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Hemin-catalyzed biomimetic oxidative phenol–indole [3 + 2] reactions in aqueous media†

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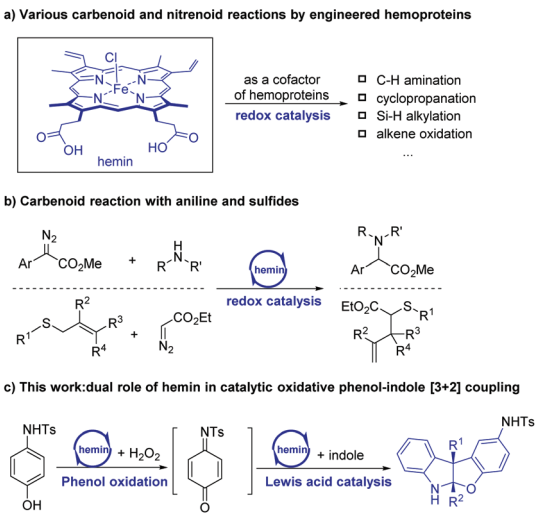
A hemin/H_2O_2 catalytic system for oxidative phenol–indole [3 + 2] coupling in aqueous solution has been developed, enabling benign synthesis of valuable benzofuroindolines under sustainable conditions. Mechanistic studies revealed the dual role of iron porphyrin responsible for both phenol oxidation and Lewis acid activation, which differs from the well-explored chemistry of hemin in carbene and nitrene insertion reactions. A preliminary experiment with cytochrome c showed that the turnover of iron porphyrin was amenable for a macromolecular setting with remarkable efficiency (*ca.* 13 300 TON).

The small molecule cofactors are of essential importance to the remarkable catalytic performance of enzymes in living systems.[1] Hemin, an abundant natural iron-containing porphyrin serving as the active center of heme-proteins such as cytochrome and myeloperoxidase, plays a vital role in oxidative biological processes.[2] Recently, viability of this complex was also frequently seen in engineered hemoprotein macromolecular settings for carbene and nitrene transferring reactions through directed evolution.[3] This approach has led to the establishment of various abiological asymmetric transformations such as C–H amination, cyclopropanation, Si–H alkylation, alkene oxidation, *etc.* (Scheme 1a).[4] In light of merits such as thermal stability, biocompatibility and low cost, hemin is arguably the most attractive small molecule model for exploiting and broadening the chemical versatility of iron-haem enzymes. However, surprisingly only sporadic studies have been disclosed in this regard. For example, Pan and co-workers exploited its performance for catalytic carbenoid reactions of diazo carbonyl compounds with anilines and sulfides (Scheme 1b).[5] In spite of remarkable advances in iron porphyrin catalysis either alone or embedded in engineered hemoproteins,[6] the potential of hemin for other types of oxidations remains largely unknown. Explorations in this direction are of high value considering the sustainable nature of hemin catalysis particularly in an aqueous medium.

Catechol oxidation is a fundamentally important process in nature for the assembly of various complex natural products. For example, catechol is oxidized *in situ* to *ortho*-quinone and then undergoes an acid-catalyzed [3 + 2] coupling with indole to construct benzofuroindoline,[7] an interesting constitutive core architecture for several bioactive alkaloids (*e.g.*, bipleiophylline and diazonamide A).[8] In many biosynthetic scenarios, phenol oxidations are typically catalyzed by copper or iron porphyrin containing oxidases such as tyrosinase, laccase, catechol oxidase, and peroxidase *via* one- or two-electron transfer processes.[9] Analogous processes with iron porphyrin are still elusive in synthetic chemistry.[10] Recently, we disclosed an oxi-



Scheme 1 The context of this study.

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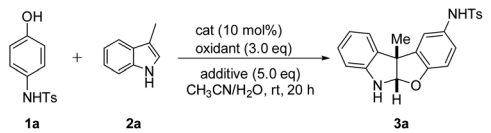
dative phenol–indole [3 + 2] coupling *via* a (salen)Mn(III)/acid relay catalysis in organic media wherein Mn(III) exhibited negligible Lewis acidity.[11] As such, we envisioned that the acidic iron center[12] of hemin might facilitate a biomimetic oxidation/cycloaddition sequence for this valuable transformation under more benign aqueous conditions (Scheme 1c).[13] In this study, we would like to disclose the details of our findings.

In view of higher electrophilicity of QMI than quinone counterparts, *N*-tosyl-4-aminophenol **1a** and indole **2a** were taken as precursors for the model reaction with H_2O_2 as the terminal oxidant in a mixture of CH_3CN/H_2O (Table 1). To our delight, hemin alone was virtually able to afford the desired benzofuroindoline **3a** in 51% yield without any additional acid co-catalyst, which was superior to other redox-active metal complexes including CuCl, $CuCl_2$, Mn(TPP)Cl, $FeCl_3$, $Fe(acac)_3$, *etc.* (Table 1, entries 1–7). Notably, a synthetic analogous Fe(Pc) was proven much less effective (entry 8). Considering the limited solubility of hemin and substrate **1a** under neutral conditions, NaOH was introduced, and we were pleased to obtain a substantially higher yield (91%) (entry 9). In contrast, a sodium salt of hemin did not perform equally well, suggesting the importance of an alkaline medium for the reaction efficiency (entry 10). Careful examination of different bases (Table S1†) and the solvent effect (entry 11 and Table S2†) identified NaOH (5.0 eq.) and CH_3CN/H_2O (v/v = 10 : 1) to be the combination of choice. In addition, alternation of the oxidants was also attempted, indicating that TBHP and CHP were inferior to H_2O_2 under identical conditions (entries 12 and 13). Intriguingly, a significantly lower yield of **3a** was obtained under an inert atmosphere (60%, entry 14). This led to our finding that hemin-catalyzed aerobic oxidation is virtually involved, which gave rise to adduct **3a** in comparably high yield in the absence of H_2O_2 (87%, entry 15), however, at the expense of reaction time (48 h). A decrease in catalyst loading would deteriorate the reaction efficiency. Still, 80% and 69% yields were recorded with 5 mol% and 2 mol% of hemin, respectively (entries 16 and 17).

We moved on to evaluate the substrate generality under optimal reaction conditions (Table 2). 3-Methylindoles bearing various sterically and electronically distinct substituents at the phenyl ring were firstly examined. Pleasingly, the respective cycloadducts **3b–n** could be isolated in good to high yields (68–85%). In particular, the appendage of a bulky group to the 3-position of indole probably posed a negative influence, as shown by the declined yield recorded for products **3o** and **3s**. Nevertheless, the latter proved the good tolerance of a pro-

Table 1 Optimization of the reaction conditions[a]

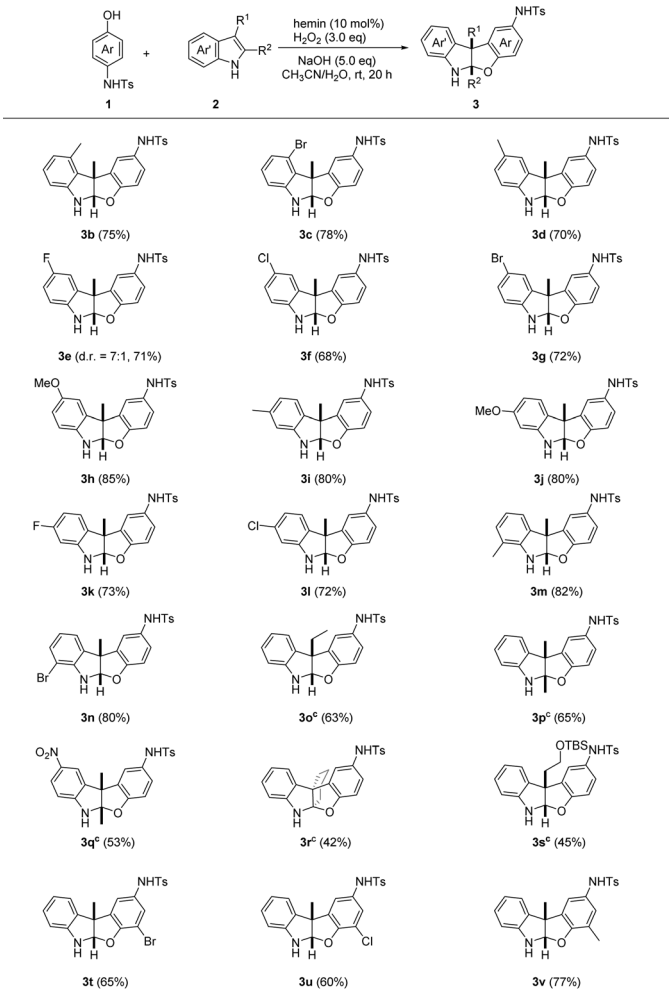


1a 2a 3a

Entry	Cat.	Additive	Oxidant	Yield[b] (%)
1	Hemin	—	H_2O_2	51
2	Mn(TPP)Cl	—	H_2O_2	39
3	CuCl	—	H_2O_2	24
4	$CuCl_2$	—	H_2O_2	30
5	$FeCl_3$	—	H_2O_2	22
6	$Fe(OTf)_3$	—	H_2O_2	15
7	$Fe(acac)_3$	—	H_2O_2	15
8	Fe(Pc)	—	H_2O_2	10
9	Hemin	NaOH	H_2O_2	91
10[c]	Hemin	—	H_2O_2	71
11[d]	Hemin	NaOH	H_2O_2	≦71
12	Hemin	NaOH	TBHP	67
13	Hemin	NaOH	CHP	75
14[e]	Hemin	NaOH	H_2O_2	60
15[f]	Hemin	NaOH	Air	87
16[g]	Hemin	NaOH	H_2O_2	80
17[h]	Hemin	NaOH	H_2O_2	69

[a] Reactions were performed with **1a** (0.25 mmol), catalyst (0.01 mmol), **2a** (0.1 mmol) and oxidant (0.3 mmol) in CH_3CN/H_2O (v/v = 1 : 10, 7.0 mL) under air. [b] Isolated yields. [c] The sodium salt of hemin was used. [d] Various other solvents were used (see Table S2†). [e] Under an N_2 atmosphere. [f] In an air balloon for 48 h. [g] 5 mol% hemin was used. [h] 2 mol% hemin was used. TBHP = *tert*-butyl hydroperoxide; CHP = cumene hydroperoxide.

Table 2 Substrate scope[a,b]



[a] For reaction conditions, see Table 1, entry 9. [b] Isolated yield. [c] Reactions were performed in CH_3CN/H_2O (v/v = 1 : 1, 7.0 mL).

tected alcoholic hydroxyl group. Also noteworthy was the nice compatibility of 2,3-disubstituted indoles. For example, reaction with 2,3-dimethylindoles and 1,2,3,4-tetrahydrocarbazole proceeded uneventfully to provide benzofuroindoles **3p–r**, albeit with somewhat compromised reaction efficiency. On the other hand, variation of the phenol part was also possible; reactions took place smoothly with 2-bromo, 2-chloro, and 2-methyl aminophenol derivatives to produce the respective products **3t–v** (60–77%). Of note, except for adduct **3e** with 7 : 1 dr, all other products were produced in a diastereoisomerically pure form. This oxidative [3 + 2] coupling reaction was found to be readily scalable, as showcased in the gram-scale preparation of compound **3a** (1.41 gram, 90%) with 10 mol% of hemin, which was proven still robust at an economized loading (2 mol% of hemin, 1.02 gram of **3a**, 65% yield, see the ESI†).

The remarkable catalytic performance of hemin herein prompted us to gain deeper insight into the working principles. As shown in control experiments, hemin was found indispensable to convert phenol **1a** to QMI **4a** (Scheme 2a). In fact, small quantities of **4a** with partial imine hydrolysis could be observed in the mixture of model reaction under standard conditions. Thus, the NHTs group in **1a** appears like a substitute for another OH group and renders it prone to undergo catechol-type two-electron oxidation, and this oxidation differs from the biological phenol oxidations by *e.g.*, tyrosine oxidase and relevant synthetic endeavors.[12a–d] This notion is in line with the comparably poor outcomes of typical one-electron metal redox systems with CuCl, $CuCl_2$, $FeCl_3$, and $Fe(acac)_3$ (Table 1, entries 3–7) *versus* contrastingly much superior performance of Mn(TPP)Cl.[14] It was also backed by the experimental outcomes that TEMPO (2.0 eq.) as a radical scavenger virtually did not inhibit the reaction (83% yield, Scheme 2b). Notably, unlike heme-based tryptophan dioxygenases that generally break the indole core in the biological kynurenine pathway,[15] hemin showed remarkable chemoselectivity keeping nucleophilic indole **2a** almost intact (Scheme 2c). In addition, the scenario of the annulation event was also intriguing. When preformed QMI **4a** was treated with indole **2a**, the coupling reaction took place effectively under standard conditions and afforded **3a** in 75% yield. In contrast, no [3 + 2] coupling occurred when hemin and NaOH were simultaneously removed. However, by obviating either of them, adduct **3a** could be produced in lower yet appreciable yields (Scheme 2d). Evidently, both hemin and the alkaline medium are promoters for the [3 + 2] coupling between **4a** and **2a**.

It is well known that hemin tends to form inactive dimers, and the presence of alkaline conditions would attenuate its aggregation.[16] As evidenced by UV-Vis studies,[17] the chloride anion of hemin was likely displaced with hydroxide in alkaline solution to form haematin, which exhibited an absorbance peak at 575 nm (Fig. 1a).[18] Hemin is known to promote the decomposition of H_2O_2,[19] and this probably accounts for the necessity of relatively high loading (3.0 eq.). The diminished yield obtained under an inert atmosphere (Table 1, entry 14) suggests the function of oxygen as the partial terminal oxidant. Moreover, a strengthened signal of indole **2a** in alkaline solution points to a tentative deprotonation of NH (Fig. 1b). Although the details of different ferric species formed in this system still necessitate further in-depth study, it would be justified to conclude that coordination of QMI **4a** to the Lewis acidic iron of hemin[8e] with co-activation of the indole partner by the alkaline medium synergistically promote the rapid annulation process.

We anticipated that the catalytic turnover of iron porphyrin might also be viable with hemoproteins for such valuable abiological annulations. To evaluate this hypothesis, small cytochrome c (12.3 kDa, from bovine heart) consisting of a single 104 amino acid peptide with a covalently attached single heme group was employed as a model enzyme (Scheme 3). The reac-

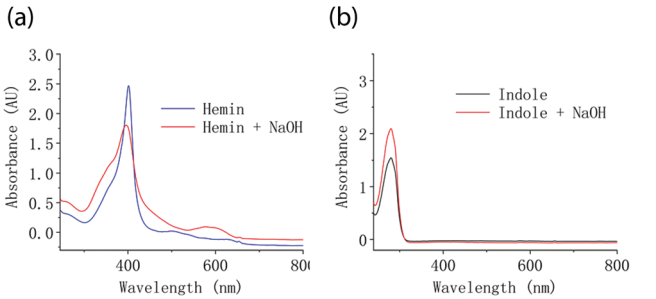
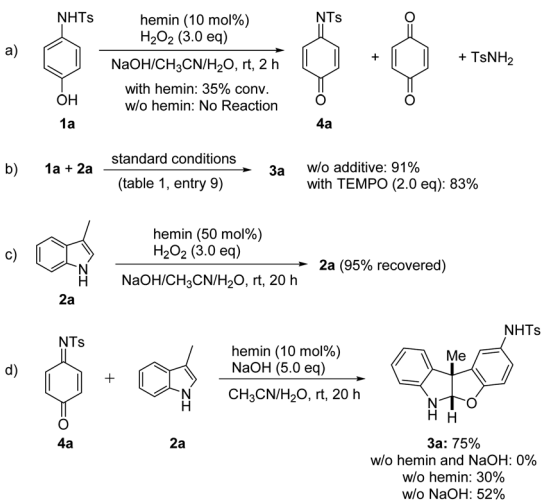
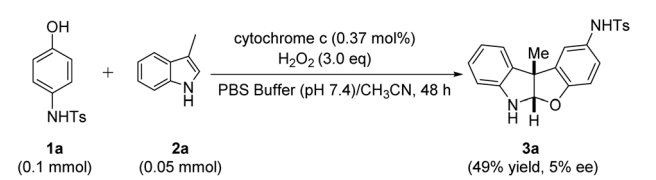


Fig. 1 (a) UV-Vis spectra of hemin in DMSO/H_2O (2 : 3) with and without NaOH. (b) UV-Vis spectra of indole in H_2O/CH_3CN (10 : 1) with and without NaOH.



Scheme 2 Mechanistic investigations.



Scheme 3 Preliminary study with cytochrome c.

tion was performed at the 0.05 mmol scale for **2a** with 0.37 mol% loading of a catalyst under neutral conditions [PBS buffer (pH 7.4)/CH_3CN = 10 : 1]. Pleasingly, product **3a** was isolated in 49% yield, corresponding to *ca.* 13 300 TON. Although asymmetric induction by this wild-type protein was very limited (5% ee), it holds promise to exhibit high enantioselectivity with other hemoproteins and by means of the state-of-the-art directed evolution.[20]

Conclusions

In summary, we have reported the catalytic oxidative phenol–indole [3 + 2] coupling reaction in aqueous media for the first time. This system is valuable not only for providing biologically significant benzofuroindolines but also for showing the potential of naturally abundant hemin for oxidative phenol coupling reaction and Lewis acid catalysis. Provided a central function of hemin for the family of cytochromes, P450 enzymes, the present study is anticipated to stimulate further exploration of hemin catalysis and, in turn, push the boundary of classic heme biocatalysis.

Conflicts of interest

The authors declare no competing financial interest.

Acknowledgements

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Notes and references

1 I. Bertini and A. Sigel, *Handbook on Metalloproteins*. CRC Press, 2001.

2 (*a*) I. G. Denisov, T. M. Makris, S. G. Sligar and I. Schlichting, *Chem. Rev.*, 2005, **105**, 2253–2278; (*b*) T. L. Poulos, *Chem. Rev.*, 2014, **114**, 3919–3962.

3 For leading reviews, see: (*a*) R. Fasan, *ACS Catal.*, 2012, **2**, 647–666; (*b*) F. H. Arnold, *Angew. Chem., Int. Ed.*, 2018, **57**, 4143–4148; (*c*) R. K. Zhang, X. Huang and F. H. Arnold, *Curr. Opin. Chem. Biol.*, 2019, **49**, 67–75; (*d*) U. Markel, D. F. Sauer, J. Schiffels, J. Okuda and U. Schwaneberg, *Angew. Chem., Int. Ed.*, 2019, **58**, 4454–4464.

4 For recent references, see: (*a*) S. C. Hammer, G. Kubik, E. Watkins, S. Huang, H. Minges and F. H. Arnold, *Science*, 2017, **358**, 215–218; (*b*) C. K. Prier, R. K. Zhang, A. R. Buller, S. Brinkmann-Chen and F. H. Arnold, *Nat. Chem.*, 2017, **9**, 629–634; (*c*) D. A. Vargas, A. Tinoco, V. Tyagi and R. Fasan, *Angew. Chem., Int. Ed.*, 2018, **57**, 9911–9915; (*d*) K. Chen, S. Q. Zhang, O. F. Brandenberg, X. Hong and F. H. Arnold, *J. Am. Chem. Soc.*, 2018, **140**, 16402–16407; (*e*) R. Fasan, D. Vargas, R. Khade and Y. Zhang, *Angew. Chem., Int. Ed.*, 2019, **58**, 10148–10152; (*f*) I. Cho, Z. Jia and F. H. Arnold, *Science*, 2019, **364**, 575–578; (*g*) J. Zhang, X. Huang, R. K. Zhang and F. H. Arnold, *J. Am. Chem. Soc.*, 2019, **141**, 9798–9802; (*h*) R. K. Zhang, K. Chen, X. Huang, L. Wohlschlager, H. Renata and F. H. Arnold, *Nature*, 2019, **565**, 67–72.

5 (*a*) X. Xu, C. Li, Z. Tao and Y. Pan, *Adv. Synth. Catal.*, 2015, **357**, 3341–3345; (*b*) X. Xu, C. Li, Z. Tao and Y. Pan, *Green Chem.*, 2017, **19**, 1245–1249; (*c*) X. Xu, C. Li, M. Xiong, Z. Tao and Y. Pan, *Chem. Commun.*, 2017, **53**, 6219–6222.

6 (*a*) P. Böhm and H. Gröger, *ChemCatChem*, 2015, **7**, 22–28; (*b*) R. A. Baglia, J. P. T. Zaragoza and D. P. Goldberg, *Chem. Rev.*, 2017, **117**, 13320–13352.

7 (*a*) A. W. G. Burgett, Q. L. Li, Q. Wei and P. G. Harran, *Angew. Chem., Int. Ed.*, 2003, **42**, 4961–4966; (*b*) K. C. Nicolaou, U. Majumder, S. P. Roche and D. Y.-K. Chen, *Angew. Chem., Int. Ed.*, 2007, **46**, 4715–4718; (*c*) T. S. Kam, S. J. Tan, S. W. Ng and K. Komiyama, *Org. Lett.*, 2008, **10**, 3749–3752; (*d*) Y. Hirasawa, H. Arai, A. Rahman, I. Kusumawati, N. C. Zaini, O. Shirota and H. Morita, *Tetrahedron*, 2013, **69**, 10869–10875.

8 (*a*) W. Tian, L. R. Chennamaneni, T. Suzuki and D. Y.-K. Chen, *Eur. J. Org. Chem.*, 2011, **2011**, 1027–1031; (*b*) L. H. Liao, C. Shu, M. Zhang, Y. Liao, X. Hu, Y. Zhang, Z. Wu, W. Yuan and X. Zhang, *Angew. Chem., Int. Ed.*, 2014, **53**, 10471–10475; (*c*) H. Ding, P. L. DeRoy, C. Perreault, A. Larive, A. Siddiqui, C. G. Caldwell, S. Harran and P. G. Harran, *Angew. Chem., Int. Ed.*, 2015, **54**, 4818–4822; (*d*) D. Lachkar, N. Denizot, G. Bernadat, K. Ahamada, M. A. Beniddir, V. Dumontet, J. F. Gallard, R. Guillot, K. Leblanc, E. O. N'nang, V. Turpin, C. Kouklovsky, E. Poupon, L. Evanno and G. Vincent, *Nat. Chem.*, 2017, **9**, 793–798; (*e*) Q. J. Liu, J. Zhu, X. Y. Song, L. Wang, S. R. Wang and Y. Tang, *Angew. Chem., Int. Ed.*, 2018, **57**, 3810–3814; (*f*) L. Zhang, J. Hu, R. Xu, S. Pan, X. Zeng and G. Zhong, *Adv. Synth. Catal.*, 2019, **361**, DOI: 10.1002/adsc.201901035.

9 M. G. Peter and U. Wollenberger, Phenol-oxidizing Enzymes: Mechanisms and Applications in Biosensors, in *Frontiers in Biosensorics I*. Birkhäuser, Basel, 1997, 63–82.

10 For uses of iron porphyrin complexes in environmental phenol degradation, see: (*a*) J. Yu, K. E. Taylor, H. Zou, N. Biswas and J. K. Bewtra, *Environ. Sci. Technol.*, 1994, **28**, 2154–2160; (*b*) U. Khan and J. A. Nicell, *J. Chem. Technol. Biotechnol.*, 2007, **82**, 818–830.

11 Q. Yu, Y. Fu, J. Huang, J. Qin, H. Zuo, Y. Wu and F. Zhong, *ACS Catal.*, 2019, **9**, 7285.

12 For selected examples of Lewis acidic iron catalyzed oxidative reactions, see: (*a*) X. Guo, R. Yu, H. Li and Z. Li, *J. Am. Chem. Soc.*, 2009, **131**, 17387; (*b*) R. Beaud, R. Guillot, C. Kouklovsky and G. Vincent, *Angew. Chem., Int. Ed.*, 2012, **51**, 12546–12550; (*c*) Z. Huang, L. Jin, Y. Feng, P. Peng, H. Yi and A. Lei, *Angew. Chem., Int. Ed.*, 2013, **52**, 7151; (*d*) T. Tomakinian, R. Guillot, C. Kouklovsky and G. Vincent, *Angew. Chem., Int. Ed.*, 2014, **53**, 11881–11885; (*e*) Y. Ni, Q. Yu, Q. Liu, H. Zuo, H. Yu, W. Wei, R. Liao and F. Zhong, *Org. Lett.*, 2018, **20**, 1404–1408; (*f*) S. Teranishi, K. Maeda, T. Kurahashi and S. Matsubara, *Org. Lett.*, 2019, **21**, 2593–2596; (*g*) K. Fujiwara, T. Kurahashi and S. Matsubara, *J. Am. Chem. Soc.*, 2012, **134**, 5512–5515.

13 For our recent work on sustainable aqueous reactions, see: (*a*) X. Lu, Y. Shi and F. Zhong, *Green Chem.*, 2018, **20**, 113–117; (*b*) Y. Shi, Y. Wang, X. Lu, Y. Zhang, Y. Wu and F. Zhong, *Green Chem.*, 2019, **21**, 780–784; (*c*) D. Wang, X. Lu, S. Sun, H. Yu, H. Su, Y. Wu and F. Zhong, *Eur. J. Org. Chem.*, 2019, **2019**, 6028.

14 Mn(TPP)Cl afforded adduct **3a** in 76% yield under the standard optimal conditions. Fe/Mn-porphyrins can mediate effective two-electron redox events; one from the metal cation and one from the π-cloud, see: M. C. Richoux, P. Neta, A. Harriman, S. Baral and P. Hambright, *J. Phys. Chem.*, 1986, **90**, 2462.

15 I. Shin, B. R. Ambler, D. Wherritt, W. P. Griffith, A. C. Maldonado, R. A. Altman and A. Liu, *J. Am. Chem. Soc.*, 2018, **140**, 4372–4379.

16 (*a*) S. B. Brown and M. Shillcock, *Biochem. J.*, 1976, **153**, 279–285; (*b*) H. Xu, Z. Yang, H. Li and Z. Gao, *Chem. – Eur. J.*, 2017, **23**, 17755–17763.

17 UV-Vis studies were performed in DMSO/H_2O due to extremely limited solubility in CH_3CN/H_2O.

18 (*a*) H. U. Wolf, W. Lang and R. Zander, *Clin. Chim. Acta*, 1984, **136**, 95–104; (*b*) R. Zander, W. Lang and H. U. Wolf, *Clin. Chim. Acta*, 1984, **136**, 83–93.

19 (*a*) J. Zhang, W. Wang, S. Chen, Y. Ruo, X. Zhong and X. Wu, *Biosens. Bioelectron.*, 2014, **57**, 71; (*b*) Y. Zang, J. Lei, L. Zhang and H. Ju, *Anal. Chem.*, 2014, **86**, 12362.

20 For a recent example of engineered cytochrome c for asymmetric oxidation reaction, see: I. Cho, C. K. Prier, Z.-J. Jia, R. K. Zhang, T. Görbe and F. H. Arnold, *Angew. Chem., Int. Ed.*, 2019, **58**, 3138.

