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Peptide/Laccase Cocatalyzed Asymmetric α-Oxyamination of Aldehydes

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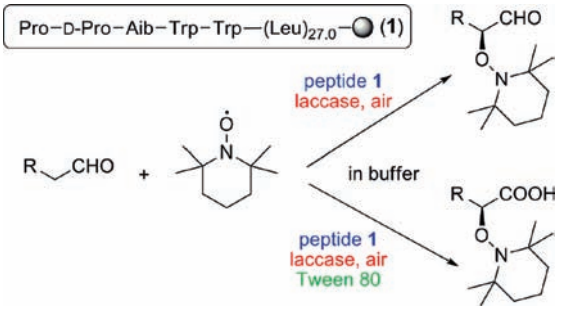
ABSTRACT



An asymmetric α-oxyamination could be successfully performed by a peptide catalyst and laccase. The combination of peptide catalysis and enzymatic air oxidation promoted the reaction smoothly in water without employing a metal reagent. The oxyaminated compounds could be obtained as both aldehyde and carboxylic acid products depending on the reaction conditions.

Recent advancements in the field of organocatalysis have offered a variety of useful synthetic methods.[1] In addition to being used alone, organocatalysts have been combined with metal reagents.[2] There are examples for organocatalyzed C–C and C–heteroatom bond formations using metals as oxidizing agents.[3] Among them, Sibi's asymmetric α-oxyamination of aldehydes using 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) and a catalytic amount of an iron salt is noteworthy in terms of enabling oxidation with molecular oxygen as a terminal oxidant.[4,5] Such air oxidation is an atom-efficient and clean reaction, only generating water as waste.[6]

On the other hand, because metal reagents are sometimes environmentally harmful, it is highly desirable to replace them with greener alternatives. Concerning this, an oxidative enzyme, laccase (EC 1.10.3.2), has been recognized as a promising candidate, which is inexpensive, stable, and widely applicable for various reactions.[7] For example,

(1) For selected reviews, see: (a) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138. (b) Erkkilä, A.; Majander, I.; Pihko, P. M. *Chem. Rev.* **2007**, *107*, 5416. (c) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471. (d) Pellissier, H. *Tetrahedron* **2007**, *63*, 9267. (e) Dondoni, A.; Massi, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 4638. (f) Melchiorre, P.; Marigo, M.; Carlone, A.; Bartoli, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 6138. (g) Bertelsen, S.; Jørgensen, K. A. *Chem. Soc. Rev.* **2009**, *38*, 2178.

(2) For reviews, see: (a) Shao, Z.; Zhang, H. *Chem. Soc. Rev.* **2009**, *38*, 2745. (b) Zhou, J. *Chem.—Asian J.* **2010**, *5*, 422. (c) Rueping, M.; Koenigs, R. M.; Atodiresei, I. *Chem.—Eur. J.* **2010**, *16*, 9350. (d) Zhong, C.; Shi, X. *Eur. J. Org. Chem.* **2010**, 2999.

(3) MacMillan et al. have developed the new class of reactions proceeding through SOMO activation with imidazolidinone catalysts and metal oxidizing reagents. For selected examples, see: (a) Beeson, T. D.; Mastracchio, A.; Hong, J.-B.; Ashton, K.; MacMillan, D. W. C. *Science* **2007**, *316*, 582. (b) Kim, H.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2008**, *130*, 398. (c) Amatore, M.; Beeson, T. D.; Brown, S. P.; MacMillan, D. W. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 5121. (d) Wilson, J. E.; Casarez, A. D.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2009**, *131*, 11332. (e) Rendler, S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2010**, *132*, 5027. (f) Jui, N. T.; Lee, E. C. Y.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2010**, *132*, 10015. For other examples, see:(g) Jang, D. O.; Kim, S. Y. *J. Am. Chem. Soc.* **2008**, *130*, 16152. (h) Nicewicz, D. A.; MacMillan, D. W. C. *Science* **2008**, *322*, 77. (i) Nicolaou, K. C.; Reingruber, R.; Sarlah, D.; Bräse, S. *J. Am. Chem. Soc.* **2009**, *131*, 2086. (j) Xie, J.; Huang, Z.-Z. *Chem. Commun.* **2010**, *46*, 1947.

(4) (a) Sibi, M. P.; Hasegawa, M. *J. Am. Chem. Soc.* **2007**, *129*, 4124. (b) Van Humbeck, J. F.; Simonovich, S. P.; Knowles, R. R.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2010**, *132*, 10012.

(5) Maruoka et al. reported the α-oxyamination with TEMPO using a peroxide instead of a metal reagent. (a) Kano, T.; Mii, H.; Maruoka, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 6638. For other examples of the α-oxyamination with TEMPO, see:(b) Koike, T.; Akita, M. *Chem. Lett.* **2009**, *38*, 166. (c) Bui, N.-N.; Ho, X.-H.; Mho, S.-i.; Jang, H.-Y. *Eur. J. Org. Chem.* **2009**, 5309. (d) Pouliot, M.; Renaud, P.; Schenk, K.; Studer, A.; Volger, T. *Angew. Chem., Int. Ed.* **2009**, *48*, 6037. (e) Inokuchi, T.; Nakagawa, K.; Torii, S. *Tetrahedron Lett.* **1995**, *36*, 3223.

(6) Wertz, S.; Studer, A. *Adv. Synth. Catal.* **2011**, *353*, 69 and references therein.

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Rutjes et al. demonstrated that laccase can be used as a catalyst for the oxidative removal of the *p*-methoxyphenyl protective group on amines under aerobic conditions, in place of the conventional stoichiometric reaction with ceric ammonium nitrate.[8] If an air oxidation mediated by laccase can be combined with an organocatalytic reaction, this will provide a new green chemical transformation.

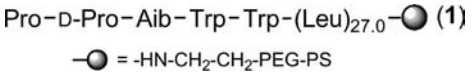
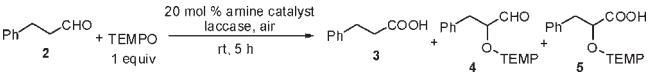


Figure 1. Resin-supported peptide catalyst.

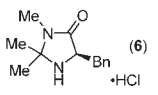
To realize such a reaction in a single flask, the organocatalyst should be active in water, since water is generally a suitable solvent for enzymatic reactions.[9] Meanwhile, our group has developed resin-supported peptide catalyst **1** (Figure 1)[10] for asymmetric organocatalytic reactions in aqueous media.[11] For example, this catalyst is quite effective for the chiral-amine-catalyzed asymmetric α-oxyamination of aldehydes in the presence of either Fe(II) or Cu(I) cocatalyst.[12,13] Because of the high efficiency of the peptide catalyst in water and the versatile applicability of the laccase oxidation, we envisaged that the peptide-catalyzed α-oxyamination could proceed through the laccase-mediated air oxidation without using a metal reagent. Herein, we report the novel system for the asymmetric α-oxyamination of aldehydes catalyzed by resin-supported peptide **1** and laccase in water.

Initially, oxidation of 3-phenylpropanal with TEMPO/laccase under various conditions was examined (Table 1).

Table 1. α-Oxyamination of 3-Phenylpropanal with Amine Catalyst and Laccase



entry	amine catalyst	solvent	**2** : **3** : **4** : **5**	cc (%) of **5**[a,b]
1	none	acetate buffer (pH 4.4)	0 : 100 : 0 : 0	–
2	pyrrolidine	acetate buffer (pH 4.4)	0 : 51 : 0 : 49	n.d.
3	pyrrolidine	H_2O	0 : 50 : 0 : 50	0
4	pyrrolidine	THF/H_2O = 1/2	58 : 31 : 11 : 0	–
5	pyrrolidine	DMF/H_2O = 1/2	18 : 80 : 1 : 1	n.d.
6	pyrrolidine	1,4-dioxane/H_2O = 1/2	3 : 56 : 19 : 22	n.d.
7	**1**	H_2O	0 : 35 : 0 : 65[c]	88 [*S*]
8	proline	H_2O	0 : 98 : 0 :2	n.d.
9	**6**	H_2O	0 : 28 : 6 : 66	63 [*R*]



[a] Determined after being reduced to the corresponding alcohol by a borane–THF complex (BH_3•THF). [b] n.d. = Not determined. [c] Isolated yield of **5** was 46%.

In the absence of an amine catalyst, the aldehyde was simply converted to carboxylic acid **3** in acetate buffer (entry 1). This type of TEMPO-mediated air oxidation of aldehydes by laccase has been reported,[14,15] and such a reaction is supposed to be brought about by the oxoammonium ion which is generated by means of laccase-catalyzed one-electron oxidation of TEMPO.[16] When the catalytic amount of pyrrolidine was added to the reaction, α-oxyaminated carboxylic acid **5** was formed along with carboxylic acid **3** (entry 2). The product **5** was considered to be generated by the further oxidation of α-oxyaminated aldehyde **4**. While acidic conditions are optimal in many laccase-catalyzed reactions,[7] in the present case, the α-oxyamination occurred smoothly in neutral water as well as in acetate buffer (entry 3). The reaction rate was low in the presence of THF or DMF (entries 4 and 5). The

(7) For reviews, see: (a) Witayakran, S.; Ragauskas, A. J. *Adv. Synth. Catal.* **2009**, *351*, 1187. (b) Hollmann, F.; Arends, I. W. C. E.; Buehler, K. *ChemCatChem* **2010**, *2*, 762.

(8) Verkade, J. M. M.; van Hemert, L. J. C.; Quaedflieg, P. J. L. M.; Schoemaker, H. E.; Schürmann, M.; van Delft, F. L.; Rutjes, F. P. J. T. *Adv. Synth. Catal.* **2007**, *349*, 1332.

(9) Gröger et al. reported the sequential reaction using an organocatalyst and alcohol dehydrogenase for the synthesis of chiral 1,3-diols. Baer, K.; Krauβer, M.; Burda, E.; Hummel, W.; Berkessel, A.; Gröger, H. *Angew. Chem., Int. Ed.* 2009, *48*, 9355.

(10) The peptide possesses a polyleucine chain synthesized with *N*-carboxyanhydride monomer, and the number of -$(Leu)_n$- means weight-average degree of polymerization.

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(12) (a) Akagawa, K.; Fujiwara, T.; Sakamoto, S.; Kudo, K. *Org. Lett.* **2010**, *12*, 1804. (b) Akagawa, K.; Fujiwara, T.; Sakamoto, S.; Kudo, K. *Chem. Commun.* **2010**, *46*, 8040.

(13) For recent selected examples of peptide-based asymmetric catalysts, see: (a) Fowler, B. S.; Mikochik, P. J.; Miller, S. J. *J. Am. Chem. Soc.***2010**, *132*, 2870. (b) Wiesner, M.; Upert, G.; Angelici, G.; Wennemers, H. *J. Am. Chem. Soc.* **2010**, *132*, 6. (c) Gustafson, J. L.; Lim, D.; Miller, S. J. *Science* **2010**, *328*, 1251. (d) Cowen, B. J.; Saunders, L. B.; Miller, S. J. *J. Am. Chem. Soc.* **2009**, *131*, 6105. (e) Wu, F.-C.; Da, C.-S.; Du, Z. X.; Guo, Q.-P.; Li, W.-P.; Yi, L.; Jia, Y.-N.; Ma, X. *J. Org. Chem.* **2009**, *74*, 4812. (f) Fiori, K. W.; Puchlopek, A. L. A.; Miller, S. J. *Nat. Chem.* **2009**, *1*, 630. (g) Müller, C. E.; Wanka, L.; Jewell, K.; Schreiner, P. R. *Angew. Chem., Int. Ed.* **2008**, *47*, 6180. (h) Lewis, C. A.; Gustafson, J. L.; Chiu, A.; Balsells, J.; Pollard, D.; Murry, J.; Reamer, R. A.; Hansen, K. B.; Miller, S. J. *J. Am. Chem. Soc.* **2008**, *130*, 16358. (i) Wiesner, M.; Revell, J. D.; Tonazzi, S.; Wennemers, H. *J. Am. Chem. Soc.* **2008**, *130*, 5610. (j) D'Elia, V.; Zwicknagl, H.; Reiser, O. *J. Org. Chem.* **2008**, *73*, 3262. (k) Peris, G.; Jakobsche, C. E.; Miller, S. J. *J. Am. Chem. Soc.* **2007**, *129*, 8710.

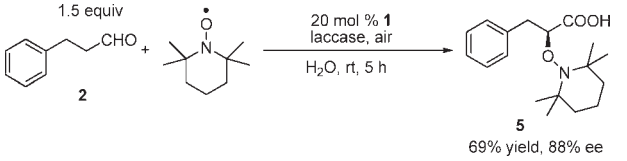
(14) This system has been used for oxidizing alcohols to aldehydes. (a) Fabbrini, M.; Galli, C.; Gentili, P.; Macchitella, D. *Tetrahedron Lett.* **2001**, *42*, 7551. (b) d'Acunzo, F.; Baiocco, P.; Fabbrini, M.; Galli, C.; Gentili, P. *Eur. J. Org. Chem.* **2002**, 4195. (c) Arends, I. W. C. E.; Li, Y.-X.; Ausan, R.; Sheldon, R. A. *Tetrahedron* **2006**, *62*, 6659. (d) Tromp, S. A.; Matijošytė, I.; Sheldon, R. A.; Arends, I. W. C. E.; Mul, G.; Kreutzer, M. T.; Moulijn, J. A.; de Vries, S. *ChemCatChem* **2010**, *2*, 827. (e) Tropm, S. A.; Matijošytė, I.; Sheldon, R. A.; Arends, I. W. C. E.; Mul, G.; Kreutzer, M. T.; Moulijn, J. A.; de Vries, S. *ChemCatChem* **2010**, *2*, 827.

(15) For examples for overoxidation of aldehydes to carboxylic acids, see: (a) Marzorati, M.; Danieli, B.; Haltrich, D.; Riva, S. *Green Chem.* **2005**, *7*, 310. (b) Baratto, L.; Candido, A.; Marzorati, M.; Sagui, F.; Riva, S.; Danieli, B. *J. Mol. Catal. B: Enzym.* **2006**, *39*, 3. (c) Monti, D.; Candido, A.; Silva, M. M. C.; Křen, V.; Riva, S.; Danieli, B. *Adv. Synth. Catal.* **2005**, *347*, 1168. (d) Viikari, L.; Niku-Paavola, M.-L.; Buchert, J.; Forssell, P.; Teleman, A.; Kruus, K. WO Patent 99/23240, 1999. (e) Jetten, J. M.; van den Dool, R. T. M.; van Hartingsveldt, W.; Besemer, A. C. WO Patent 00/50463, 2000.

(16) (a) Anelli, P. L.; Biffi, C.; Montanari, F.; Quici, S. *J. Org. Chem.* **1987**, *52*, 2559. (b) de Nooy, A. E. J.; Besemer, A. C.; van Bekkum, H. *Synthesis* **1996**, 1153.

reaction in water/1,4-dioxane afforded the oxyaminated products as a mixture of aldehyde **4** and carboxylic acid **5** (entry 6). When resin-supported peptide catalyst **1**, which has been previously reported by us for the enantioselective α-oxyamination of aldehydes, was employed instead of pyrrolidine, oxyaminated carboxylic acid **5** was obtained in a highly enantioselective manner (entry 7). Simple proline was not effective for the α-oxyamination reaction (entry 8). Imidazolidinone catalyst **6** was able to promote the oxyamination; however, the enantioselectivity was only moderate (entry 9). In all the cases, the oxyamination reaction competed with the oxidation of the starting aldehyde to carboxylic acid **3**. Use of 1.5 mol equiv of aldehyde **2** afforded the desired product **5** in an acceptable yield based on the amount of TEMPO (Scheme 1).

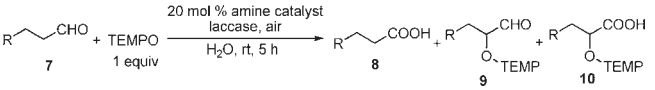
Scheme 1. Reaction of 3-Phenylpropanal to Chiral α-Oxyaminated Carboxylic Acid

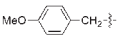


Further optimization of the reaction conditions was carried out using 4-arylbutanals, and somewhat different results were obtained (Table 2). When 4-phenylbutanal was used as a substrate, pyrrolidine did not promote the oxyamination (entry 1). The reaction with imidazolidinone **6** afforded oxyaminated carboxylic acid **10**; however, the yield and enantioselectivity were low (entry 2). On the contrary, use of peptide catalyst **1** exclusively gave oxyaminated aldehyde **9** with good yield and enantioselectivity (entry 3). It should be mentioned that further oxidation to the corresponding carboxylic acid did not occur. In the case of 4-(4-methoxyphenyl)butanal, the oxyaminated aldehyde was also obtained as a main product with peptide catalyst **1** (entry 5), while imidazolidinone **6** showed low catalytic efficiency (entry 4). Although the isolated yield of **9** was moderate in water (entry 5), it could be improved in acetate buffer (entry 6). We speculate the reason for the different product distributions for 3-phenylpropanal and 4-arylbutanals is the differences in hydrophobicity of the oxyaminated aldehydes. For the oxidation of 4-(4-methoxyphenyl)butanal, addition of a nonionic surfactant, Tween 80, resulted in changing the main product from aldehyde **9** to carboxylic acid **10** (entry 7).

The asymmetric α-oxyamination of aldehydes with peptide **1** and laccase was performed in both the absence and presence of Tween 80 (Tables 3 and 4). In acetate buffer without a surfactant, the oxyamination proceeded smoothly and completed within 1 h to afford aldehyde product **9** with good to moderate yields (Table 3). Compared to the cases with a longer reaction time (Table 2, entries 3 and 5), enantioselectivities were slightly higher. This indicates that aldehyde **9** racemizes under the reaction

Table 2. α-Oxyamination of 4-Arylbutanals

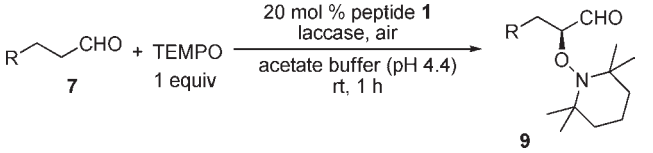


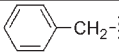
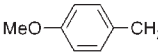
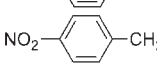
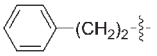
entry	R	amine catalyst	7 : 8 : 9 : 10	isolated yield, ee[a] of 9 or 10
1		pyrrolidine	72 : 28 : 0 : 0	–
2		**6**	0 : 64 : 2 : 34	**10** = 22%, 52% ee [*R*]
3		**1**	0 : 1 : 99 : 0	**9** = 71%, 82% ee [*S*]
4		**6**	58 : 6 : 36 : 0	**9** = 30%, 60% ee [*R*]
5		**1**	0 : 0 : 100 : 0	**9** = 53%, 80% ee [*S*]
6[b]		**1**	0 : 0 : 100 : 0	**9** = 74%, 84% ee [*S*]
7[b,c]		**1**	0 : 0 : 19 : 81	**10** = 64%, 91% ee [*S*]

[a] Determined after being reduced to the corresponding alcohol by $NaBH_4$ for aldehyde **9** or by BH_3•THF for carboxylic acid **10**. [b] Reaction was performed in acetate buffer (pH 4.4). [c] Amount of TEMPO was 1.5 equiv. Tween 80 was added, after 2 h had passed.

conditions. When the reaction was conducted with Tween 80, oxyaminated carboxylic acid **10** was obtained with good enantioselectivity in 5 to 8 h (Table 4, entries 1–4 and 6). The presence of Tween 80 accelerated the oxidation of α-oxyaminated aldehydes to carboxylic acids as expected from the results in Table 2. It is worth noting that the yield of oxyaminated carboxylic acid **10** was not significantly decreased by the potential competitive reaction of **7** to **8**

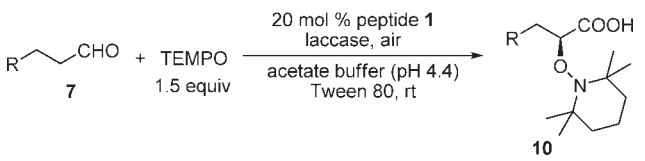
Table 3. α-Oxyamination of Aldehydes with Peptide and Laccase

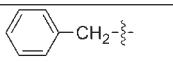
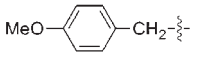
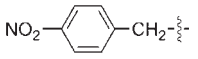
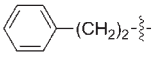
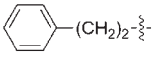


entry	R		isolated yield (%)	ee (%)[a]
1		**a**	77	86
2		**b**	77	87
3		**c**	80	87
4		**d**	71	90
5		**e**	65	88

[a] Determined after being reduced to the corresponding alcohol by $NaBH_4$.

Table 4. Direct Conversion of Aldehydes to α-Oxyaminated Carboxylic Acids



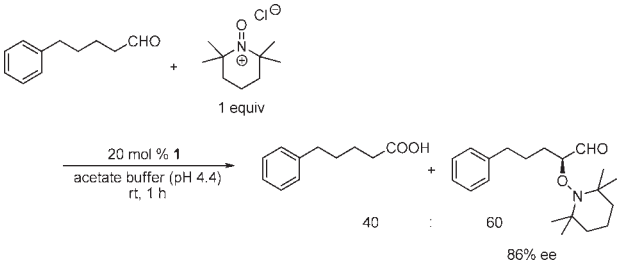
entry	R		time (h)	isolated yield (%)	ee (%)[a]
1		**a**	5	78	91
2		**b**	5	73	90
3		**c**	5	77	92
4		**d**	8	72	92
5[b]		**d**	20	70	89
6		**e**	8	69	92[c]

[a] Unless otherwise noted, determined after being reduced to the corresponding alcohol by BH_3•THF. [b] Reaction was performed with 5 mol % of peptide **1** and 1.0 equiv of TEMPO. [c] Determined after being reduced to the corresponding alcohol by $LiAlH_4$.

even in the presence of Tween 80 from the beginning of the reaction. This type of tandem conversion has not been reported and is useful to obtain the chiral α-oxyaminated carboxylic acids directly from aldehydes while avoiding the possible racemization of α-substituted aldehyde **9**. The catalytic system using peptide **1** and laccase was so efficient that the amount of catalysts could be reduced to 5 mol % with only a slight decrease in the yield and enantioselectivity (entry 5). The active site of laccase contains four copper atoms, and the weight of copper accounts for less than 1% of the whole enzyme. Therefore, the amount of the metal species employed in the reaction is quite low.[17]

(17) In entry 5 of Table 4, 0.05 mg (< 0.002 mol %) of laccase was used for 0.05 mmol of the aldehyde. In other cases, 0.5 mg of laccase was used for the same amount of aldehydes. For experimental details, see Supporting Information.

Scheme 2. α-Oxyamination with Oxoammonium Ion



The α-oxyamination of the aldehydes is most likely to proceed through the reaction of the oxoammonium ion generated by the laccase oxidation of TEMPO and the enamine formed between the peptide catalyst and the aldehyde.[5a] In fact, when the preformed oxoammonium ion was used as an oxidizing agent, the enantioselectively α-oxyaminated product was obtained (Scheme 2). Another plausible pathway for the oxyamination is the oxidation of the enamine by laccase and subsequent coupling with TEMPO. Because there is a report showing that an enamine is easier to be oxidized than TEMPO,[5b] such a mechanism cannot be excluded.

In conclusion, an efficient asymmetric α-oxyamination of aldehydes was realized by combining the oxidative enzyme, laccase, and the peptide catalyst in water. It is synthetically advantageous that both the oxyaminated aldehydes and carboxylic acids could be obtained depending on the reaction conditions. The present study demonstrates the usefulness of enzymes instead of metal reagents as a cocatalyst for organocatalytic oxidation, and this might contribute to the field of green chemistry. Further expansion of the system employing enzymes and organocatalysts is currently underway in our laboratory.

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Supporting Information Available. Experimental procedure and spectroscopic data for products. This material is available free of charge via the Internet at http://pubs.acs.org.