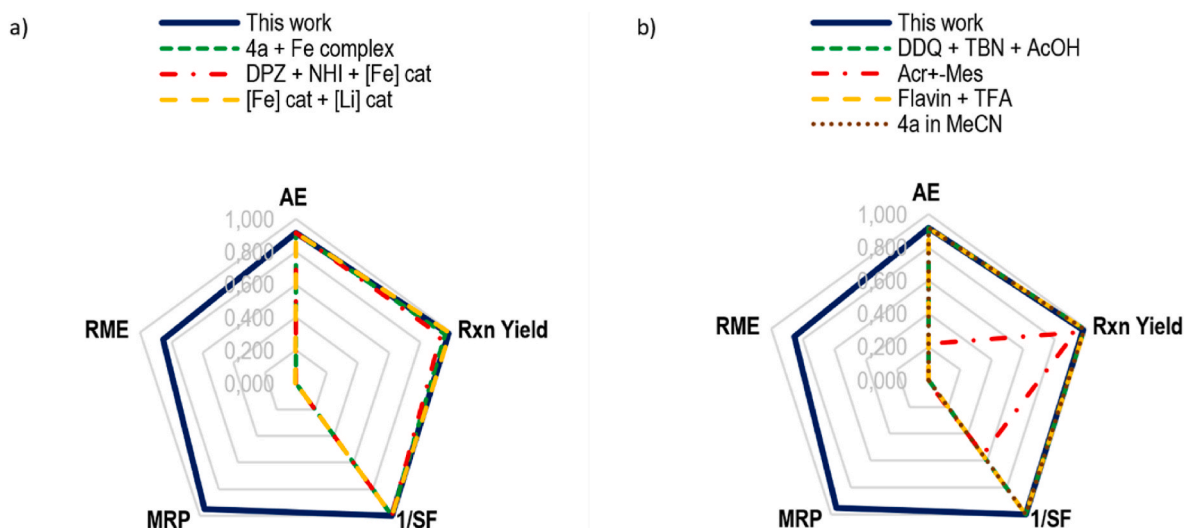
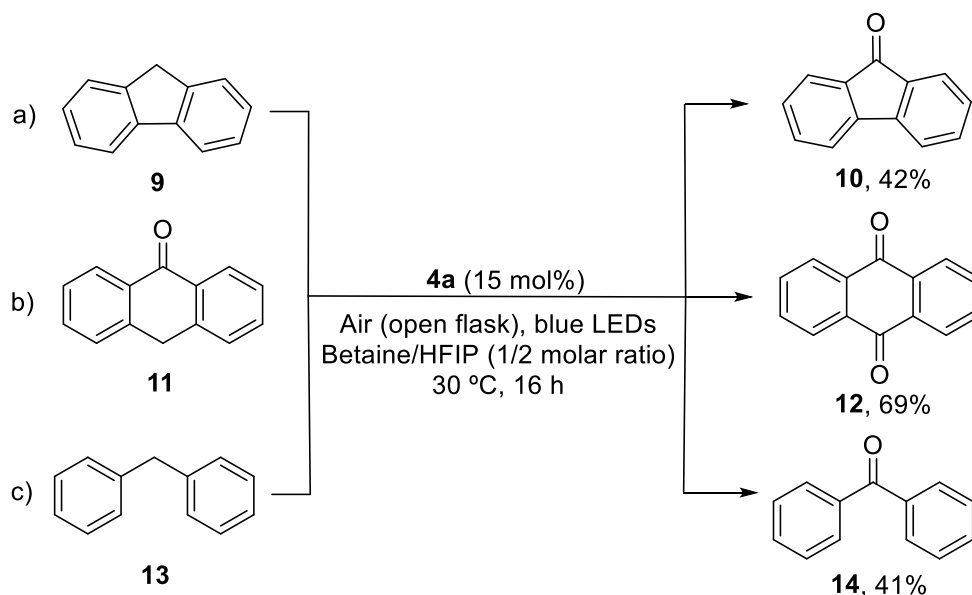


Fig. 4. Radial-pentagon diagram of metrics: Reaction yield (Rxn Yield), atom economy (AE), inverse of stoichiometric factor (1/SF), material recovery parameter (MRP), and reaction mass efficiency (RME). Comparison for preparing compound **2a** of the protocol in this work with reported (a) metal-photocatalyzed methodologies, (b) metal-free-photocatalyzed methodologies.



Scheme 2. Photooxidation in DES of: a) 9H-fluorene; b) anthrone; c) diphenylmethane. Yields obtained after purification by flash column chromatography.

Acknowledgments

The authors acknowledge the financial support by the Spanish Ministerio de Ciencia e Innovación (PID2021-127332NB-I00), the Generalitat Valenciana (AICO 2021/013) and the University of Alicante (VIGROB-173 and UAUUSTI 2022).

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.tgchem.2023.100030>.

References

- [1] Q. Liu, L.-Z. Wu, *Natl. Sci. Rev.* 4 (2017) 359–380.
- [2] C.R.J. Stephenson, T.P. Yoon, D.W.C. MacMillan, *Visible Light Photocatalysis in Organic Chemistry*, Wiley-VCH, Weinheim, 2018.
- [3] J.M.R. Narayanan, C.R.J. Stephenson, *Chem. Soc. Rev.* 40 (2011) 102–113.
- [4] J.W. Tucker, C.R.J. Stephenson, *J. Org. Chem.* 77 (2012) 1617–1622.
- [5] J. Xuan, W.-J. Xiao, *Angew. Chem. Int. Ed.* 51 (2012) 6828–6838.
- [6] C. Gambarotti, L. Melone, T. Caronna, C. Punta, *Curr. Org. Chem.* 17 (2013) 2406–2419.
- [7] C.K. Prier, D.A. Rankic, D.W.C. MacMillan, *Chem. Rev.* 113 (2013) 5322–5363.
- [8] D.A. Nicewicz, T.M. Nguyen, *ACS Catal.* 4 (2014) 355–360.
- [9] R.A. Angnes, Z. Li, C.R.D. Correia, G.B. Hammond, *Org. Biomol. Chem.* 13 (2015) 9152–9167.
- [10] M.H. Shaw, J. Twilton, D.W.C. MacMillan, *J. Org. Chem.* 81 (2016) 6898–6926.
- [11] G.E.M. Crisenza, P. Melchiorre, *Nat. Commun.* 11 (2020) 803.
- [12] J.B. Mateus-Ruiz, A. Cordero-Vargas, *Synthesis* 52 (2020) 3111–3128.
- [13] S. Fukuzumi, K. Ohkubo, *Org. Biomol. Chem.* 12 (2014) 6059–6071.
- [14] D. Ravelli, M. Fagnoni, *ChemCatChem* 4 (2012) 169–171.
- [15] M. Uygur, O. Garcia Mancheño, *Org. Biomol. Chem.* 17 (2019) 5475–5489.
- [16] L. Revathi, L. Ravindar, W.-Y. Fang, K.P. Rakesh, H.-L. Qin, *Adv. Synth. Catal.* 360 (2018) 4652–4698.
- [17] Y. Zhang, W. Schilling, S. Das, *ChemSusChem* 12 (2019) 2898–2910.
- [18] X. Zhang, K.P. Rakesh, L. Ravindar, H.-L. Qin, *Green Chem.* 20 (2018) 4790–4833.
- [19] A. Torregrosa-Chinillach, R. Chinchilla, *Molecules* 27 (2022) 497.
- [20] D.I.S.P. Resende, F. Durães, M. Maia, E. Sousa, M.M.M. Pinto, *Org. Chem. Front.* 7 (2020) 3027–3066.
- [21] S. Ramakrishnan, S. Paramewaran, N.M. Nasir, *Chem. Pap.* 75 (2020) 455–470.
- [22] L.C. Klein-Júnior, A. Campos, R. Niero, R. Corrêa, Y. Vander Heyden, V. Cechinel Filho, *Chem. Biodivers.* 17 (2020), e1900499.

- [23] Z. Feng, X. Lu, L. Gan, Q. Zhang, L. Lin, *Molecules* 25 (2020) 598.
- [24] I.M.J. Ng, C.L.L. Chua, *Phcog. Rev.* 13 (2019) 28–33.
- [25] P. Bedi, R. Gupta, T. Pramanik, *Asian J. Pharmaceut. Clin. Res.* 11 (2018) 12–20.
- [26] A.M. Paiva, M.M. Pinto, E. Sousa, *Curr. Med. Chem.* 20 (2013) 2438–2457.
- [27] W.S. Alwan, R.A. Rane, A.A. Amritkar, S.S. Naphade, M.C. Yerigiri, R. Karpooomath, A.A. Mahajan, *Anti-cancer agents, Med. Chem.* 15 (2015) 1012–1025.
- [28] C.S. Sepúlveda, M.L. Fascio, C.C. García, N.B. D'Accorso, E.B. Damonte, *Curr. Med. Chem.* 20 (2013) 2402–2414.
- [29] G. Cholewiński, K. Dzierzbicka, A.M. Kołodziejczyk, *Pharmacol. Rep.* 63 (2011) 305–336.
- [30] E. Vanover, Y. Huang, L. Xu, M. Newcomb, R. Zhang, *Org. Lett.* 12 (2010) 2246–2249.
- [31] B. Mühldorf, R. Wolf, *Angew. Chem. Int. Ed.* 55 (2016) 427–430.
- [32] X. Liu, L. Lin, X. Ye, C.-H. Tan, Z. Jiang, *Asian J. Org. Chem.* 6 (2017) 422–425.
- [33] S. Li, B. Zhu, R. Lee, B. Qiao, Z. Jiang, *Org. Chem. Front.* 5 (2018) 380–385.
- [34] L.C. Finney, L.J. Mitchell, C.J. Moody, *Green Chem.* 20 (2018) 2242–2249.
- [35] D. Sarma, B. Majumdar, T.K. Sarma, *Green Chem.* 21 (2019) 6717–6726.
- [36] P. Geng, Y. Tang, G. Pan, W. Wang, J. Hu, Y. Cai, *Green Chem.* 21 (2019) 6116–6122.
- [37] D. Pan, Y. Wang, M. Li, X. Hu, N. Sun, L. Jin, B. Hu, Z. Shen, *Synlett* 30 (2019) 218–224.
- [38] M. Xiang, Z.-K. Xin, B. Chen, C.-H. Tung, L.-Z. Wu, *Org. Lett.* 19 (2017) 3009–3012.
- [39] A.H. Tolba, F. Vávra, J. Chudoba, R. Cibulka, *Eur. J. Org. Chem.* (2020) 1579–1585.
- [40] J. Jung, K. Ohkubo, K.A. Prokop-Prigge, H.M. Neu, D.P. Goldberg, S. Fukuzumi, *Inorg. Chem.* 52 (2013) 13594–13604.
- [41] G. Pandey, D. Jadhav, S.K. Tiwari, B. Singh, *Adv. Synth. Catal.* 356 (2014) 2813–2818.
- [42] J.H. Clark, A. Hunt, C. Topi, G. Paggiola, J. Sherwood, *Sustainable Solvents: Perspectives from Research, Business and International Policy*, Royal Society of Chemistry, 2017.
- [43] C.J. Clarke, W.-C. Tu, O. Levers, A. Brohl, J.P. Hallett, *Chem. Rev.* 118 (2018) 747–800.
- [44] J. García-Alvarez, *Eur. J. Inorg. Chem.* (2015) 5147–5157.
- [45] P. Liu, J.-W. Hao, L.-P. Mo, Z.-H. Zhang, *RSC Adv.* 5 (2015) 48675–48704.
- [46] D.A. Alonso, A. Baeza, R. Chinchilla, G. Guillena, I.M. Pastor, D.J. Ramón, *Eur. J. Org. Chem.* (2016) 612–632.
- [47] N. Guajardo, C.R. Müller, R. Schrebler, C. Carlesi, P. Domínguez de María, *ChemCatChem* 8 (2016) 1020–1027.
- [48] Y. Liu, J.B. McAlpine, D.C. Lankin, S.-N. Chen, G.F. Pauli, J.B. Friesen, *J. Nat. Prod.* 81 (2018) 679–690.
- [49] Y. Marcus, *Deep Eutectic Solvents*, Springer, Switzerland, 2019.
- [50] J. Liu, X. Li, K.H. Row, *J. Mol. Liq.* 362 (2022), 119654.
- [51] A. Thakur, M. Verma, R. Bharti, R. Sharma, *Curr. Org. Chem.* 26 (2022) 299–323.
- [52] D. Yu, Z. Xue, T. Mu, *Cell Rep. Phys. Sci.* 3 (2022), 100809.
- [53] S.E. Hooshmand, S. Kumar, I. Bahadur, T. Singh, R.S. Varma, *J. Mol. Liq.* 371 (2023), 121013.
- [54] A. Prabhune, R. Dey, *J. Mol. Liq.* 379 (2023), 121676.
- [55] D.J. Ramón, G. Guillena, *Deep Eutectic Solvents. Synthesis, Properties and Applications*, Wiley-VCH, Weinheim, 2019.
- [56] D. Procopio, X. Marset, G. Guillena, M.L. Di Gioia, D.J. Ramón, *Adv. Synth. Catal.* 365 (2023) 1–8.
- [57] CGA. <https://www.cganet.com/cga-m-24-publication-guides-mitigation-of-ox-gen-hazards-in-healthcare-environments/>.
- [58] EIGA. <https://www.eiga.eu/uploads/documents/DOC004.pdf>.
- [59] A. Torregrosa-Chinillach, R. Chinchilla, *Molecules* 26 (2021) 974.
- [60] W. Deng, L. Yu, X. Li, J. Chen, X. Wang, Z. Deng, Y. Xiao, *Food Chem.* 274 (2019) 891–899.
- [61] K. van Aken, L. Streckowski, L. Patiny, *Beilstein J. Org. Chem.* 2 (2006) 3.
- [62] J. Andraos, *Reaction Green Metrics-Problems, Exercises, and Solutions*, CRC Press (Taylor & Francis Group), Boca Raton (FL, USA), 2019.