Published on 17 July 2019. Downloaded by Universitätsbibliothek Bern on 3/31/2020 5:19:38 PM.

Green Chemistry

ROYAL SOCIETY OF CHEMISTRY

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Green Chem.*, 2019, **21**, 4324

Received 30th May 2019,
Accepted 16th July 2019

DOI: 10.1039/c9gc01802f

rsc.li/greenchem

Cascade bio-hydroxylation and dehalogenation for one-pot enantioselective synthesis of optically active β-halohydrins from halohydrocarbons†

Hai-Bo Cui,‡[a] Ling-Zhi Xie,‡[a] Nan-Wei Wan, [a] Qing He,[a] Zhi Li[b] and Yong-Zheng Chen *[a]

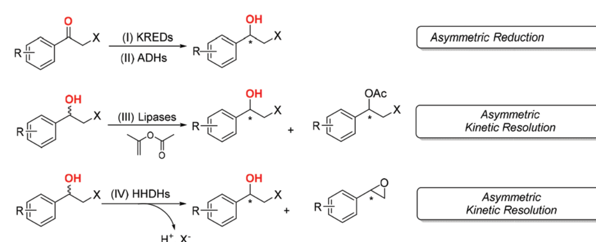
A stereoselective hydroxylation and enantioselective dehalogenation cascade reaction was developed for the synthesis of optically active β-haloalcohols from halohydrocarbons. This cascade system employed P450 and halohydrin dehalogenase as two compatible biocatalysts, allowing a straightforward, greener and efficient access to β-halohydrins with excellent enantioselectivities (98–99%).

It is well known that enantiopure β-halohydrins are particularly interesting as synthons for the preparation of a large number of bioactive products including natural products, agrochemicals and pharmaceuticals.[1] Optically active 2-chloro-1-phenylethanol, for instance, is the key precursor for the synthesis of anti-depressants α- or β-adrenergic drugs such as tomoxetine, fluoxetine and nisoxetine.[2] They can also be easily converted into the corresponding chiral epoxides with controlled stereochemistry,[3] which opens a wide spectrum of further synthetic applications. In addition, many new methods have been developed for the transformation of enantiopure halohydrins into a broad range of functional groups to construct various useful chiral organic compounds, including aminoalcohols,[4] azidoalcohols,[5] hydroxynitriles,[6] and 1,2-diols,[7] which provides a powerful strategy for asymmetric synthesis.

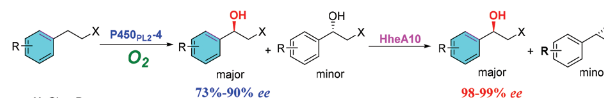
Even though some methods to access enantiopure β-halohydrins have been developed, especially *via* transition metal catalyzed asymmetric transfer hydrogenation of the corresponding β-halo-ketones,[3b,8] it is still a challenge to synthesize these enantiopure β-halohydrins with more greener and atom-economic strategies. In the past few decades, many biocatalytic routes have been developed to synthesize enantioenriched β-halohydrins due to their high selectivity, mild reaction conditions and environmental compatibility.[9] To date, four biocatalytic methods have been developed to prepare enantioenriched β-halohydrins that are summarized as follows: (I) carbonyl reductase (KRED)[10] and (II) alcohol dehydrogenase (ADH)[11] catalyzed asymmetric reduction of prochiral haloketones and (III) lipase[12] and (IV) halohydrin dehalogenase (HHDH)[13] catalyzed kinetic solution of racemic halohydrins. Some of these methods have been exploited and applied to synthesize halohydrins with excellent yields, enantiomeric excess (ee) and a broad substrate scope.[14] However, it should be noted that all the methods mentioned above absolutely require prior oxygen-functionalization at the target C–H bonds to form carbonyl or hydroxyl group substituted precursors (Fig. 1).

Cytochrome P450 monooxygenases (P450s) are the most versatile enzymes and capable of catalyzing a wide range of synthetically challenging oxidation reactions such as hydroxylation,[15] sulfoxidation,[16] and C–H amination.[17] P450s are able

Previous work: *Using Oxygen-Functionalized Substrates*



This work: *Using Oxygen as Oxidant*



One-Pot Cascade Reaction System Combining Asymmetric Hydroxylation and Enantioselective Dehalogenation

Fig. 1 Biocatalytic approaches to access enantiopure β-halohydrins.

[a]*Key Laboratory of Biocatalysis & Chiral Drug Synthesis of Guizhou Province, Green Pharmaceuticals Engineering Research Center of Guizhou Province, School of Pharmacy, Zunyi Medical University, Zunyi, 563000, China.*
E-mail: yzchen@zmu.edu.cn
[b]*Department of Chemical and Biomolecular Engineering, National University of Singapore, 4 Engineering Drive 4, Singapore 117585, Singapore*

†Electronic supplementary information (ESI) available. See DOI: 10.1039/c9gc01802f

‡These authors contributed equally to this work.

This journal is © The Royal Society of Chemistry 2019

Published on 17 July 2019. Downloaded by Universitätsbibliothek Bern on 3/31/2020 5:19:38 PM.

to introduce an oxygen atom into a C–H bond under normal pressure and room temperature. We therefore were interested in the synthesis of enantiopure β-halohydrins through a P450-catalyzed direct asymmetric hydroxylation of prochiral halohydrocarbons. Herein, enantioenriched β-halohydrins **2a–2m** were synthesized from the corresponding halohydrocarbons **1a–1m** through $P450_{PL2}$-4 catalyzed asymmetric hydroxylation. In addition, the ee values were improved up to 98–99% by developing a one-pot cascade biocatalysis using $P450_{PL2}$-4 and halohydrin dehalogenase HheA10 (Fig. 1).

Previously, we have expressed several P450s from the *Parvibaculum lavamentivorans* strain DS-1 and constructed a series of recombinant *Escherichia coli* strains harboring the P450 enzyme and redox partner Fdx–Fdr (ferredoxin–ferredoxin reductase).[18] In addition, we have obtained another thirteen *E. coli* strains containing P450pyr mutants and the corresponding Fdx–Fdr from professor Li's group.[19] With these P450 biocatalysts in hand (Table S1†), we initially examined their catalytic activity and stereoselectivity using (2-chloroethyl) benzene (**1a**) as a model substrate. Biocatalytic reactions were carried out using recombinant *E. coli* cells as the catalyst without the addition of any exogenous cofactor. After incubation at 30 °C for 24 h, the yield and ee of the product 2-chloro-1-phenlyehthanol (**2a**) were determined using chiral HPLC (Table 1). The results indicated that all the *E. coli* strains containing $P450_{PL2}$ or $P450_{PL7}$ exhibited hydroxylation activity and *R* stereoselectivity to **1a**, which produced **2a** in 17–49% yields with up to 76% ee (Table 1, entries 1–10). Similar to our previous study on sulfoxidation reactions, the hydroxylation activity of these P450 strains was also dependent on the redox partner.[18] For the same P450, the Fdx2–Fdr or Fdx4–Fdr redox partner gave relatively higher yields than other redox partners (Tables S1 and S2†). Surprisingly, most of the P450pyr mutants could not convert **1a** to **2a**, except for P450pyr-M4, P450pyr-M6 and P450pyr-M9 (Table 1, entries 12–14). These three P450pyr variants showed the opposite stereoselectivity to $P450_{PL}$ strains, which produced (*S*)-**2a** with an ee value up to 90%. However, their yields were much lower than those of $P450_{PL}$ strains. As we know, P450pyr is able to catalyze the terminal-selective hydroxylation of non-activated C–H bonds and has been successfully engineered for the subterminal hydroxylation of alkanes with excellent regio- and enantioselectivity.[15a,20] Herein, we tested thirteen P450pyr mutants containing 1–6 mutations and found that three variants could convert **1a** to **2a**, catalyzing the hydroxylation of the activated C–H bond at the subterminal position. Interestingly, the best active mutant *E. coli* P450pyr-M4 (N100S/F430I) for the subterminal hydroxylation of propylbenzene almost lost its hydroxylation activity,[15a] and the yield was not detectable under normal reaction conditions (Table 1, entry 11). The F430I mutation also existed in the best enantioselective P450pyr-M6, and its role in the stereocontrol of the *S*-selective hydroxylation of propylbenzene has been explained by molecular dynamics and docking simulations.[15a] What needs to be emphasized is that all the *E. coli* strains in the absence of P450 and Fdx–Fdr genes were also used as controls, and no hydroxylation activity was observed (Table S2,† entries 24–27).

Table 1 Screening of P450 strains for the asymmetric hydroxylation of **1a**

1a → (R) or (S)-2a; *E. coli* cells (P450x), pH 8.0, 30 °C, 24 h

Entry[a]	Biocatalyst	Yield **2a**[b] (%)	ee **2a**[b] (%)	Conf.[c]
1	$P450_{PL2}$-1	48	75	*R*
2	$P450_{PL2}$-2	26	76	*R*
3	$P450_{PL2}$-3	33	77	*R*
4	$P450_{PL2}$-4	49	77	*R*
5	$P450_{PL2}$-5	20	77	*R*
6	$P450_{PL7}$-1	48	77	*R*
7	$P450_{PL7}$-2	32	76	*R*
8	$P450_{PL7}$-3	33	76	*R*
9	$P450_{PL7}$-4	49	76	*R*
10	$P450_{PL7}$-5	17	76	*R*
11	P450pyr-M2	n.d.	n.d.	n.d.
12	P450pyr-M4	Trace	35	*S*
13	P450pyr-M6	17	90	*S*
14	P450pyr-M9	8	57	*S*

[a] Reactions were carried out in 5 mL PBS buffer (50 mM, pH 8.0) containing 2 mM of substrate **1a** and 10 g cdw per L of recombinant *E. coli* cells. [b] Yield and ee were measured by chiral HPLC analysis after reaction for 24 h; see Table S2† for details. [c] Absolute configuration was confirmed using commercial (*R*)-**2a** and (*R*,*S*)-**2a** as references. n.d. = not detected.

Subsequently, the strains $P450_{PL2}$-4 and P450pyr-M6 were selected for the optimization of the reaction conditions. Although P450pyr-M6 exhibited excellent *S* enantioselectivity toward **1a** (entry 11, Table 1), its catalytic activity was really low, giving only 37% yield of **2a** after the reaction optimization (data not shown). Herein, we only discuss the optimization results of strain $P450_{PL2}$-4 (Fig. 2). The results in Fig. 2A indicate that the yield was dramatically influenced by the cell density. Increasing the cell density from 5 to 30 g cdw per L improved the yield; however, further increasing the cell density to 50 g cdw per L by no means led to a higher yield. The highest yield was obtained at pH 8.5, which is illustrated in Fig. 2B. In addition, both the yield and ee were influenced by the reaction temperature (Fig. 2C). The highest ee was observed at 20 °C, while the corresponding yield was only 40% of that obtained at 35 °C. With an increase in temperature from 35 to 50 °C, the ee slowly reduced to 73% and the yield significantly decreased to 16%. To sum up, the reaction conditions were set at pH 8.5 and 35 °C using 30 g cdw per L of the recombinant *E. coli* cells.

Under the optimized conditions, the substrate scope was investigated with various chlorohydrocarbons and bromohydrocarbons. As shown in Table 2, substrates with diverse *ortho*-, *meta*-, and *para*-substituted groups on the phenyl ring, such as F, Cl, Br and methyl, were found to be suitable for the biotransformation, generating β-halohydrin products in 16–81% yields with moderate ee. Among *ortho*-, *meta*-, and *para*-substi-

Published on 17 July 2019. Downloaded by Universitätsbibliothek Bern on 3/31/2020 5:19:38 PM.

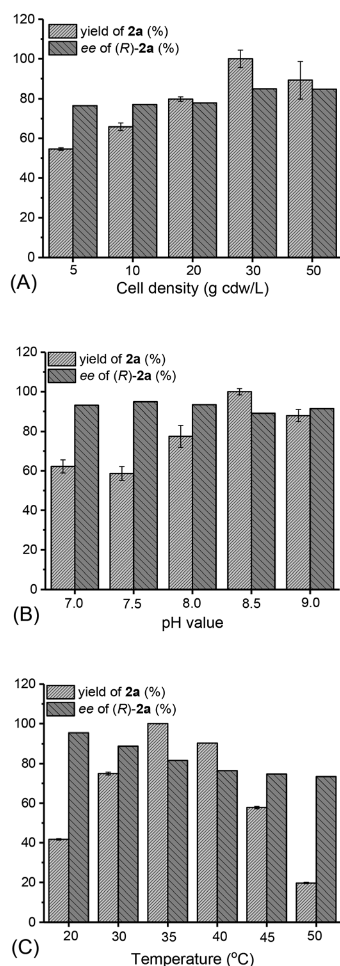


Fig. 2 Reaction condition optimization for the *E. coli* ($P450_{PL2}$-4) catalyzed asymmetric hydroxylation of **1a**: cell density (A); reaction pH (B); reaction temperature (C) (see Tables S3–S5† for details).

Table 2 Asymmetric hydroxylation of pro-chiral halohydrocarbons **1a–1m** using *E. coli* ($P450_{PL2}$-4) cells

E. coli ($P450_{PL2}$-4), pH 8.5, 35 °C, 12 h: **1a-1m** → **2a-2m**

Entry[a]	R	X	Subs.	Prod.	Yield 2[b] (%)	ee (R)-2[b] (%)
1	H	Cl	**1a**	**2a**	80	82
2	o-CH_3	Cl	**1b**	**2b**	Trace	n.d.
3	m-CH_3	Cl	**1c**	**2c**	80	85
4	p-CH_3	Cl	**1d**	**2d**	10	99
5	p-F	Cl	**1e**	**2e**	81	87
6	m-Br	Cl	**1f**	**2f**	29	84
7	H	Br	**1g**	**2g**	75	82
8	o-CH_3	Br	**1h**	**2h**	Trace	n.d.
9	m-CH_3	Br	**1i**	**2i**	35	90
10	p-CH_3	Br	**1j**	**2j**	36	80
11	p-F	Br	**1k**	**2k**	26	95
12	p-Cl	Br	**1l**	**2l**	22	80
13	m-Br	Br	**1m**	**2m**	16	88

[a] All the reactions were performed in 5 mL PBS buffer (50 mM, pH 8.5) containing 2 mM of substrates **1a–1m** and 30 g cdw per L of *E. coli* ($P450_{PL2}$-4) cells. [b] The yield and ee of halohydrins were determined by chiral HPLC analysis after incubation at 35 °C for 12 h. Subs. = substrate; Prod. = product; n.d. = not detected.

tuted halohydrocarbons, the *ortho*-substituted derivatives were not suitable substrates for hydroxylation by $P450_{PL2}$-4 (entry 2 and 8) and gave very low yields (<5%). These results revealed that the steric size of the *ortho*-substituted group had a great effect on its activity, which was also in agreement with the results reported for P450 BM3[21] and P450tol for the benzylic hydroxylation of aromatic hydrocarbons.[22] The substitution at the *ortho* position might have a steric effect on the oxygen attack from the ferryl species (cytochrome P450, compound I),[23] and reduces the oxidation activation efficiency at the benzylic C–H bond. Interestingly, the yields of most chlorohydrins with either a substituted or non-substituted group were generally higher than those of the corresponding bromohydrins. These results might be attributed to the fact that the higher electronegativity of the chloro group enabled the benzylic C–H bond to accept oxygen more easily. A decrease in activity was also observed in the wake of a decrease in the electron-withdrawing capability of a substituent on the phenyl ring (Table 2, entry 5 *vs.* 6). Most chlorohydrins exhibited similar ee values to the corresponding bromohydrins. It was worth noting that almost all the tested halohydrocarbons yielded the corresponding *R* halohydrins with 80–90% ee, and only **2d** and **2k** showed >90% ee.

In recent years, biocatalytic cascade reactions have been rapidly developed and lead to the generation of complex valuable chemicals from simple precursors.[24] The P450s have also been used to develop cascade reactions for multiple biotransformation reactions.[25] Recently, we have expressed and characterized a novel HHDH (HheA10) from *Tsukamurella* sp. 1534, which exhibited high *S* enantioselectivity toward β-halohydrins.[26] Inspired by the combination of sequential biocatalytic reactions, we attempted to improve the ee of halohydrins **2a–2m** by consumption of the *S* isomer halohydrins with HheA10. With this idea in mind, a "one-pot" biocatalytic cascade reaction was developed using $P450_{PL2}$-4 and HheA10 (Fig. 3). In the first step, the halohydrocarbon was catalyzed by $P450_{PL2}$-4 to generate a major *R* and a minor *S* halohydrin with moderate ee (*R* isomer). Subsequently, HheA10 converted the

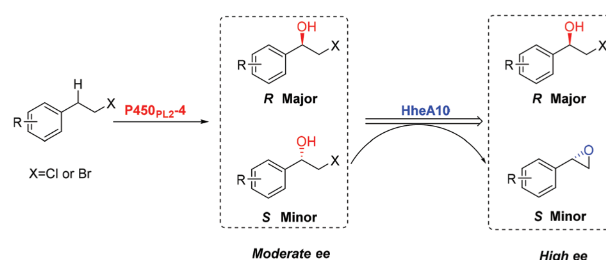


Fig. 3 The hydroxylation–dehalogenation cascade process for one-pot enantioselective synthesis of chiral β-haloalcohols.

 This journal is © The Royal Society of Chemistry 2019

Published on 17 July 2019. Downloaded by Universitätsbibliothek Bern on 3/31/2020 5:19:38 PM.

minor *S* halohydrin into *S* epoxide. As a result, the ee of the *R* halohydrin reached a higher value.

To avoid the excessive dehalogenation of the *R* halohydrin in the second step, the cell-free extract of HheA10 was added after hydroxylation for 8 h by *E. coli* cells ($P450_{PL2}$-4). As we have observed, HHDH was more active towards bromohalohydrins than chlorohalohydrins. Consequently, the dehalogenation reaction times in the cascade process for bromohalohydrins and chlorohalohydrins were 1 h and 4 h, respectively. The yield and ee of the β-halohydrin products **2a–2m** were determined and are shown in Table 3 (except **2b** and **2h** with low activity). As expected, an increase in ee was observed for the halohydrin product (such as entry 1, Table 3 *vs*. entry 1, Table 2), and all the tested halohydrins were generated with >98% ee. The yields of some halohydrins reduced slightly, which might have resulted from the conversion of the *S* isomer and the excessive conversion of the *R* isomer in the dehalogenation process. In general, the optical purity of β-halohydrins could be improved by using the hydroxylation–dehalogenation cascade strategy in a short time. This strategy might be more effective than obtaining a stereoselectivity-improved P450 variant *via* a complicated and time-consuming engineering process, especially for the asymmetric hydroxylation reaction. More importantly, the P450-catalyzed C–H direct hydroxylation process provides greener access and does not need the preoxidation treatment at the target C–H bond.

In summary, we developed a direct and greener route for the synthesis of enantioenriched β-halohydrins *via* a $P450_{PL2}$-4-catalyzed asymmetric hydroxylation of halohydrocarbons at benzylic C–H bonds. In addition, a hydroxylation–dehalogenation enzymatic cascade reaction was developed by using $P450_{PL2}$-4 and HheA10, which afforded β-halohydrin products with excellent ee. This synthetic method uses oxygen as an oxidant, avoids the use of oxygen-functionalized substrates, and achieves the desired product with excellent ee by a biocatalytic process in "one-pot".

Table 3 Synthesis of optically active β-halohydrins **2** *via* one-pot cascade biocatalysis

1a-1m → 2a-2m: *E. coli* cells ($P450_{PL2-4}$), Cell-free extract (HheA10), pH 8.5, 35 °C

Entry[a]	R	X	Subs.	Prod.	Yield **2**[b] (%)	ee (*R*)-**2**[b] (%)
1	H	Cl	**1a**	**2a**	85	98
2	*o*-CH_3	Cl	**1b**	**2b**	n.d.	n.d.
3	*m*-CH_3	Cl	**1c**	**2c**	45	99
4	*p*-CH_3	Cl	**1d**	**2d**	5	99
5	*p*-F	Cl	**1e**	**2e**	62	99
6	*m*-Br	Cl	**1f**	**2f**	41	99
7	H	Br	**1g**	**2g**	46	99
8	*o*-CH_3	Br	**1h**	**2h**	n.d.	n.d.
9	*m*-CH_3	Br	**1i**	**2i**	31	99
10	*p*-CH_3	Br	**1g**	**2g**	12	98
11	*p*-F	Br	**1k**	**2k**	28	99
12	*p*-Cl	Br	**1l**	**2l**	23	99
13	*m*-Br	Br	**1m**	**2m**	24	99

[a] All the reactions were performed in 5 mL PBS buffer (50 mM, pH 8.5) containing 2 mM of substrates **1a–1m** and 30 g cdw per L of *E. coli* cells ($P450_{PL2}$-4). After reaction at 35 °C for 8 h, 2 mL of the cell-free extract of HheA10 were added, and the reaction proceeded for another 3 h (**1a–1f**) or 1 h (**1g–1m**). [b] The yield and ee values were determined by chiral HPLC analysis. Subs. = substrate; Prod. = product; n.d. = not detected.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We are grateful for financial support from the National Natural Science Foundation of China (No. 21562054 and 21662050), the Guizhou Science and Technology Department (QKHRC-2016-4029, QKHPTRC-2016-5801, QKHJC-2019-1467 and QKHZC-2019-2579), the Program for Outstanding Youth of Zunyi Medical University (17zy-001), the National First-Rate Construction Discipline of Guizhou Province (Pharmacy) (YLXKJS-YX-04) and the Fifth Batch of Talent Base in Guizhou Province (2016).

Notes and references

1 (*a*) H. Hamada, T. Miura, H. Kumobayashi, T. Matsuda, T. Harada and K. Nakamura, *Biotechnol. Lett.*, 2001, **23**, 1603; (*b*) S. Eirik, H. Jarle, V. Anders and A. Thorleif, *Eur. J. Org. Chem.*, 2004, 1239; (*c*) J. Y. L. Chung, R. Cvetovich, J. Amato, J. C. McWilliams, R. Reamer and L. DiMichele, *J. Org. Chem.*, 2005, **70**, 3592; (*d*) M. C. Bryan, D. J. Burdick, B. K. Chan, Y. Chen, S. Clausen, J. Dotson, C. Eigenbrot, R. Elliott, E. J. Hanan, R. Heald, P. Jackson, H. La, M. Lainchbury, S. Malek, S. E. Mann, H. E. Purkey, G. Schaefer, S. Schmidt, E. Seward, S. Sideris, S. Wang, I. Yen, C. Yu and T. P. Heffron, *ACS Med. Chem. Lett.*, 2016, **7**, 100; (*e*) T. D. Fonseca, L. D. Lima, M. D. de Oliveira, T. L. de Lemos, D. Zampieri, F. Molinari and M. C. de Mattos, *Eur. J. Org. Chem.*, 2018, 2110.

2 D. Zhu, C. Mukherjee and L. Hua, *Tetrahedron: Asymmetry*, 2005, **16**, 3275.

3 (*a*) P. Besse, T. Sokoltchik and H. Veschambre, *Tetrahedron: Asymmetry*, 1998, **9**, 4441; (*b*) T. Hamada, T. Torii, K. Izawa, R. Noyori and T. Ikariya, *Org. Lett.*, 2002, **4**, 4373; (*c*) R. Imashiro and M. Seki, *J. Org. Chem.*, 2004, **69**, 4216; (*d*) T. Poessl, B. Kosjek, U. Ellmer, C. Gruber, K. Edegger, K. Faber, P. Hildebrandt, U. Bornscheuer and W. Kroutil, *Adv. Synth. Catal.*, 2005, **347**, 1827; (*e*) K. Wu, H. Wang, L. Chen, H. Fan, Z. Zhao and D. Wei, *Appl. Microbiol. Biotechnol.*, 2016, **100**, 8757.

4 (*a*) S. P. Hameed, M. Chinnapattu, G. Shanbag, P. Manjrekar, K. Koushik, A. Raichurkar, V. Patil, S. Jatheendranath, S. S. Rudrapatna, S. P. Barde,

Published on 17 July 2019. Downloaded by Universitätsbibliothek Bern on 3/31/2020 5:19:38 PM.

N. Rautela, D. Awasthy, S. Morayya, C. Narayan, S. Kavanagh, R. Saralaya, S. Bharath, P. Viswanath, K. Mukherjee, B. Bandodkar, A. Srivastava, V. Panduga, J. Reddy, K. R. Prabhakar, A. Sinha, B. Jiménez-Díaz, M. M. S. Martínez, I. Angulo-Barturen, S. Ferrer, L. M. Sanz, F. J. Gamo, S. Duffy, V. M. Avery, P. A. Magistrado, A. K. Lukens, D. F. Wirth, D. Waterson, V. Balasubramanian, P. S. Iyer, S. Narayanan, V. Hosagrahara, V. K. Sambandamurthy and S. Ramachandran, *J. Med. Chem.*, 2014, **57**, 5702; (*b*) A. Murugan, V. K. Kadambar, S. Bachu, M. R. Reddy, V. Torlikonda, S. G. Manjunatha, S. Ramasubramanian, S. Nambiar, G. P. Howell and J. Withnall, *Tetrahedron Lett.*, 2012, **53**, 5739.

5 (*a*) T. Ohkuma, K. Tsutsumi, N. Utsumi, N. Arai, R. Noyori and K. Murata, *Org. Lett.*, 2007, **9**, 255; (*b*) L. S. Campbell-Verduyn, W. Szymański, C. P. Postema, R. A. Dierckx, P. H. Elsinga, D. B. Janssen and B. L. Feringa, *Chem. Commun.*, 2010, **46**, 898.

6 (*a*) I. Kévin, S. Jérémie, R. Pascal, B. Jean-François and M. Angela, *Eur. J. Org. Chem.*, 2014, 4099; (*b*) S. Jérémy, I. Kévin, P. Julien, F. Gilles, R. Pascal, V. Arnaud, B. Jean-François and M. Angela, *Adv. Synth. Catal.*, 2013, **355**, 3613.

7 J. Barluenga, J. Flórez and M. Yus, *J. Chem. Soc., Chem. Commun.*, 1982, 1153.

8 (*a*) C. Yin, W. Wu, Y. Hu, X. Tan, C. You, Y. Liu, Z. Chen, X.-Q. Dong and X. Zhang, *Adv. Synth. Catal.*, 2018, **360**, 2119; (*b*) T. Touge, T. Hakamata, H. Nara, T. Kobayashi, N. Sayo, T. Saito, Y. Kayaki and I. Takao, *J. Am. Chem. Soc.*, 2011, **133**, 14960; (*c*) Y. Yamato, T. Taichiro, N. Hideki, M. Kazuhiko, F. Mitsuhiko, K. Yoshihito and I. Takao, *Adv. Synth. Catal.*, 2018, **360**, 568.

9 (*a*) A. Schmid, J. S. Dordick, B. Hauer, A. Kiener, M. Wubbolts and B. Witholt, *Nature*, 2001, **409**, 258; (*b*) J. Tao and J.-H. Xu, *Curr. Opin. Chem. Biol.*, 2009, **13**, 43; (*c*) R. A. Sheldon and J. M. Woodley, *Chem. Rev.*, 2018, **118**, 801; (*d*) Z.-M. Wu, R.-C. Zheng, X.-L. Tang and Y.-G. Zheng, *Appl. Microbiol. Biotechnol.*, 2017, **101**, 1953.

10 (*a*) Y. Xie, J.-H. Xu and Y. Xu, *Bioresour. Technol.*, 2010, **101**, 1054; (*b*) Y. Xie, J.-H. Xu, W.-Y. Lu and G.-Q. Lin, *Bioresour. Technol.*, 2009, **100**, 2463; (*c*) S.-Y. Chen, C.-X. Yang, J.-P. Wu, G. Xu and L.-R. Yang, *Adv. Synth. Catal.*, 2013, **355**, 3179; (*d*) F. Qin, B. Qin, T. Mori, Y. Wang, L. Meng, X. Zhang, X. Jia, I. Abe and S. You, *ACS Catal.*, 2016, **6**, 6135; (*e*) X. Chen, H. Zhang, J. Feng, Q. Wu and D. Zhu, *ACS Catal.*, 2018, **8**, 3525.

11 (*a*) N. Itoh, K. Isotani, M. Nakamura, K. Inoue, Y. Isogai and Y. Makino, *Appl. Microbiol. Biotechnol.*, 2012, **93**, 1075; (*b*) J. Mangas-Sánchez, E. Busto, V. Gotor-Fernández, F. Malpartida and V. Gotor, *J. Org. Chem.*, 2011, **76**, 2115; (*c*) D. Zhu, B. A. Hyatt and L. Hua, *J. Mol. Catal. B: Enzym.*, 2009, **56**, 272.

12 (*a*) I. M. Ferreira, R. H. V. Nishimura, A. B. A. Souza, G. C. Clososki, S. A. Yoshioka and A. L. M. Porto, *Tetrahedron Lett.*, 2014, **55**, 5062; (*b*) A. Träff, K. Bogár, M. Warner and J.-E. Bäckvall, *Org. Lett.*, 2008, **10**, 4807; (*c*) O. Pàmies and J.-E. Bäckvall, *J. Org. Chem.*, 2002, **67**, 9006.

13 (*a*) M. Majerić Elenkov, L. Tang, B. Hauer and D. B. Janssen, *Org. Lett.*, 2006, **8**, 4227; (*b*) R. M. Haak, C. Tarabiono, D. B. Janssen, A. J. Minnaard, J. G. de Vries and B. L. Feringa, *Org. Biomol. Chem.*, 2007, **5**, 318; (*c*) A. Westerbeek, J. G. E. van Leeuwen, W. Szymanski, B. L. Feringa and D. B. Janssen, *Tetrahedron*, 2012, **68**, 7645; (*d*) H. Arabnejad, M. Dal Lago, P. A. Jekel, R. J. Floor, A.-M. W. H. Thunnissen, A. C. Terwisscha van Scheltinga, H. J. Wijma and D. B. Janssen, *Protein Eng., Des. Sel.*, 2017, **30**, 175.

14 (*a*) W. Borzęcka, I. Lavandera and V. Gotor, *J. Org. Chem.*, 2013, **78**, 7312; (*b*) G.-C. Xu, H.-L. Yu, X.-Y. Zhang and J.-H. Xu, *ACS Catal.*, 2012, **2**, 2566; (*c*) Y.-P. Shang, Q. Chen, X.-D. Kong, Y.-J. Zhang, J.-H. Xu and H.-L. Yu, *Adv. Synth. Catal.*, 2017, **359**, 426.

15 (*a*) Y. Yang, J. Liu and Z. Li, *Angew. Chem., Int. Ed.*, 2014, **53**, 3120; (*b*) S. Kille, F. E. Zilly, J. P. Acevedo and M. T. Reetz, *Nat. Chem.*, 2011, **3**, 738; (*c*) E. Weber, A. Seifert, M. Antonovici, C. Geinitz, J. Pleiss and V. B. Urlacher, *Chem. Commun.*, 2011, **47**, 944.

16 (*a*) P. Gao, A. Li, H. H. Lee, D. I. C. Wang and Z. Li, *ACS Catal.*, 2014, **4**, 3763; (*b*) J.-D. Zhang, A.-T. Li, Y. Yang and J.-H. Xu, *Appl. Microbiol. Biotechnol.*, 2010, **85**, 615.

17 (*a*) C. K. Prier, R. K. Zhang, A. R. Buller, S. Brinkmann-Chen and F. H. Arnold, *Nat. Chem.*, 2017, **9**, 629; (*b*) T. K. Hyster, C. C. Farwell, A. R. Buller, J. A. McIntosh and F. H. Arnold, *J. Am. Chem. Soc.*, 2014, **136**, 15505; (*c*) A. McIntosh, J. P. S. Coelho, C. C. Farwell, Z. J. Wang, J. C. Lewis, T. R. Brown and F. H. Arnold, *Angew. Chem., Int. Ed.*, 2013, **52**, 9309; (*d*) R. Singh, M. Bordeaux and R. Fasan, *ACS Catal.*, 2014, **4**, 546.

18 K. Wu, L. Tang, H. Cui, N. Wan, Z. Liu, Z. Wang, S. Zhang, B. Cui, W. Han and Y. Chen, *ChemCatChem*, 2018, **10**, 5410.

19 J. B. van Beilen, E. G. Funhoff, A. van Loon, A. Just, L. Kaysser, M. Bouza, R. Holtackers, M. Röthlisberger, Z. Li and B. Witholt, *Appl. Environ. Microbiol.*, 2006, **72**, 59.

20 W. Zhang, W. L. Tang and Z. Li, *Adv. Synth. Catal.*, 2010, **352**, 3380.

21 K. Neufeld, J. Marienhagen, U. Schwaneberg and J. Pietruszka, *Green Chem.*, 2013, **15**, 2408.

22 A. Li, S. Wu, J. P. Adams, R. Snajdrova and Z. Li, *Chem. Commun.*, 2014, **50**, 8771.

23 J. Rittle and M. T. Green, *Science*, 2010, **330**, 933.

24 (*a*) S. P. France, L. J. Hepworth, N. J. Turner and S. L. Flitsch, *ACS Catal.*, 2017, **7**, 710; (*b*) J. H. Schrittwieser, S. Velikogne, M. Hall and W. Kroutil, *Chem. Rev.*, 2018, **11**, 270; (*c*) J. M. Sperl and V. Sieber, *ACS Catal.*, 2018, **8**, 2385.

25 (*a*) R. Agudo and M. T. Reetz, *Chem. Commun.*, 2013, **49**, 10914; (*b*) A. Li, A. Ilie, Z. Sun, R. Lonsdale, J.-H. Xu and M. T. Reetz, *Angew. Chem., Int. Ed.*, 2016, **55**, 12026; (*c*) M. Tavanti, F. Parmeggiani, J. R. G. Castellanos, A. Mattevi and N. J. Turner, *ChemCatChem*, 2017, **9**, 3338.

26 N. Wan, J. Tian, H. Wang, M. Tian, Q. He, R. Ma, B. Cui, W. Han and Y. Chen, *Bioorg. Chem.*, 2018, **81**, 529.

 This journal is © The Royal Society of Chemistry 2019