OL Organic Letters

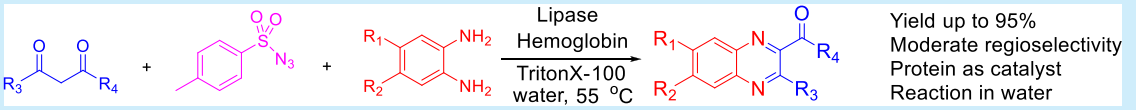
pubs.acs.org/OrgLett Letter

A Dual-Protein Cascade Reaction for the Regioselective Synthesis of Quinoxalines

Fengxi Li, Xuyong Tang, Yaning Xu, Chunyu Wang, Zhi Wang, Zhengqiang Li,* and Lei Wang*

Cite This: https://dx.doi.org/10.1021/acs.orglett.0c01186 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information



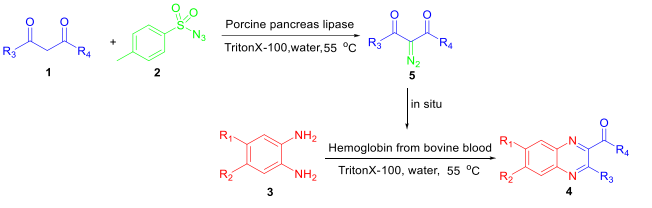
ABSTRACT: In this work, an efficient dual-protein (lipase and hemoglobin) system was successfully constructed for the regioselective synthesis of quinoxalines in water. A set of quinoxalines were obtained in high yields under optimal reaction conditions. This dual-protein method exhibited a regioselectivity higher than those of previously reported methods. This study not only provides a green and mild strategy for the synthesis of quinoxalines but also expands the application of lipase and hemoglobin in organic synthesis.

Quinoxaline derivatives are important structural motifs that exhibit a wide range of biological activities, such as antitumor, antiviral, antibacterial, anti-inflammatory, and anti-HIV activities.[1−6] Moreover, quinoxalines have been widely used for the synthesis of dyes, organic semiconductors, dehydroannulenes, solar cells, cavitands, etc.[7−12] Many chemical methods, including double condensation of aromatic 1,2-diamine with 1,2-dicarbonyl compounds, cascade oxidation−condensation of 1,2-ketoalcohols with aromatic 1,2-diamine, deoxidation of quinoxaline *N*-oxides, oxidative cyclization of terminal or internal alkynes or ketones with 1,2-diamines, coupling of epoxides with ene-1,2-diamines, and tandem annulation of *o*-phenylenediamines with diazocarbonyls, have been developed for the construction of quinoxalines.[13−20] However, most of these methods suffer from expensive and detrimental metal catalysts, unsatisfactory product yields, low regioselectivity, harsh reaction conditions, and volatile or hazardous solvents, thereby limiting their wide application. Thus, developing a more efficient, regioselective, and environmentally benign synthetic route is the primary challenge in constructing quinoxalines.

Biocatalysis has become increasingly attractive for the development of more efficient and cleaner chemical processes.[21] High regio- and stereoselectivity and the use of mild reaction conditions provide an excellent "green" profile for reactions catalyzed by enzymes. These enzymatic systems can involve one enzyme that catalyzes one specific reaction or multiple enzymes that catalyze cascade reactions. Multienzymatic cascade reactions in one pot can offer many considerable advantages: they are not time-consuming, the costs and chemicals for product recovery may be reduced, reversible reactions can be driven to completion, and the concentration of harmful or unstable compounds can be kept to a minimum. Therefore, multienzymatic cascade reactions are considered important strategies for establishing environmentally benign and sustainable chemical processes. Numerous attempts have been made to produce novel compounds and natural products by multienzymatic cascade reactions.[22,23]

Recently, researchers have shown an increased level of interest in mining non-natural reactions of proteins, and many studies on this topic have been reported.[24−30] Lipases and hemoglobins are ideal candidates because of their low cost, commercial availability, broad catalytic abilities, and good stability. Herein, we designed a novel lipase−hemoglobin cascade reaction for the efficient synthesis of quinoxalines via a three-component reaction of 1,3-dicarbonyl compounds, sulfonyl azides, and 1,2-diamines (Scheme 1). In such a dual-protein system, lipase was used to catalyze the *in situ* generation of diazodicarbonyls by a diazo transfer reaction to 1,3-dicarbonyl compounds with sulfonyl azides. Then, the *in situ*-generated α-diazo carbonyl compounds were reacted with 1,2-diamines via a condensation catalyzed by hemoglobin to

Scheme 1. Lipase−Hemoglobin System for the Synthesis of Quinoxalines



Received: April 2, 2020

afford quinoxalines. This dual-protein system is an environmentally benign, efficient, and regioselective system for the synthesis of quinoxalines. To the best of our knowledge, this is the first report of a dual-protein system containing lipase and hemoglobin, and no report on the regioselective synthesis of quinoxalines using proteins as catalysts has been published.

Initially, ethyl acetoacetate, *p*-toluenesulfonyl azide (TsN_3), and 1,2-diaminobenzene were used as the model substrates for this lipase−hemoglobin-catalyzed cascade reaction. By using this model reaction, we investigated the effect of the type of proteins. As shown in Table 1, all of the used lipases and heme proteins could catalyze the reaction (entries 1−7), and the combination of porcine pancreas lipase (PPL) and hemoglobin from bovine blood (HbBv) achieved the highest yield of quinoxaline (**4a**). Accordingly, PPL always exhibits a satisfactory catalytic ability in many lipase-catalyzed promiscuous reactions.[31−33] The higher catalytic performance of hemoglobin compared with those of other heme proteins may be due to the synergistic effect of hemoglobin, which is composed of four subunits.[34] Therefore, we selected these two proteins as the catalysts for further studies. No corresponding product was observed when PPL or HbBv was used independently in this reaction (entry 8 or 9, respectively), whereas one of the proteins combined with the other denatured one could not catalyze this reaction (entries 10 and 11). When Apo-HbBv replaced HbBv as the catalyst in this dual-protein-catalyzed reaction, the reaction did not occur (entry 12). These control experiments were the same as the blank experiment (entry 13). These results suggest that both proteins are involved in this catalytic process and their active catalytic conformations of proteins are necessary for this dual-protein-catalyzed reaction. The commercial ferric chloride hemes [hemin and Fe(TPP)Cl] afforded poor yields of **4a** in this reaction even when the heme concentration was increased to 1 mol % (entries 14 and 15). We also used Et_3N and $Fe(OTf)_3$ as the chemical catalysts (dosage of ≤1 mol %), and an only 14% yield was obtained after reaction for 48 h (entry 16). The combination of Et_3N and HbBv was investigated to clarify the necessity of lipase, and the yield was obviously lower than that of the combination of PPL and HbBv (entry 17). An excessive dosage of Et_3N could lead to a decrease in the catalytic activity of HbBv (data listed in Table S1). Furthermore, the optimum operational ratio of PPL and HbBv is also important for this dual-protein cascade reaction. We fixed the dosage of HbBv at 16 mg (0.1 mol %) and investigated the effects of the ratio of PPL and HbBv (data listed in Table S2). The quinoxaline yield (**4a**) increased as the amount of PPL increased to 4 mg. However, further increasing the amount of PPL did not improve the yield. Considering the high efficiency, mild condition, and low catalyst dosage, the dual-protein strategy is a more practical method for the synthesis of quinoxalines.

Table 1. Synthesis of Quinoxaline (4a) by a Dual-Protein System (lipase and hemoglobin)[a]

entry	lipase	hemoglobin	isolated yield (%)
1	PPL	HbBv	90
2	Cal-B	HbBv	76
3	PSL	HbBv	41
4	CRL	HbBv	35
5	PPL	HbSv	61
6	PPL	Mb	47
7	PPL	HP	28
8	PPL	–	ND[b]
9	–	HbBv	ND[b]
10	denatured PPLc	HbBv	ND[b]
11	PPL	denatured HbBv[c]	ND[b]
12	PPL	apo-HbBv	ND[b]
13	–	–	ND[b]
14	PPL	hemin[d]	26
15	PPL	Fe(TPP)Cl[d]	31
16	Et_3N[e]	$Fe(OTf)_3$[e]	14
17	Et_3N[f]	HbBv	67

[a]Reaction conditions: ethyl acetoacetate (**1a**, 1.0 mmol), TsN_3 (**2**, 1.2 equiv), 1,2-diaminobenzene (**3a**, 1.0 equiv), hemoprotein (heme concentration of 0.1 mol %), lipase (protein content of 4 mg), water (2 mL), Triton X-100 (5% mol), 55 °C, 6 h. Abbreviations: PPL, porcine pancreas lipase; Cal-B, lipase B from *Candida antarctica*; PSL, *Pseudomonas* sp. lipase; CRL, *Candida rugosa* lipase; HbBv, hemoglobin from bovine blood; HbSv, hemoglobin from swine blood; Mb, myoglobin from equine heart; HP, horseradish peroxidase; hemin, chloroprotoferriheme. [b]Not detected. [c]Denatured by heating. [d]Heme concentration of 1 mol %. [e]Using 1% mol, 48 h. [f]Using 1% mol, 6 h.

Using environmentally friendly solvents as the ideal alternative to hazardous organic solvents has attracted considerable interest in organic synthesis.[35] In this dual-protein system, we used water as the reaction medium because of its nontoxic characteristics. However, the yield was not very satisfactory due to the poor solubility or dispersibility of substrates in water (Table 2, entry 1). Generally, surfactants not only can enhance the biocatalytic efficiency and stability of proteins but also can substantially increase the degree of dispersion of the organic substrate in aqueous media.[36,37] In the study presented here, the effects of four types of surfactants, namely, sodium di-2-ethylhexylsulfosuccinate (AOT, anionic surfactant), sodium dodecyl sulfate (SDS, anionic surfactant), Triton X-100 (non-ionic surfactant), and Tween 80 (non-ionic surfactant), on the dual-protein-catalyzed synthesis of quinoxalines were investigated. The non-ionic surfactants (entries 2 and 3) were remarkably more effective in accelerating the reaction, whereas the anionic surfactants (entries 4 and 5) decreased the reaction rate. The highest yield was obtained when Triton X-100 was adopted. These results are consistent with the findings of other researchers who reported that anionic surfactants can interact strongly with proteins and cause their denaturation.[38−40] Furthermore, the

Table 2. Effects of Surfactants on the Dual-Protein-Catalyzed Synthesis of Quinoxaline (4a)[a]

entry	solvent	surfactant	surfactant concentration (mol %)	isolated yield (%)
1	water	–	–	45
2	water	Triton X-100	5	90
3	water	Tween 80	5	72
4	water	SDS	5	34
5	water	AOT	5	29
6	water	Triton X-100	2.5	77
7	water	Triton X-100	10	81

[a]Reaction conditions: ethyl acetoacetate (1.0 mmol), TsN_3 (1.2 equiv), 1,2-diaminobenzene (1.0 equiv), PPL (protein content of 4 mg), HbBv (heme concentration of 0.1 mol %), water, 2 mL, surfactant, 55 °C, 6 h.

https://dx.doi.org/10.1021/acs.orglett.0c01186
Org. Lett. XXXX, XXX, XXX−XXX

effect of the amount of Triton X-100 was also examined, and the optimal concentration was 5 mol %. Triton X-100 markedly decreased the yield of quinoxaline.

Temperature is another key factor that affects enzymatic reactions. Our results (Figure 1) demonstrated that the yield

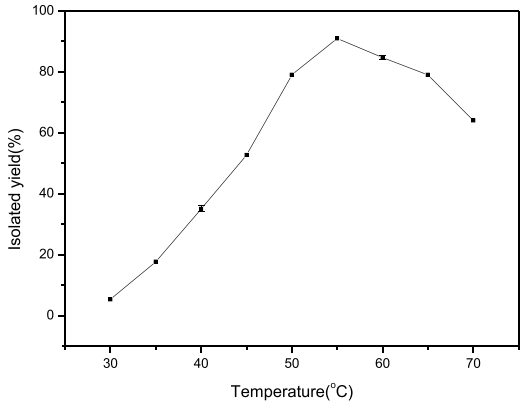


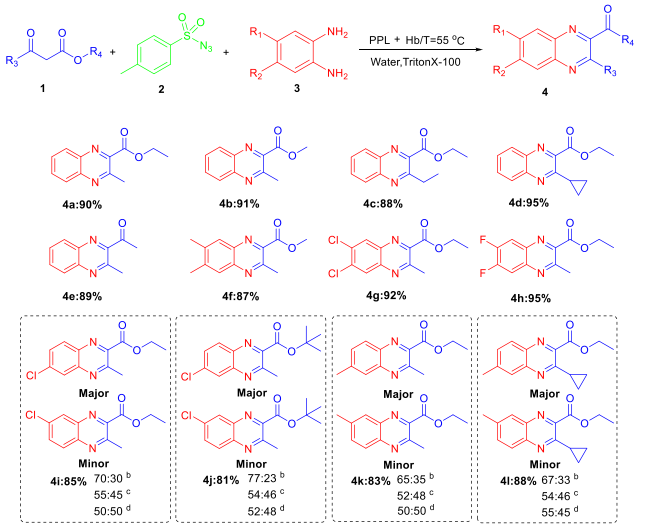
Figure 1. Effect of temperature on the dual-protein-catalyzed synthesis of quinoxalines. Reaction conditions: ethyl acetoacetate (**1a**, 1.0 mmol), TsN_3 (**2**, 1.2 equiv), 1,2-diaminobenzene (**3a**, 1.0 equiv), HbBv (heme concentration of 0.1 mol %), PPL (protein content of 4 mg), water (2 mL), Triton X-100 (5% mol), 6 h.

increased as the temperature increased from 30 to 55 °C, and the maximum yield was achieved at 55 °C. The catalytic performance of the dual-protein system gradually declined as the temperature was further increased. Generally, higher temperatures can increase the frequency of the collision between protein and substrate molecules and improve the catalytic efficiency. However, the temperature beyond 55 °C may destroy the active conformation of the protein, which may decrease the catalytic activity. Under the optimum conditions, we scaled up the biocatalytic process by 100-fold [water (2 L), ethyl acetoacetate (100 mmol), TsN_3 (120 mmol), 1,2-diaminobenzene (100 mmol), lipase (0.4 g), HbBv (heme concentration of 0.1 mol %), and Triton X-100 (5 mol %) at 55 °C]. The yield of quinoxaline reached 93% (20.06 g, 92.9 mmol) after 6 h. This result implies that this green method has high potential for industrial production.

To test the robustness of this reaction, various substituted 1,2-diaminobenzenes and β-ketoesters were used for the synthesis of quinoxalines. As shown in Scheme 2, all of the used 1,2-diamines and β-ketoesters can react with TsN_3 in one pot and afford the desired quinoxalines with satisfactory yields (81−95%). It was noteworthy that hemoglobin exhibited moderate regioselectivity when monosubstituted 1,2-diaminobenzenes were used as the substrates (**4i**−**4l**). To prove that this regioselectivity was derived from hemoglobin, hemin and PPL were combined to catalyze the reaction, and a poor regioselectivity was achieved as expected. Compared with the result catalyzed by Et_3N and $Fe(OTf)_3$, HbBv also exhibited obviously higher regioselectivity. The regioselectivity of the protein can be improved by the current tools of enzyme engineering or directed evolution. Further study of the directed evolution of hemoglobin for the synthesis of quinoxalines is now in progress in our laboratory.

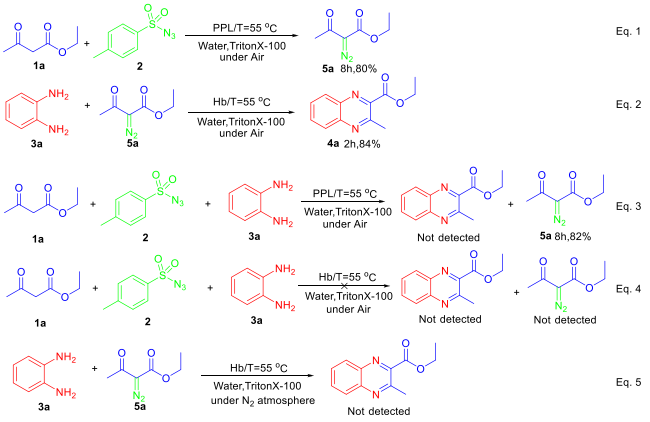
To understand the dual-protein-catalyzed reaction, control experiments were conducted, and the results are presented in Scheme 3. Diazo transfer reaction to ethyl acetoacetate with *p*-toluenesulfonyl azide could be catalyzed by lipase, and α-diazo

Scheme 2. Dual-Protein-Catalyzed Synthesis of Quinoxalines[a]



[a]Reaction conditions: (a) β-ketoester (1.0 mmol), TsN_3 (1.2 equiv), 1,2-diamine (1.0 equiv), PPL (protein content of 4 mg), HbBv (heme concentration of 0.1 mol %), water, Triton X-100 (5 mol %), 55 °C, 6 h, isolated yield; (b) ratio determined by ^1H NMR; (c) catalyzed by hemin (1 mol %) and PPL; (d) catalyzed by Et_3N and $Fe(OTf)_3$.

Scheme 3. Control Experiments

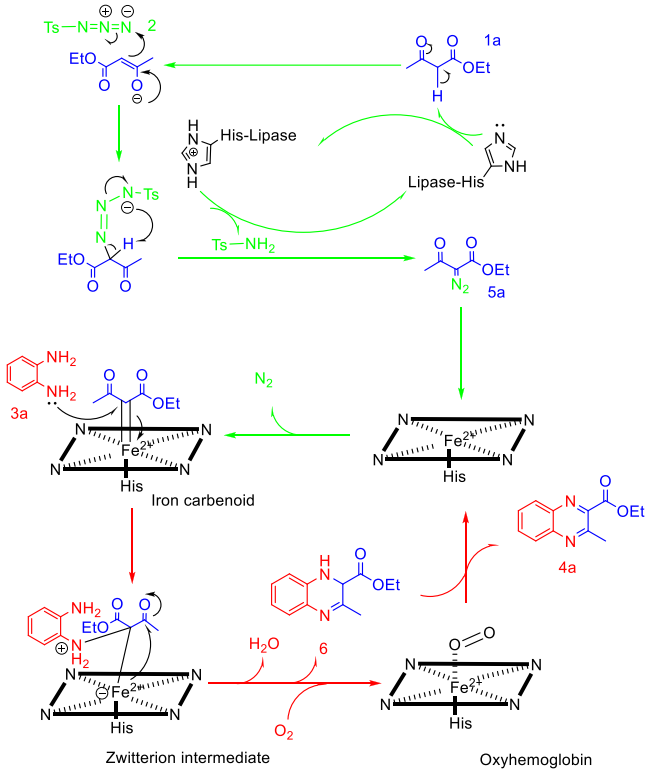


carbonyl compound **5a** was isolated with 60% yield (eq 1). Compound **5a** was reacted with 1,2-diaminobenzene to generate quinoxaline **4a** in 84% yield in the presence of hemoglobin (eq 2). Only compound **5a** was obtained when PPL was used for this three-component reaction (eq 3), whereas no reaction occurred when HbBv was applied as the catalyst (eq 4), suggesting that the diazotization reaction cannot proceed in the presence of 1,2-diaminobenzene and this dual-protein-catalyzed reaction comprises two sequential steps: (1) lipase-catalyzed diazo transfer reaction and (2) hemoglobin-catalyzed annulation. No quinoxaline **4a** was obtained when the reaction was conducted under a nitrogen atmosphere in a closed system (eq 5). This result confirmed that an oxidative aromatization was involved in the process of hemoglobin-catalyzed annulation.

On the basis of our experimental results and previous reports,[41−45] a reasonable mechanism of this cascade reaction is proposed in Scheme 4. First, ethyl acetoacetate (**1a**) is deprotonated by the catalytic triad of lipase forming an enolate

https://dx.doi.org/10.1021/acs.orglett.0c01186
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 4. Mechanism of the Dual-Protein-Catalyzed Synthesis of Quinoxalines



ion that is necessary for the diazo transfer reaction. Second, TsN_3 can be reacted with the enolate ion to produce the α-diazo carbonyl compound **5a**. Third, **5a** is catalyzed by heme in hemoglobin to generate an iron carbenoid with N_2 elimination, which can be attacked by the NH_2 group of 1,2-diaminobenzene (**3a**) to produce the zwitterion intermediate. The regioselective product could be formed in this step, and the regioselectivity observed might be due to the steric hindrance in the active center of hemoglobin. Then, 2*H*-quinoxaline intermediate **6** is formed by proton transfer and intramolecular dehydration, which is similar to Lee's work.[20] Finally, an oxidative aromatization of intermediate **6** is catalyzed by oxyhemoglobin (HbO_2) to afford target quinoxaline **4a**.

In conclusion, we have demonstrated that a dual-protein (lipase and hemoglobin) system can be applied for the regioselective synthesis of quinoxalines in water. This green and efficient method not only can be easily scaled up but also exhibits a moderate regioselectivity in the synthesis of quinoxalines. Therefore, this novel dual-protein system has high potential for the development of new synthetic approaches and green technology in organic synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01186.

Experimental details, characterization data, and NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

Lei Wang − *Key Laboratory of Molecular Enzymology and Engineering of Ministry of Education, School of Life Sciences, Jilin University, Changchun 130023, P. R. China*; orcid.org/0000-0002-9728-0613; Email: w_lei@jlu.edu.cn

Zhengqiang Li − *Key Laboratory of Molecular Enzymology and Engineering of Ministry of Education, School of Life Sciences, Jilin University, Changchun 130023, P. R. China*; Email: lzq@jlu.edu.cn

Authors

Fengxi Li − *Key Laboratory of Molecular Enzymology and Engineering of Ministry of Education, School of Life Sciences, Jilin University, Changchun 130023, P. R. China*

Xuyong Tang − *Key Laboratory of Molecular Enzymology and Engineering of Ministry of Education, School of Life Sciences, Jilin University, Changchun 130023, P. R. China*

Yaning Xu − *Key Laboratory of Molecular Enzymology and Engineering of Ministry of Education, School of Life Sciences, Jilin University, Changchun 130023, P. R. China*

Chunyu Wang − *State Key Laboratory of Supramolecular Structure and Materials, Jilin University, Changchun 130023, P. R. China*

Zhi Wang − *Key Laboratory of Molecular Enzymology and Engineering of Ministry of Education, School of Life Sciences, Jilin University, Changchun 130023, P. R. China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c01186

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authots gratefully acknowledge the National Natural Science Foundation of China (31670797) and the National Defense Science and Technology Innovation Zone Foundation of China.

■ REFERENCES

(1) Rodrigues, F. A. R.; Bomfim, I. D.; Cavalcanti, B. C.; Pessoa, C. D.; Wardell, J. L.; Wardell, S. M. S. V.; Pinheiro, A. C.; Kaiser, C. R.; Nogueira, T. C. M.; Low, J. N.; Gomes, L. R.; de Souza, M. V. N. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 934−939.

(2) Hazeldine, S. T.; Polin, L.; Kushner, J.; Paluch, J.; White, K.; Edelstein, M.; Palomino, E.; Corbett, T. H.; Horwitz, J. P. *J. Med. Chem.* **2001**, *44*, 1758−1776.

(3) Smits, R. A.; Lim, H. D.; Hanzer, A.; Zuiderveld, O. P.; Guaita, E.; Adami, M.; Coruzzi, G.; Leurs, R.; de Esch, I. J. P. *J. Med. Chem.* **2008**, *51*, 2457−2467.

(4) Moorthy, N. S.; Manivannan, E.; Karthikeyan, C.; Trivedi, P. *Mini-Rev. Med. Chem.* **2013**, *13*, 1415−1420.

(5) Parhi, A. K.; Zhang, Y.; Saionz, K. W.; Pradhan, P.; Kaul, M.; Trivedi, K.; Pilch, D. S.; LaVoie, E. J. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 4968−4974.

(6) Kim, Y. B.; Kim, Y. H.; Park, J. Y.; Kim, S. K. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 541−544.

(7) Dailey, S.; Feast, W. J.; Peace, R. J.; Sage, A. C.; Till, S.; Wood, E. L. *J. Mater. Chem.* **2001**, *11*, 2238−2243.

(8) O'brien, D.; Weaver, M.; Lidzey, D.; Bradley, D. *Appl. Phys. Lett.* **1996**, *69*, 881−883.

(9) Ott, S.; Faust, R. *Synlett* **2004**, *2004*, 1509−1512.

(10) Chesneau, B.; Hardouin-Lerouge, M.; Hudhomme, P. *Org. Lett.* **2010**, *12*, 4868−4871.

https://dx.doi.org/10.1021/acs.orglett.0c01186
Org. Lett. XXXX, XXX, XXX−XXX

(11) Sessler, J. L.; Maeda, H.; Mizuno, T.; Lynch, V. M.; Furuta, H. *J. Am. Chem. Soc.* **2002**, *124*, 13474−13479.
(12) Castro, P. P.; Zhao, G.; Masangkay, G. A.; Hernandez, C.; Gutierrez-Tunstad, L. M. *Org. Lett.* **2004**, *6*, 333−336.
(13) More, S. V.; Sastry, M. N. V.; Yao, C. *Green Chem.* **2006**, *8*, 91−95.
(14) Srinivas, C.; Kumar, C. N. S. S. P.; Rao, V. J.; Palaniappan, S. *J. Mol. Catal. A: Chem.* **2007**, *265*, 227−230.
(15) Kim, S. Y.; Park, K. H.; Chung, Y. *Chem. Commun. (Cambridge, U. K.)* **2005**, 1321−1323.
(16) Sithambaram, S.; Ding, Y.; Li, W.; Shen, X.; Gaenzler, F.; Suib, S. L. *Green Chem.* **2008**, *10*, 1029−1032.
(17) Chen, F.; Huang, X.; Li, X.; Shen, T.; Zou, M.; Jiao, N. *Angew. Chem., Int. Ed.* **2014**, *53*, 10495−10499.
(18) Wang, W.; Shen, Y.; Meng, X.; Zhao, M.; Chen, Y.; Chen, B. *Org. Lett.* **2011**, *13*, 4514−4517.
(19) Okumura, S.; Takeda, Y.; Kiyokawa, K.; Minakata, S. *Chem. Commun.* **2013**, *49*, 9266−9268.
(20) Pandit, R. P.; Kim, S. H.; Lee, Y. R. J. A. S. *Adv. Synth. Catal.* **2016**, *358*, 3586−3599.
(21) Truppo, M. D. *ACS Med. Chem. Lett.* **2017**, *8*, 476−480.
(22) Yang, F.; Zhang, X.; Li, F.; Wang, Z.; Wang, L. *Green Chem.* **2016**, *18*, 3518−3521.
(23) Liu, Z.; Wang, B.; Jin, S.; Wang, Z.; Wang, L.; Liang, S. *ACS Appl. Mater. Interfaces* **2018**, *10*, 41504−41511.
(24) Ma, N.; Chen, Z.; Chen, J.; Chen, J.; Wang, C.; Zhou, H.; Yao, L.; Shoji, O.; Watanabe, Y.; Cong, Z. *Angew. Chem., Int. Ed.* **2018**, *57*, 7628−7633.
(25) Li, F.; Li, Z.; Tang, X.; Cao, X.; Wang, C.; Li, J.; Wang, L. *ChemCatChem* **2019**, *11*, 1192−1195.
(26) Tyagi, V.; Fasan, R. *Angew. Chem., Int. Ed.* **2016**, *55*, 2512−2516.
(27) Chen, K.; Huang, X.; Kan, S. B. J.; Zhang, R. K.; Arnold, F. H. *Science* **2018**, *360*, 71−75.
(28) Zhang, J.; Qian, W.; Wang, C.; Cao, Z.; Chen, S.; Zhang, L.; Zhang, Y.; Wang, L. *Green Chem. Lett. Rev.* **2018**, *11*, 508−512.
(29) Li, F.; Tang, X.; Xu, Y.; Wang, C.; Zhang, L.; Zhang, J.; Liu, J.; Li, Z.; Wang, L. *Eur. J. Org. Chem.* **2019**, *2019*, 7720−7724.
(30) Cho, I.; Prier, C. K.; Jia, Z.; Zhang, R.; Gorbe, T.; Arnold, F. H. *Angew. Chem., Int. Ed.* **2019**, *58*, 3138−3142.
(31) Li, C.; Feng, X.; Wang, N.; Zhou, Y.; Yu, X. *Green Chem.* **2008**, *10*, 616−618.
(32) Yang, F.; Wang, Z.; Wang, H.; Zhang, H.; Yue, H.; Wang, L. *RSC Adv.* **2014**, *4*, 25633−25636.
(33) Yang, F.; Zhang, X.; Li, F.; Wang, Z.; Wang, L. *Eur. J. Org. Chem.* **2016**, *2016*, 1251−1254.
(34) Edelstein, S. J. *Annu. Rev. Biochem.* **1975**, *44*, 209−232.
(35) Prat, D.; Wells, A.; Hayler, J.; Sneddon, H.; McElroy, C. R.; Abou-Shehada, S.; Dunn, P. J. *Green Chem.* **2016**, *18*, 288−296.
(36) Xu, X.; Li, C.; Tao, Z.; Pan, Y. G. C. *Green Chem.* **2017**, *19*, 1245−1249.
(37) Kraïem, J.; Ollevier, T. G. C. *Green Chem.* **2017**, *19*, 1263−1267.
(38) Gelamo, E. L.; Itri, R.; Tabak, M. *J. Biol. Chem.* **2004**, *279*, 33298−33305.
(39) Honda, C.; Kamizono, H.; Matsumoto, K.; Endo, K. *J. Colloid Interface Sci.* **2004**, *278*, 310−317.
(40) Wangsakan, A.; Chinachoti, P.; McClements, D. J. *Langmuir* **2004**, *20*, 3913−3919.
(41) Regitz, M. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 733−749.
(42) Tyagi, V.; Bonn, R. B.; Fasan, R. *Chem. Sci.* **2015**, *6*, 2488−2494.
(43) Huang, X.; Garcia-Borras, M.; Miao, K.; Kan, S. B. J.; Zutshi, A.; Houk, K. N.; Arnold, F. H. *ACS Cent. Sci.* **2019**, *5*, 270−276.
(44) Shi, T.; Teng, S.; Wei, Y.; Guo, X.; Hu, W. *Green Chem.* **2019**, *21*, 4936−4940.
(45) Alavala, G. K. R.; Sajjad, F.; Shi, T.; Kang, Z.; Ma, M.; Xing, D.; Hu, W. *Chem. Commun. (Cambridge, U. K.)* **2018**, *54*, 12650−1265.

https://dx.doi.org/10.1021/acs.orglett.0c01186
Org. Lett. XXXX, XXX, XXX−XXX