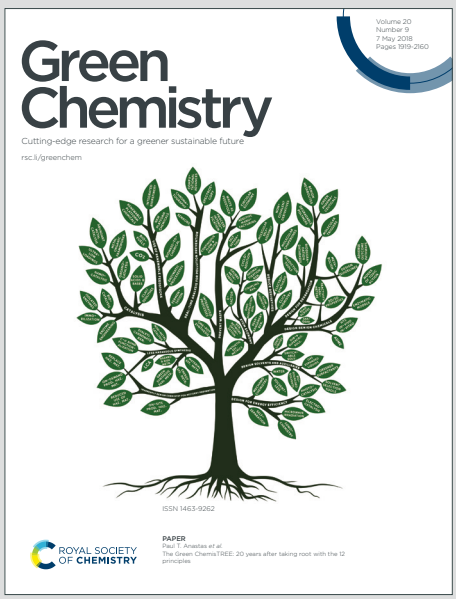
Green Chemistry

Cutting-edge research for a greener sustainable future

Accepted Manuscript



ROYAL SOCIETY OF CHEMISTRY

rsc.li/greenchem

ROYAL SOCIETY OF CHEMISTRY
View Article Online
DOI: 10.1039/C9GC02270H

Green Chemistry

ARTICLE

Cercosporin-Bioinspired Selective Photooxidation Reactions under Mild Conditions

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Jia Li,[a] Wenhao Bao,[a] Zhaocheng Tang,[a] Baodang Guo[a] Shiwei Zhang,[b] Haili Liu,[a] Shuping Huang,[c] Yan Zhang, *[b] and Yijian Rao*[a]

The development of an efficient system for selective oxidation of organic compounds to generate more valuable compounds with molecular oxygen is a significant challenge in industrial chemistry. Bioinspired by the ability of naturally-occurring perylenequinonoid pigments (PQPs) to generate reactive oxygen species (ROS) upon photoirradiation, here we report that cercosporin, one of perylenequinonoid pigments, can function as a cost-effective and environmentally friendly photocatalyst for a wide range of selective oxidations, including benzylic C–H bonds to carbonyls, amines to aldehydes, and sulfides to sulfoxides. All of representative reactions proceeded smoothly with high efficiency under mild conditions. Owing to the use of inexpensive metal-free visible light-driven photocatalyst produced from microbial fermentation with cheap glucose as starting material, and the ease of handling, we expect that this developed method will be particularly attractive for much more applications in synthetic transformation.

Introduction

Selective oxidation of organic compounds is one of the most fundamental reactions in organic synthesis, as well as one of the most significant challenges in industrial chemistry.[1] Traditionally, toxic or hazardous oxidizing agents, such as toxic metal oxides and peroxides, in stoichiometric amounts were usually used for these chemical transformations.[2] Due to growing attention on the environmental concerns, extensive efforts have been devoted to develop cleaner synthetic strategies by using molecular oxygen as it is the most economical and green terminal oxidant.[3] However, owing to the inherent triplet ground state conformation of oxygen, it is difficult to be activated to oxidize the substrates,[4] especially for the inert C–H bonds. To overcome the high oxidation potential of the substrates, a porous graphene/carbon nitride composite or precious and toxic noble-metal-based catalysts at high temperature under high oxygen pressure have been commonly employed for the oxidation of organic compounds.[5]

Additionally, since photocatalysis has been recognized as a useful routine and its applications are rapidly growing,[6] metal-based photocatalysis was also developed for the oxidation reactions.[7] But the use of precious and toxic metals significantly limit their industrial applications. In fact, as metal-free photocatalysts usually have cheap prices, broad availability and some other properties superior to their related inorganic and organometallic counterparts,[8] metal-free photocatalytic system provides an alternative environmentally friendly synthetic route in the selective oxidation. However, the application of metal-free photocatalysts in selective oxidation is somewhat less familiar.[9]

As most of photocatalysis reactions are performed under aerobic environment with water vapor, oxygen as well as water are the important and widespread reaction species.[10] Upon irradiation with a photocatalyst, oxygen is able to be converted into chemical reactive oxygen species (ROS), including singlet oxygen ($^1O_2$), the hydroxyl radical (HO$^\bullet$), superoxide ($O_2^{\bullet-}$), and peroxide (O_2^{2-}).[10] These ROS can be important resources for advance oxidation processes in multiple organic transformations,[11] thus searching or designing a versatile metal-free photocatalyst to efficiently generate ROS is the critical step for a wide range of selective oxidations of organic compounds. In fact, nature has evolved various oxygen-utilization systems that molecular oxygen reacts spontaneously with many organic compounds at or below room temperature in a free radical chain process called autoxidation.[12] For instance, plant pathogenic fungi *Cercospora* species can produce cercosporin (CP),[13] one of natural product perylenequinonoid pigments (PQP), and works together with molecular oxygen as a powerful "weapon" after absorption of sunlight to infect plants and then obtain nutrients for their propagation through the autoxidation process (Fig. 1). So far, cercosporin together with other PQP, such as hypocrellin A, have been widely investigated at aspects of photophysics, photochemistry and photobiology owing to their excellent properties of photosensitization.[14] Cercosporin can be activated to singlet excited state by visible light absorption and then partially excited-state molecules convert into longer-lived triplet state through intersystem crossing.[14a] The excited-state of cercosporin can then prompt two favorable reactions, i.e., Type-I single electron transfer reaction (SET) and Type-II energy transfer reaction (EnT) (Fig. 1a).[13c, 15] In Type-I

[a] Key Laboratory of Carbohydrate Chemistry and Biotechnology, Ministry of Education, School of Biotechnology, Jiangnan University, Wuxi 214122, P. R. China. E-mail: raoyijian@jiangnan.edu.cn.
[b] School of Pharmaceutical Science, Jiangnan University, Wuxi 214122, P. R. China. E-mail: zhangyan@jiangnan.edu.cn.
[c] College of Chemistry, Fuzhou University, Fuzhou, Fujian 350108, P. R. China.
† Footnotes relating to the title and/or authors should appear here.
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

reaction, the excited-state of cercosporin directly reacts with another reductive substrate to yield semiquinone anion radical, which can react with other compounds causing oxidative damage or free radical. This photoinduced electron-transfer process is a predominant pathway in the radical formation. When molecular oxygen (O_2) exists, the semiquinone anion radical can transfer electron to ground state oxygen (O_2) to generate superoxide ($O_2^{\bullet-}$), whereby other active oxygen species such as hydroxyl radical ($HO^{\bullet}$) and hydrogen peroxide (H_2O_2) can also be generated. These highly ROS then can oxidize other compounds. In Type-II reaction, the excited state of cercosporin directly reacts with O_2 to form highly toxic singlet oxygen ($^1O_2$). Despite these remarkable properties of photosensitization, there is no report on the use of cercosporin as a visible-light driven-photocatalyst for selective aerobic oxidations. Bioinspired by the ability of cercosporin to generate ROS, together with its photochemical properties[14a] and photostability (Fig. S1),[15] we envisioned that this natural product PQP can be used as an effective "metal-free" organic photocatalyst for selective oxidative reactions.

In this study, cercosporin was obtained via microbial liquid fermentation using glucose as a very cheap starting material with a maximum of production,[16] which is substantially higher than that of the previously reported methods.[17] Then, it was applied as a metal-free photocatalyst for three representative selective oxidation reactions, namely: visible-light driven selective oxidation of benzylic C–H bonds to carbonyls, amines to aldehydes, and sulfides to sulfoxides (Fig. 1b). All of them showed great conversion efficiency under mild conditions, indicating that cercosporin is a versatile green metal-free photocatalyst.

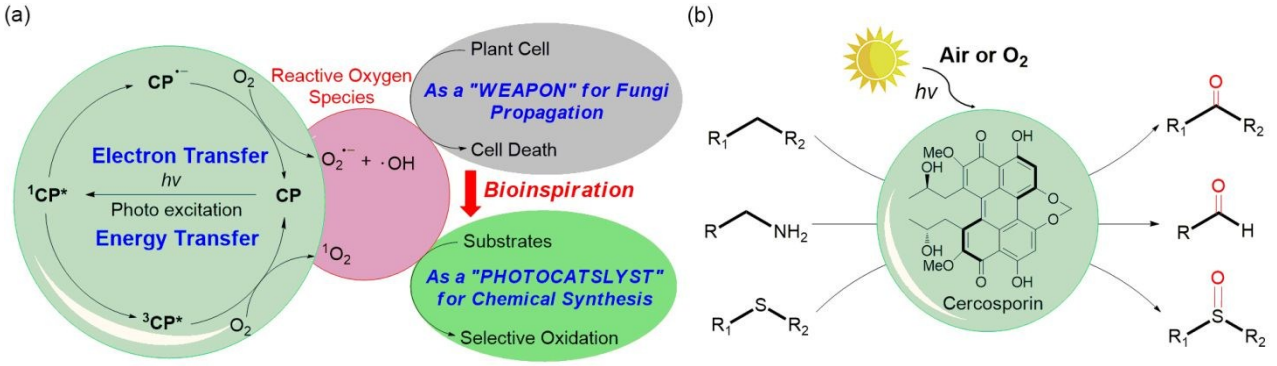


Fig. 1 The organic photocatalyst cercosporin. (a) Cercosporin (CP) as a phytotoxin and a photoredox catalyst through forming reactive oxygen species upon photoirradiation. (b) Representative visible-light driven-photocatalysis of aerobic selective oxidation reactions by cercosporin.

Experimental

General procedure for the selective oxidation benzylic C-H bonds with cercosporin: In a dried schlenk tube, benzylic derivatives **1** (0.25 mmol), potassium bromide (0.2 equiv) and cercosporin (2 mol%) was added in 2.0 mL methanol. Next, a balloon was purged with oxygen and fixed on the top of the schlenk tube. The reaction mixture was stirred and irradiated by 23 W white CFL at room temperature under an atmospheric pressure oxygen atmosphere. When the reaction was finished, the reaction mixture was washed with brine. The aqueous phase was re-extracted with ethyl acetate. The combined organic extracts were dried over Na_2SO_4, concentrated in vacuum, and the resulting residue was purified by silica gel column chromatography to afford the desired product **2**.

General procedure for the selective oxidation of amines with cercosporin: In a dried schlenk tube, amines **3** (0.25 mmol) and cercosporin (1 mol%) was added in 2.0 mL methanol. Next, a balloon was purged with oxygen and fixed on the top of the schlenk tube. The reaction mixture was stirred and irradiated by 15 W white CFL at room temperature under an atmospheric pressure oxygen atmosphere. The reaction progress was monitored by GC analysis. Photooxidation yields of **4** were calculated from GC measurements using internal standards.

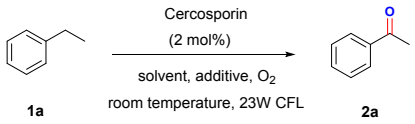
General procedure for the selective oxidation of sulfides with cercosporin: In a dried schlenk tube, sulfides **6** (0.25 mmol) and cercosporin (1 mol%) was added in 2.0 mL methanol. Next, a balloon was purged with oxygen and fixed on the top of the schlenk tube. The reaction mixture was stirred and irradiated by 15 W white CFL at room temperature under an atmospheric pressure oxygen atmosphere. When the reaction was finished, the reaction mixture was washed with brine. The aqueous phase was re-extracted with ethyl acetate. The combined organic extracts were dried over Na_2SO_4, concentrated in vacuum, and the resulting residue was purified by silica gel column chromatography to afford the desired product **7**.

Results and discussion

The selective oxidation of C(sp^3)-H bonds in alkanes to obtain higher-value compounds is of great importance due to its broad applications in fine chemical industry and pharmaceutical industry.[18] Among them, C(sp^3)-H oxidation process is much more elaborate and can be only achieved to limited extent, so it's still a grand challenge to improve this kind of reaction.[19] Since C(sp^3)-H bonds are both thermodynamically stable and kinetically inert, traditional catalytic strategies as well as photocatalytic strategies,[20] suffer from limited substrates scope, the use of expensive and complicated catalysts,[21] and stoichiometric amounts of strong oxidants.[22] Here, the convenient and sustainable oxidative strategy with ROS derived from cercosporin was first tested for this reaction to investigate its photocatalytic effectiveness. Initially, we used ethylbenzene **1a** as the model substrate with 2 mol % cercosporin as the photocatalyst

to evaluate the reaction parameters (Table 1, see also Table S1). The reaction was first performed in DMSO solvent under an oxygen atmosphere at room temperature upon irradiation by 23W CFL (Table 1), but the desired product was synthesized only in negligible amount (entry 1). Other solvents, such as toluene, DMF, CH_3CN and DCE were also tested with the similar catalytic activity (entries 2-5). However, when the solvent was changed to methanol, desired product **2a** was achieved in 20% yield after 40 hours (entry 6). Since the use of an additive together with the photocatalyst can normally enhances the reaction rate and chemoselectivity.[6a-f] Thus, our subsequent effort was to screen a suitable additive to improve the selective photooxidation of benzylic C(sp^3)–H with cercosporin as a catalyst. After screening a wide range of inorganic salts as additives (entries 7-14), it showed that acetophenone **2a** as a single product with 78% yield was obtained when 0.2 equiv. of KBr was added (entry 7, see Supporting Information). Other perylenequinonoid derivatives, such as hypocrellins A and B, were also examined as the photocatalysts in this reaction with the same products, but in low yields of 30% and 15%, respectively (entries 15 and 16). No reaction proceeded in the absence of either cercosporin (entry 17), light (entry 18) or even O_2 (entry 19).

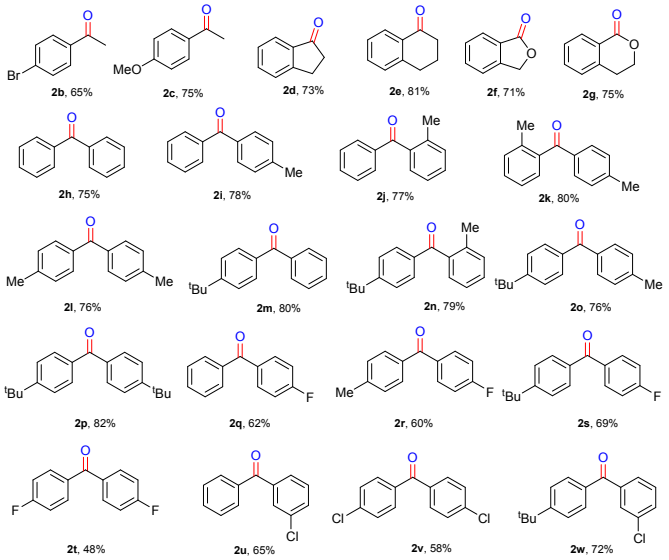
Table 1 Optimization of the reaction conditions for the selective oxidation of sp^3 C–H bonds.



Entry	Conditions[a]	Yield (%)[b]
1	DMSO	trace
2	Toluene	trace
3	DMF	trace
4	DCE	trace
5	CH_3CN	5
6	CH_3OH	20
7	0.2 equiv. of KBr, CH_3OH	78
8	0.2 equiv. of LiBr, CH_3OH	26
9	0.2 equiv. of NaBr, CH_3OH	25
10	0.2 equiv. of CsBr, CH_3OH	20
11	0.2 equiv. of KF, CH_3OH	30
12	0.2 equiv. of KCl, CH_3OH	24
13	0.2 equiv. of KI, CH_3OH	35
14	0.2 equiv. of KO^{t}Bu, CH_3OH	29
15[c]	0.2 equiv. of KBr, CH_3OH	30
16[d]	0.2 equiv. of KBr, CH_3OH	15
17	0.2 equiv. of KBr, CH_3OH, no catalyst	trace
18	0.2 equiv. of KBr, CH_3OH, no light	trace
19	0.2 equiv. of KBr, CH_3OH, N_2	trace

[a]All reactions were carried out on a scale of 0.25 mmol of 1a in 2 mL of solvent under 23W CFL for 30h. See also Table S1. [b]Yields of isolated product. [c]2 mol% of Hypocrellin A as the photocatalyst. [d]2 mol% of Hypocrellin B as the photocatalyst.

With this optimal reaction condition, we next explored the scope of substrates with C(sp^3)-H bond and tested whether they were able to be converted into the corresponding ketones (Scheme 1). It showed that these reactions completed within 20–30 h and gave the corresponding ketones (**2a–2e**, **2h–2w**) and ester (**2f**, **2g**) in moderate to good yields. The substrate scope included non-cyclic alkyl- (**2a–2c**), cyclic- (**2d–2g**) and aryl-substituted benzylic methylenes substrates (**2h–2w**), which demonstrated the diversity of this protocol. This oxidative reaction tolerated with aryl-Me, ^{t}Bu, F, Cl and Br groups (**2b**, **2i–2t**, **2u–2w**). The C–Cl group could be further modified to other functional groups. Compared with electron-deficient alkylbenenes, electron-rich ones were more competent substrates in this selective oxidation. However, substrates bearing strong electron-withdrawing groups, like $-CO_2Me$ and $-NO_2$, were unable to be activated.



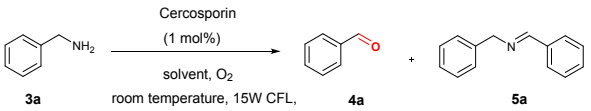
Scheme 1 Cercosporin-photocatalyzed selective oxidation of sp^3 C–H with visible light.

Having realized the cercosporin-photocatalyzed selective oxidation of benzylic C–H with visible light, we next investigated the cercosporin-generated ROS oxidative system to a more challenging reaction, namely photocatalytic selective oxidation of amines to aldehydes. Selective oxidation of amines is a very useful reaction to get functional group interconversions in organic transformation. Different products, such as imines, carbonyl compounds, amides and nitriles, can be obtained depending on the amine-catalytic reaction systems.[7c, 23] However, many of these reactions still require harsh reaction conditions and leave metal-containing wastes and products with low selectivity. Particularly, as carbonyl compounds are the most useful building blocks for a wide range of fine chemicals and pharmaceuticals, there is ongoing demand for a highly efficient approach to synthesize these compounds through the selective oxidation of amines, which has not been realized with ROS by photocatalysis before.[24]

To determine the photocatalytic activity of cercosporin in the selective oxidation of amines to aldehydes, initial investigations focused on the oxidation of benzyl amine **3a** using 1 mol % cercosporin as the catalyst under an oxygen atmosphere at room

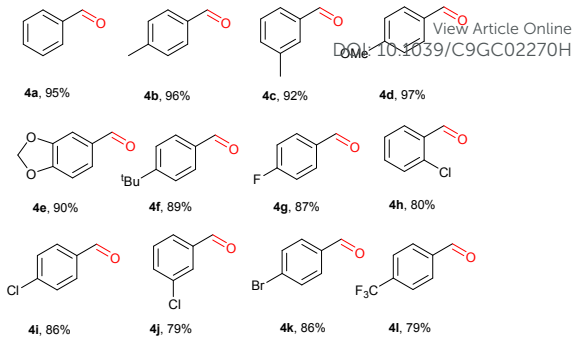
temperature with photoirradiation by 15 W CFL (Table 2, see also Table S2). It shows that the solvents play an important role in the oxidation reactions. The use of solvents such as $CHCl_3$, THF and CH_3CN afforded a mixture of imines and aldehyde (Table 2, entries 1-3), but CH_3OH delivered the highest conversion (95%) and selectivity (100%) without any further optimization after 8h at room temperature, with no imine product **5a** found in the reaction (Table 2, entry 4). No product was observed when DMSO or DMF was used as the solvent (Table 2, entries 5-6). The control experiments showed that trace product was detected in the absence of either cercosporin (Table 2, entry 7), light (Table 2, entry 8) or even O_2 (Table 2, entry 9). The amine scope was then explored (Scheme 2), showing that a lot of amines containing different substituents were efficiently converted in high yields to aldehydes when the optimized reaction conditions were utilized. Substrates bearing electron-donating substituents (**4b**-**4f**) gave relatively higher yields than those with electron-withdrawing groups on the aromatic ring (**4g**-**4l**). The reactions tolerated ortho-, meta- and para-substitutes, providing the products in moderate to high yields. Furthermore, functional groups, such as aromatic halides (**4g**-**4k**) were unaffected under the reaction conditions, showing the advantages of cercosporin-generated ROS-driven synthetic transformation.

Table 2 Optimization of the reaction conditions for the selective oxidation of amines.



Entry	Conditions[a]	Yield (%)[b]	
		4a	**5a**
1	$CHCl_3$	60	23
2	THF	59	31
3	CH_3CN	49	29
4	CH_3OH	95	0
5	DMF	trace	trace
6	DMSO	trace	trace
7	CH_3OH, no catalyst	trace	0
8	CH_3OH, no light	trace	0
9	CH_3OH, N_2	trace	0

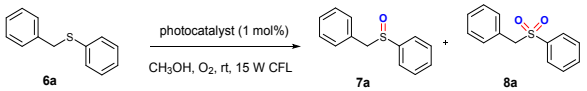
[a]All reactions were carried out on a scale of 0.25 mmol of **3a** in 2 mL of solvent under 15W CFL for 8h. See also Table S2. [b]Yields were calculated from GC measurements using internal standards.



Scheme 2 Cercosporin-photocatalyzed selective oxidation of amines with visible light.

Last, since sulfoxides are one of most important and valuable building blocks utilized in organic synthesis as well as drug candidates,[25] the synthesis of sulfoxides has aroused great interests. Traditionally, sulfoxides are synthesized through the oxidation of sulfides using stoichiometric amounts of peracid or inorganic oxidative reagents.[26] Nowadays, they can also be synthesized through a photocatalytic oxidation reaction.[27] Given the significance of these moieties, ROS oxidative system produced by cercosporin was also applied to the synthesis of substituted sulfoxides from sulfides. Different from other photocatalysis, selective oxidations of sulfides to sulfoxides were realized in CH_3OH using 1 mol % cercosporin as the catalyst under an oxygen atmosphere at room temperature upon photoirradiation by 15W CFL and no sulfone was found (Table 3, see also Table S3). Diverse alkyl (**7a**-**7f**) and aryl sulfoxides (**7g**-**7m**) were produced within 6h, in 80–95% yields (Scheme 3). This process was compatible with aryl-Me, OMe, ^{t}Bu groups (**7h**-**7k**). Additionally, the Cl and Br group were well tolerated in this reaction **(7d**, **7e**, **7i**, **7l**, **7m**), providing the possibility for further modification. Importantly, the electron-withdrawing groups, like NO_2 (**7f**), can also afford the desired sulfoxide products in excellent yields. Surprisingly, other metal-free photocatalysts, such as Acr^+-Mes, rhodamine B and eosin Y, and metal-based photocatalysts, such as $Ru(bpy)_3Cl_2$ and $Ir(ppy)_2bpy$, were unable to deliver the desired products in this reaction condition (Table 3), again, showing the great advantages of cercosporin-generated ROS-driven synthetic transformation. The reason could be that the absorption spectrum of cercosporin overlapped with the emission spectrum of CFL to a large extent compared with other catalysts (Fig. S2), as the catalytic reactivity of a photocatalyst is mainly related to the extent of absorption spectrum overlapped with the emission spectrum of light source.

Table 3 Optimization of the reaction conditions for the selective oxidation of sulfides.

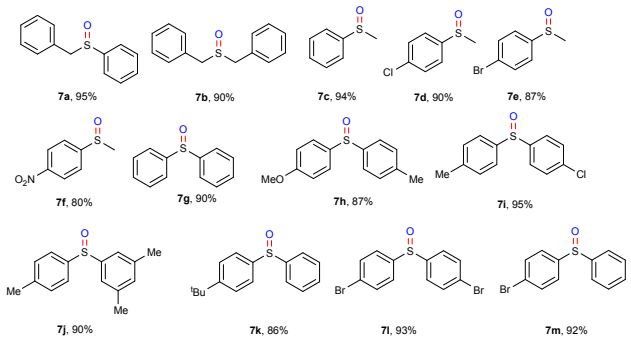


Entry[a]	Photocatalyst	Yield (%)[b]	
		7a	**8a**
1	Cercosporin	95	0
2	Acr^+-Mes	12	trace

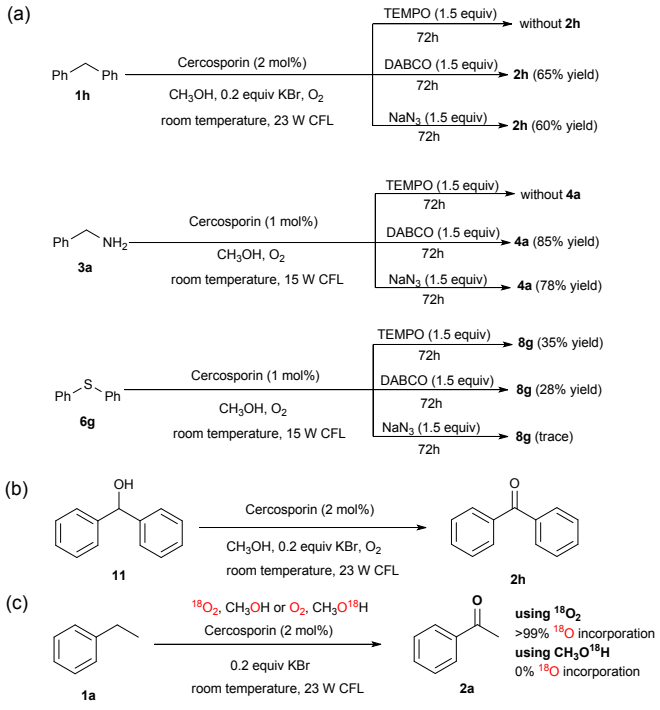
View Article Online
DOI: 10.1039/C9GC02370H

3	Eosin Y	10	trace
4	Rhodamine B	trace	trace
4	$Ru(bpy)_3Cl_2$	15	trace
5	$Ir(ppy)_2bpy$	trace	trace

[a]All reactions were carried out on a scale of 0.25 mmol of **6a** in 2 mL of CH_3OH under 15 W CFL for 6h. See also Table S3. [b]Yields of isolated product.



Scheme 3 Cercosporin-photocatalyzed selective oxidation of sulfides with visible light.



Scheme 4 Control experiments.

Since all above experiments showed that oxygen (O_2), photoirradiation, and cercosporin as the selective oxidation system are all essential for these photooxidative reactions with high activity and selectivity. It motivated us to study the mechanistic details of the reactions. The time profiles of the photooxidations (Tables S4-S6, Figs. S3-S5) revealed that the reactions were totally inhibited in the absence of light, indicating that continuous irradiation with visible light was essential to the photocatalytic transformations. The addition of the radical inhibitors 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) or 1,4-benzoquinone significantly inhibited all three transformations (Scheme 4a). Furthermore, the effects of singlet oxygen scavengers, such as 1,4-diazabicyclo [2.2.2]-octane (DABCO) and sodium azide, on the photo oxidative reactions were also studied. They revealed that the photooxidations of benzylic C–H bonds and amines proceeded without obvious inhibition, while the photooxidative reaction of sulfides can be significantly suppressed (Scheme 4a). Therefore, we propose that a radical pathway with a single-electron transfer (SET) process should be involved in the photocatalytic selective oxidation of benzylic C–H bonds and amines, while the presence of both $O_2^{\bullet-}$ and $^1O_2$ are responsible for the photooxidation reaction of sulfides.

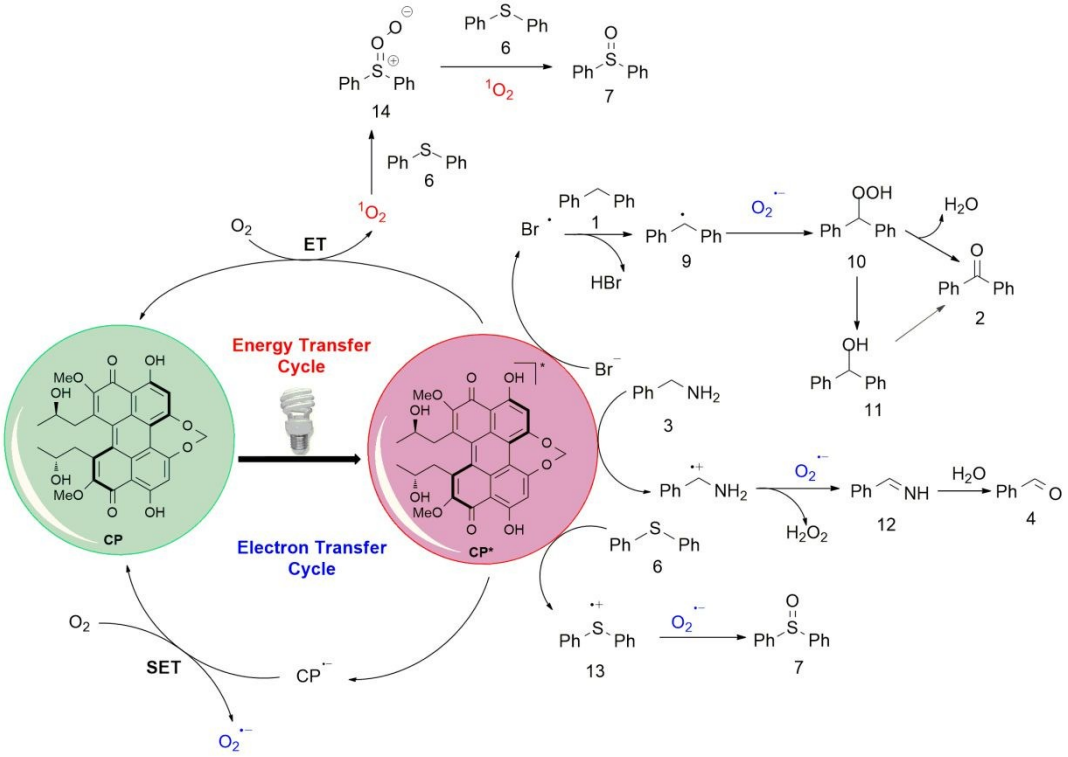
The reaction mechanism of the ROS-mediated selective oxidative reactions is summarized in Scheme 5. For the selective ROS oxidation of benzylic C–H bonds, the photocatalyst cercosporin was excited by white light irradiation to generate the excited species CP^* and then bromo radical was formed by SET from KBr to cercosporin, which was supported by the comparison of E^*_{red} ($CP^*/CP^{\bullet-}$) = 1.87 V vs SCE[16] and E ($Br^{\bullet}/Br^-$) = 1.79 V vs SCE.[28] This SET process was then followed by C–H hydrogen atom abstraction by the bromo radical at the benzyl position to generate the alkane radical **9**, which was detected by GC-MS (Fig. S6). Then, a hydroperoxide intermediate **10** was formed through oxidation of alkane radical **9** by either O_2 or O_2 radical anion. The intermediate **10** was then either directly converted to the desired ketone product **2** after losing one water molecule,[6a, 20j] or to the benzyl alcohol derivative **11**, which can further be oxidized to ketone **2** verified by control experiment (Scheme 4b). Meanwhile, the $CP^{\bullet-}$ radical anion can then be oxidized by O_2 to regenerate the catalyst. Isotope labelling studies revealed that carbonyl oxygen of **2** was originated from molecular oxygen but not from CH_3OH (Scheme 4c). Similarly, the photocatalytic oxidation of amine was induced by CP, generating the iminium intermediate **12**, which was then transformed to the carbonyl compound **4** through hydrolysis.[29] The obvious solvent effect of the above reactions may be related to the stability of the oxygen radical anion. This active intermediate may have longer lifetime in methanol compared with in other solvents due to its slower deactivation rate constant in methanol,[30] which facilitated its reaction through electron transfer process.

Different from the above two selective oxidations, both electron transfer (ET) and energy transfer (EnT) may exist in the photocatalytic oxidation of sulfide to sulfoxides.[31] Employing EnT process, sulfide radical cation **13** was generated, which can be oxidized to sulfoxide **7**. While $^1O_2$ was produced by CP when employing energy transfer pathway. Then, $^1O_2$ could take one electron from the lone pair electron of sulfide **6**, forming radical cation **14**, which could react with another molecule of **6** to afford **7** as the product.

View Article Online
DOI: 10.1039/C9GC02270H

Green Chemistry

ARTICLE



Scheme 5 Proposed mechanism.

Conclusions

In summary, we have documented perylenequinonoid derivative cercosporin as a versatile costeffective, and environmentally friendly photocatalyst by activating molecular oxygen (O_2) for selective oxidation of benzylic C–H bonds to carbonyls, selective oxidation of amines to aldehydes, and selective oxidation of sulfides to sulfoxides with high efficiency under mild conditions. The developed methods utilize irradiation of low-cost household light and inexpensive photocatalyst, which can be easily produced from microbial fermentation with very cheap glucose as the starting material and purified at a large scale. These advantages make this method particularly attractive for much more applications with respect to selective oxidation in a sustainable and environmentally friendly manner. Meanwhile, this class of photoredox catalyst may be used for other chemical reactions, awaiting further investigation.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We thank for the National Key R&D Program of China (2018YFA0901700), National Natural Science Foundation of China (21703036), Natural Science Foundation of Jiangsu Province (Grants No BK20160167), the Thousand Talents Plan (Young Professionals), the Fundamental Research Funds for the Central Universities (JUSRP51712B), Postdoctoral Foundation in Jiangsu Province (2018K153C) and the National First-class Discipline Program of Light Industry Technology and Engineering (LITE2018-14) for the funding support.

References

1. (a) C. K. Hill and J. F. Hartwig, *Nat. Chem*. 2017, **9**, 1213-1221; (b) A. R. Kulkarni, Z. J. Zhao, S. Siahrostami, J. K. Norskov and F. Studt, *Catal. Sci. Technol*. 2018, **8**, 114-123; (c) X. J. Lang, J. C. Zhao and X. D. Chen, *Angew. Chem. Int. Ed.* 2016, **55**, 4697-4700; (d) A. E. Wendlandt and S. S. Stahl, *Angew. Chem. Int. Ed.* 2015, **54**, 14638-14658; (e) S. L. Yang, L. Peng, P. P. Huang, X. S. Wang, Y. B. Sun, C. Y. Cao

and W. G. Song, *Angew. Chem. Int. Ed.* 2016, **55**, 4016-4020.

2. (a) X. Y. Huang and J. T. Groves, *J. Biol. Inorg. Chem*. 2017, **22**, 185-207; (b) L. Que and W. B. Tolman, *Nature*, 2008, **455**, 333-340; (c) J. M. Howell, K. B. Feng, J. R. Clark, L. J. Trzepkowski and M. C. White, *J. Am. Chem. Soc*. 2015, **137**, 14590-14593; (d) K. Chen, A. Eschenmoser and P. S. Baran, *Angew. Chem. Int. Ed.* 2009, **48**, 9705-9708; (e) N. D. Litvinas, B. H. Brodsky and J. Du Bois, *Angew. Chem. Int. Ed.* 2009, **48**, 4513-4516.
3. (a) Q. Q. Lu, J. Zhang, F. L. Wei, Y. Qi, H. M. Wang, Z. L. Liu and A. W. Lei, *Angew. Chem. Int. Ed.* 2013, **52**, 7156-7159; (b) S. D. McCann and S. S. Stahl, *Acc. Chem. Res*. 2015, **48**, 1756-1766; (c) Q. Cao, L. M. Dornan, L. Rogan, N. L. Hughes and M. J. Muldoon, *Chem. Commun*. 2014, **50**, 4524-4543; (d) S. E. Allen, R. R. Walvoord, R. Padilla-Salinas and M. C. Kozlowski, *Chem. Rev.* 2013, **113**, 6234-6458; (e) E. Roduner, W. Kaim, B. Sarkar, V. B. Urlacher, J. Pleiss, R. Glaser, W. D. Einicke, G. A. Sprenger, U. Beifuss, E. Klemm, C. Liebner, H. Hieronymus, S. F. Hsu, B. Plietker and S. Laschat, *Chemcatchem*, 2013, **5**, 82-112.
4. (a) R. Eisenberg and H. B. Gray, *Inorg. Chem*. 2008, **47**, 1697-1699; (b) D. Ricci, G. Bano, G. Pacchioni and F. Illas, *Phys. Rev. B*, 2003, **68**, 224105.
5. (a) Y. Kawamata, M. Yan, Z. Q. Liu, D. H. Bao, J. S. Chen, J. T. Starr and P. S. Baran, *J. Am. Chem. Soc*. 2017, **139**, 7448-7451; (b) A. N. Campbell and S. S. Stahl, *Acc. Chem. Res*. 2012, **45**, 851-863; (c) W. Q. Wu and H. F. Jiang, *Acc. Chem. Res*. 2012, **45**, 1736-1748; (d) C. Parmeggiani and F. Cardona, *Green Chem*. 2012, **14**, 547-564; (e) Z. Z. Shi, C. Zhang, C. H. Tang and N. Jiao, *Chem. Soc. Rev*. 2012, **41**, 3381-3430.
6. (a) D. A. Nicewicz and T. M. Nguyen, *ACS Catal*. 2014, **4**, 355-360; (b) C. K. Prier, D. A. Rankic and D. W. C. MacMillan, *Chem. Rev.* 2013, **113**, 5322-5363; (c) J. W. Tucker and C. R. Stephenson, *J. Org. Chem*. 2012, **77**, 1617-1622; (d) J. M. Narayanam and C. R. Stephenson, *Chem. Soc. Rev*. 2011, **40**, 102-113; (e) M. Reckenthaler and A. G. Griesbeck, *Adv. Synth. Catal*. 2013, **355**, 2727-2744; (f) M. L. Marin, L. Santos-Juanes, A. Arques, A. M. Amat and M. A. Miranda, *Chem. Rev.* 2012, **112**, 1710-1750; (g) L. Marzo, S. K. Pagire, O. Reiser and B. Konig, *Angew. Chem. Int. Ed.* 2018, **57**, 10034-10072; (h) C. S. Wang, P. H. Dixneuf and J. F. Soule, *Chem. Rev.* 2018, **118**, 7532-7585.
7. (a) X. Li, J. G. Yu and M. Jaroniec, *Chem. Soc. Rev*. 2016, **45**, 2603-2636; (b) S. Biswas, B. Dutta, K. Mullick, C. H. Kuo, A. S. Poyraz and S. L. Suib, *ACS Catal*. 2015, **5**, 4394-4403; (c) Z. M. Li, C. Liu, H. Abroshan, D. R. Kauffman and G. Li, *ACS Catal*. 2017, **7**, 3368-3374; (d) X. Lang, W. Ma, Y. Zhao, C. Chen, H. Ji and J. Zhao, *Chem. Eur. J.* 2012, **18**, 2624-2631.
8. (a) D. Ravelli, M. Fagnoni and A. Albini, *Chem. Soc. Rev*. 2013, **42**, 97-113; (b) D. P. Hari and B. König, *Chem. Commun*. 2014, **50**, 6688-6699; (c) S. Fukuzumi and K. Ohkubo, *Org. Biomol. Chem*. 2014, **12**, 6059-6071; (d) S. P. Pitre, C. D. McTiernan and J. C. Scaiano, *Acc. Chem. Res*. 2016, **49**, 1320-1330; (e) N. A. Romero and D. A. Nicewicz, *Chem. Rev.* 2016, **116**, 10075-10166.
9. (a) I. Krivtsov, E. I. Garcia-Lopez, G. Marci, L. Palmisano, Z. Amghouz, J. R. Garcia, S. Ordonez and E. Diaz, *Appl. Catal. B-Environ*. 2017, **204**, 430-439; (b) M. Ilkaeva, I. Krivtsov, E. I. Garcia-Lopez, G. Marci, O. Khainakova, J. R. Garcia, L. Palmisano, E. Diaz and S. Ordonez, *J. Catal*. 2018, **359**, 212-222; (c) M. Ilkaeva, I. Krivtsov, J. R. Garcia, E. Diaz, S. Ordonez, E. I. Garcia-Lopez, G. Marci, L. Palmisano, M. Maldonado and S. Malato, *Catal. Today*, 2018, **315**, 138-148.
10. (a) Y. Nosaka and A. Y. Nosaka, *Chem. Rev*. 2017, **117**, 11302-11336; (b) W. T. Wu, Q. G. Zhang, X. K. Wang, C. C. Han, X. D. Shao, Y. X. Wang, J. L. Liu, Z. T. Li, X. Q. Lu and M. B. Wu, *ACS Catal*. 2017, **7**, 7267-7273; (c) Y. Z. Chen, Z. U. Wang, H. W. Wang, J. L. Lu, S. H. Yu and H. L. Jiang, *J. Am. Chem. Soc*. 2017, **139**, 2035-2044; (d) Z. Zhou, J. Song, L. Nie and X. Chen, *Chem. Soc. Rev*. 2016, **45**, 6597-6626.
11. (a) M. Hayyan, M. A. Hashim and I. M. AlNashef, *Chem. Rev*. 2016, **116**, 3029-3085; (b) J. Schneider, M. Matsuoka, M. Takeuchi, J. L. Zhang, Y. Horiuchi, M. Anpo and D. W. Bahnemann, *Chem. Rev*. 2014, **114**, 9919-9986; (c) Y. Shiraishi, S. Kanazawa, D. Tsukamoto, A. Shiro, Y. Sugano and T. Hirai, *ACS Catal*. 2013, **3**, 2222-2227; (d) W. Kim, T. Tachikawa, G. h. Moon, T. Majima and W. Choi, *Angew. Chem. Int. Ed.* 2014, **53**, 14036-14041.
12. (a) C. M. Bergamini, S. Gambetti, A. Dondi and C. Cervellati, *Curr. Pharm. Design*, 2004, **10**, 1611-1626; (b) D. Harman, *Radiat. Res*. 1962, **16**, 753-763.
13. (a) S. Kuyama and T. Tamura, *J. Am. Chem. Soc*. 1957, **79**, 5725-5726; (b) S. Kuyama and T. Tamura, *J. Am. Chem. Soc*. 1957, **79**, 5726-5729; (c) M. E. Daub and M. Ehrenshaft, *Annu. Rev. Phytopathol*. 2000, **38**, 461-490; (d) M. E. Daub, *Phytopathology*, 1987, **77**, 1515-1520.
14. (a) Z. Diwu and J. W. Lown, *J. Photoch. Photobio. A* 1992, **64**, 273-287; (b) R. C. Guedes and L. A. Eriksson, *Photoch. Photobio. Sci*. 2007, **6**, 1089-1096; (c) C. A. Mulrooney, E. M. O'Brien, B. J. Morgan and M. C. Kozlowski, *Eur. J. Org. Chem.* 2012, **2012**, 3887-3904; (d) Z. Diwu, *J. Photochem. Photobiol. B*, 1993, **18**, 131-143.
15. (a) M. E. Daub and R. P. Hangarter, *Plant Physiol*. 1983, **73**, 855-857; (b) M. E. Daub, G. B. Leisman, R. A. Clark and E. F. Bowden, *P. Natl. Acad. Sci. USA*, 1992, **89**, 9588-9592; (c) M. E. Daub, G. B. Leisman, R. A. Clark and E. F. Bowden, *P. Natl. Acad. Sci. USA*, 1992, **89**, 12208-12208; (d) P. Bilski, M. Y. Li, M. Ehrenshaft, M. E. Daub and C. F. Chignell, *Photochem. Photobiol*. 2000, **71**, 129-134; (e) M. Z. Xing, X. Z. Zhang, Z. L. Sun and H. Y. Zhang, *J. Agr. Food Chem*. 2003, **51**, 7722-7724; (f) Y. Z. Hu, L. J. Jiang and L. C. Chiang, *J. Photoch. Photobio. A*, 1996, **94**, 37-41; (g) M. Weng, M. H. Zhang and T. Shen, *J. Chem. Soc. Perkin Trans. 2*, 1997, 2393-2397; (h) M. E. Daub, M. Li, P. Bilski and C. F. Chignell, *Photochem. Photobiol.* 2000, **71**, 135-140.
16. (a) S. W. Zhang, Z. C. Tang, W. H. Bao, J. Li, B. D. Guo, S. P. Huang, Y. Zhang and Y. J. Rao, *Org. Biomol. Chem*. 2019, **17**, 4364-4369; (b) Y. Zhang, Y. Cao, L. S. Lu, S. W. Zhang, W. H. Bao, S. P. Huang and Y. J. Rao, *J. Org. Chem*. 2019, **84**, 7711-7721.
17. M. M. Jimenez, S. M. Bahena, C. Espinoza and A. Trigos, *Mycopathologia*, 2010, **169**, 309-314.
18. (a) J. He, M. Wasa, K. S. L. Chan, Q. Shao and J. Q. Yu, *Chem. Rev*. 2017, **117**, 8754-8786; (b) T. Gensch, M. N. Hopkinson, F. Glorius and J. Wencel-Delord, *Chem. Soc. Rev*. 2016, **45**, 2900-2936; (c) C. Coperet, *Chem. Rev.* 2010, **110**, 656-680; (d) J. A. Labinger and J. E. Bercaw, *Nature*, 2002, **417**, 507-514; (e) L. Kesavan, R. Tiruvalam, M. H. Ab Rahim, M. I. bin Saiman, D. I. Enache, R. L. Jenkins, N. Dimitratos, J. A. Lopez-Sanchez, S. H. Taylor, D. W. Knight, C. J. Kiely and G. J. Hutchings, *Science*, 2011, **331**, 195-199; (f) X. H. Li, J. S.

Chen, X. C. Wang, J. H. Sun and M. Antonietti, *J. Am. Chem. Soc*. 2011, **133**, 8074-8077; (g) J. F. Hartwig, *J. Am. Chem. Soc*. 2016, **138**, 2-24; (h) T. W. Lyons and M. S. Sanford, *Chem. Rev.* 2010, **110**, 1147-1169.

19. (a) V. Dantignana, M. Milan, O. Cusso, A. Company, M. Bietti and M. Costas, *ACS Cent. Sci*. 2017, **3**, 1350-1358; (b) R. R. Karimov and J. F. Hartwig, *Angew. Chem. Int. Ed.* 2018, **57**, 4234-4241; (c) T. Newhouse and P. S. Baran, *Angew. Chem. Int. Ed.* 2011, **50**, 3362-3374; (d) M. C. White, *Science*, 2012, **335**, 807-809.

20. (a) G. Laudadio, S. Govaerts, Y. Wang, D. Ravelli, H. F. Koolman, M. Fagnoni, S. W. Djuric and T. Noel, *Angew. Chem. Int. Ed.* 2018, **57**, 4078-4082; (b) S. L. Li, B. Zhu, R. Lee, B. K. Qiao and Z. Y. Jiang, *Org. Chem. Front*. 2018, **5**, 380-385; (c) L. C. Finney, L. J. Mitchell and C. J. Moody, *Green Chem*. 2018, **20**, 2242-2249; (d) B. Chandra, K. K. Singh and S. Sen Gupta, *Chem. Sci*. 2017, **8**, 7545-7551; (e) L. Capaldo and D. Ravelli, *Eur. J. Org. Chem*. 2017, 2056-2071; (f) G. Pandey, R. Laha and D. Singh, *J. Org. Chem*. 2016, **81**, 7161-7171; (g) B. Muhldorf and R. Wolf, *Chem. Commun*. 2015, **51**, 8425-8428; (h) M. Xiang, Z. K. Xin, B. Chen, C. H. Tung and L. Z. Wu, *Org. Lett*. 2017, **19**, 3009-3012; (i) S. A. Yang, P. H. Li, Z. H. Wang and L. Wang, *Org. Lett*. 2017, **19**, 3386-3389; (j) H. Yi, C. L. Bian, X. Hu, L. B. Niu and A. W. Lei, *Chem. Commun*. 2015, **51**, 14046-14049; (k) E. Vanover, Y. Huang, L. B. Xu, M. Newcomb and R. Zhang, *Org. Lett*. 2010, **12**, 2246-2249; (l) F. Rusch, J. C. Schober and M. Brasholz, *Chemcatchem*, 2016, **8**, 2881-2884; (m) X. F. Liu, L. Lin, X. Y. Ye, C. H. Tan and Z. Y. Jiang, *Asian J. Org. Chem*. 2017, **6**, 422-425; (n) R. S. Yuan, S. L. Fan, H. X. Zhou, Z. X. Ding, S. Lin, Z. H. Li, Z. Z. Zhang, C. Xu, L. Wu, X. X. Wang and X. Z. Fu, *Angew. Chem. Int. Ed.* 2013, **52**, 1035-1039.

21. (a) D. P. Hruszkewycz, K. C. Miles, O. R. Thiel and S. S. Stahl, *Chem. Sci*. 2017, **8**, 1282-1287; (b) N. Sauermann, T. H. Meyer, C. Tian and L. Ackermann, *J. Am. Chem. Soc*. 2017, **139**, 18452-18455; (c) G. Olivo, G. Farinelli, A. Barbieri, O. Lanzalunga, S. Di Stefano and M. Costas, *Angew. Chem. Int. Ed.* 2017, **56**, 16347-16351; (d) T. Nanjo, E. C. de Lucca and M. C. White, *J. Am. Chem. Soc*. 2017, **139**, 14586-14591; (e) M. S. Chen and M. C. White, *Science*, 2007, **318**, 783-787; (f) J. N. Jaworski, S. D. McCann, I. A. Guzei and S. S. Stahl, *Angew. Chem. Int. Ed.* 2017, **56**, 3605-3610.

22. (a) R. Mello, L. Cassidei, M. Fiorentino, C. Fusco, W. Hummer, V. Jager and R. Curci, *J. Am. Chem. Soc*. 1991, **113**, 2205-2208; (b) R. Mello, M. Fiorentino, C. Fusco and R. Curci, *J. Am. Chem. Soc*. 1989, **111**, 6749-6757.

23. (a) P. Galletti, F. Funiciello, R. Soldati and D. Giacomini, *Adv. Synth. Catal*. 2015, **357**, 1840-1848; (b) Golime, G. Bogonda, H. Y. Kim and K. Oh, *ACS Catal.* 2018, **8**, 4986-4990; (c) W. R. Leow, W. K. H. Ng, T. Peng, X. F. Liu, B. Li, W. X. Shi, Y. Lum, X. T. Wang, X. J. Lang, S. Z. Li, N. Mathews, J. W. Ager, T. C. Sum, H. Hirao and X. D. Chen, *J. Am. Chem. Soc*. 2017, **139**, 269-276; (d) C. H. Zhang, P. S. Zhao, Z. L. Zhang, J. W. Zhang, P. Yang, P. Gao, J. Gao and D. Liu, *Rsc Adv*. 2017, **7**, 47366-47372; (e) S. Naya, T. Niwa, R. Negishi, H. Kobayashi and H. Tada, *Angew. Chem. Int. Ed.* 2014, **53**, 13894-13897; (f) J. Q. Wang, S. L. Lu, X. Q. Cao and H. W. Gu, *Chem. Commun*. 2014, **50**, 5637-5640; (g) H. Yu, Y. Y. Zhai, G. Y. Dai, S. Ru, S. Han and Y. G. Wei, *Chem. Eur. J*. 2017, **23**, 13883-13887; (h) A. Kumar, P. Kumar, C. Joshi, S. Ponnada, A. K. Pathak, A. Ali, B. Sreedhar and S. L. Jain, *Green Chem*. 2016, **18**, 2514-2521; (i) A. Mukherjee, A. Nerush, G. Leitus, L. J. W. Shimon, Y. Ben David, N. A. E. Jalapa and D. Milstein, *J. Am. Chem. Soc*. 2016, **138**, 4298-4301; (j) R. Ray, S. Chandra, V. Yadav, P. Mondal, D. Maiti and G. K. Lahiri, *Chem. Commun*. 2017, **53**, 4006-4009; (k) A. T. Murray, M. J. H. Dowley, F. Pradaux-Caggiano, A. Baldansuren, A. J. Fielding, F. Tuna, C. H. Hendon, A. Walsh, G. C. Lloyd-Jones, M. P. John and D. R. Carbery, *Angew. Chem. Int. Ed.* 2015, **54**, 8997-9000; (l) B. Chen, L. Y. Wang, W. Dai, S. S. Shang, Y. Lv and S. Gao, *ACS Catal*. 2015, **5**, 2788-2794; (m) M. Largeron and M. B. Fleury, *Angew. Chem. Int. Ed.* 2012, **51**, 5409-5412; (n) M. Rueping, C. Vila, A. Szadkowska, R. M. Koenigs and J. Fronert, *ACS Catal*. 2012, **2**, 2810-2815.

24. N. Iqbal and E. J. Cho, *Adv. Synth. Catal*. 2015, **357**, 2187-2192.

25. (a) G. A. Doherty, T. Kamenecka, E. McCauley, G. Van Riper, R. A. Mumford, S. Tong and W. K. Hagmann, *Bioorg. Med. Chem. Lett*. 2002, **12**, 729-731; (b) M. Artico, R. Silvestri, E. Pagnozzi, B. Bruno, E. Novellino, G. Greco, S. Massa, A. Ettorre, A. G. Loi, F. Scintu and P. La Colla, *J. Med. Chem*. 2000, **43**, 1886-1891; (c) R. A. Hartz, A. G. Arvanitis, C. Arnold, J. P. Rescinito, K. L. Hung, G. Zhang, H. Wong, D. R. Langley, P. J. Gilligan and G. L. Trainor, *Bioorg. Med. Chem. Lett*. 2006, **16**, 934-937; (d) M. Artico, R. Silvestri, S. Massa, A. G. Loi, S. Corrias, G. Piras and P. La Colla, *J. Med. Chem*. 1996, **39**, 522-530.

26. (a) J. Legros, J. R. Dehli and C. Bolm, *Adv. Synth. Catal*. 2005, **347**, 19-31; (b) Y. L. Hu, D. Fang and R. Xing, *Rsc Adv*. 2014, **4**, 51140-51145; (c) K. P Bryliakov and E. P Talsi, *Curr. Org. Chem*. 2012, **16**, 1215-1242.

27. (a) T. Nevesely, E. Svobodova, J. Chudoba, M. Sikorski and R. Cibulka, *Adv. Synth. Catal*. 2016, **358**, 1654-1663; (b) A. Casado-Sanchez, R. Gomez-Ballesteros, F. Tato, F. J. Soriano, G. Pascual-Coca, S. Cabrera and J. Aleman, *Chem. Commun*. 2016, **52**, 9137-9140; (c) J. Dad'ova, E. Svobodova, M. Sikorski, B. Konig and R. Cibulka, *Chemcatchem*, 2012, **4**, 620-623; (d) X. Y. Gu, X. Li, Y. H. Chai, Q. Yang, P. X. Li and Y. M. Yao, *Green Chem*. 2013, **15**, 357-361.

28. W. H. Woodruff and D. W. Margerum, *Inorg. Chem*. 1973, **12**, 962-964.

29. (a) R. S. Rohokale, B. Koenig and D. D. Dhavale, *J. Org. Chem*. 2016, **81**, 7121-7126; (b) J. H. Park, K. C. Ko, E. Kim, N. Park, J. H. Ko, D. H. Ryu, T. K. Ahn, J. Y. Lee and S. U. Son, *Org. Lett*. 2012, **14**, 5502-5505.

30. M. J. Weaver, *Chem. Rev.* 1992, **92**, 463-480.

31. (a) C. Ye, Y. B. Zhang, A. S. Ding, Y. Hu and H. Guo, *Sci. Rep.* 2018, **8**, 2205; (b) E. Baciocchi, C. Crescenzi and O. Lanzalunga, *Tetrahedron*, 1997, **53**, 4469-4478.