Aqueous chemoenzymatic one-pot enantioselective synthesis of tertiary α-aryl cycloketonesviaPd-catalyzed C-C formation and enzymatic C=C asymmetric hydrogenation

Luan, Pengqian; Liu, Yunting; Li, Yongxing; Chen, Ran; Huang, Chen; Gao, Jing; Hollmann, Frank; Jiang, Yanjun

DOI
10.1039/d1gc00372k

Publication date
2021

Document Version
Final published version

Published in
Green Chemistry

Green Chemistry

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Green Chem.*, 2021, **23**, 1960

Received 1st February 2021,
Accepted 22nd February 2021

DOI: 10.1039/d1gc00372k

rsc.li/greenchem

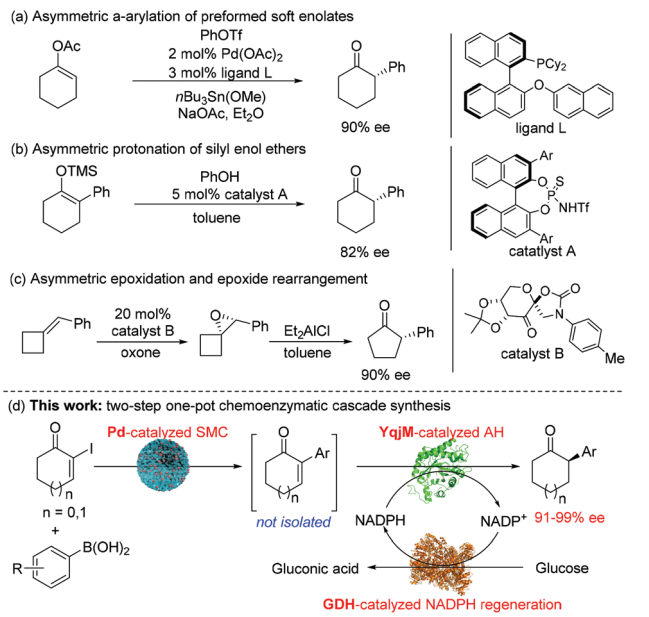
Aqueous chemoenzymatic one-pot enantioselective synthesis of tertiary α-aryl cycloketones *via* Pd-catalyzed C–C formation and enzymatic C=C asymmetric hydrogenation†

Pengqian Luan,[a] Yunting Liu,*[a,b] Yongxing Li,[a] Ran Chen,[a] Chen Huang,[a] Jing Gao,[a] Frank Hollmann [c] and Yanjun Jiang *[a]

An aqueous chemoenzymatic cascade reaction combining Pd-catalyzed C–C formation and enzymatic C=C asymmetric hydrogenation (AH) was developed for enantioselective synthesis of tertiary α-aryl cycloketones in good yields and excellent enantioselectivities. The stereopreference of the enzyme in AH of α-aryl cyclohexenones was studied. An enantiocomplementary enzyme was obtained by site-directed mutation.

Biocatalysts have become one of the fundamental pillars in the toolbox of synthetic chemistry due to their high stereoselectivity. More importantly, biocatalysis can produce enantioenriched molecules in a green way based on the mild reaction conditions and the use of water as the preferred solvent, which meets the requirements of environmentally friendly catalytic processes and sustainable development strategy.[1] Although the catalytic repertoire of enzymes is striking, many valuable transformations catalyzed by artificial catalysts until now have no known enzyme-catalysed counterparts,[2] and the catalytic capabilities of enzyme towards non-natural substrates are limited.[3] The chemoenzymatic catalysis has proven to be effective to tackle these limitations, where the wide catalytic capabilities of chemocatalysts and the exquisite selective properties of biocatalysts are usually merged in a one-pot aqueous system.[4] The pioneering work on combining Pd-catalyzed C–C bond formation with the enzymatic carbonyl reduction developed by Gröger,[5a] provides a paradigm for aqueous chemoenzymatic cascade catalysis, which is becoming a popular trend in asymmetric synthesis.[5] However, this strategy often suffers from the poor stability of the free enzymes and the incompatibilities between the two catalytic disciplines,[6] motivating the development of stable and compatible systems to realize aqueous chemoenzymatic processes.

Chiral tertiary α-aryl cycloketones are prevalent structural motifs in pharmaceuticals, bioactive molecules and natural products.[7] The enantioselective synthesis of such acidic α-H-containing compounds has always been a challenging task due to their prone-to-racemization nature under basic conditions.[8] Metal-catalyzed asymmetric α-arylation of preformed soft enolates with low basicity carbonyls,[9] and enantioselective protonation of achiral enolate complexes using Lewis-acid assisted chiral Brønsted acid catalysts,[10] have proven to be a powerful tool to deliver tertiary α-aryl cyclohexanones (Scheme 1a and b). Shi *et al.* achieved the asymmetric synthesis of more challenging tertiary α-aryl cyclopentanones by enantioselective



Scheme 1 Strategies for asymmetric synthesis of chiral tertiary α-substituted cycloketones.

[a]*School of Chemical Engineering and Technology, Hebei University of Technology, Tianjin 300130, China. E-mail: ytliu@hebut.edu.cn, yanjunjiang@hebut.edu.cn*
[b]*Tianjin Key Laboratory of Brine Chemical Engineering and Resource Eco-utilization (Tianjin University of Science and Technology), Tianjin 300457, China*
[c]*Department of Biotechnology, Delft University of Technology, 2629 HZ Delft, The Netherlands*

†Electronic supplementary information (ESI) available. See DOI: 10.1039/d1gc00372k

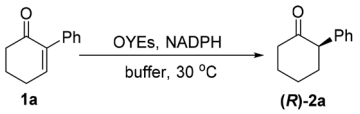
epoxidation of benzylidene cyclobutane and subsequent epoxide rearrangement (Scheme 1c).[11] Albeit effective, none of these approaches enable the direct use of ketone substrates. The asymmetric hydrogenation (AH) of readily available prochiral enones catalyzed by transition metals or organocatalysts, is one of the straightforward and simple strategies for access to chiral ketones.[12] Although great progress has been made in AH of acyclic and exocyclic enones,[13,14] only few methodologies have been developed for endocyclic enones,[15] and no reports on AH of α-aryl endocyclic enones. In addition, for most of the above strategies, toxic organic solvents and expensive chiral ligands are inevitably used, deviating from the principles of Green Chemistry. Therefore, it is still highly urgent to develop a facile, general and green method for enantioselective synthesis of chiral tertiary α-aryl cycloketones.

Old yellow enzymes (OYEs) are an important class of enereductases (ERs), which possess the ability to generate up to two chiral centers *via* the stereospecific *trans*-hydrogenation (hydride addition/protonation) of conjugated C=C bonds.[16] OYEs-catalyzed AH has emerged as a valuable synthetic approach, which enabled various chiral compounds to be reduced in mild reaction conditions with high enantioselectivities, such as α-alkyl endocyclic enones.[17] However, the ability of OYEs in AH of α-aryl endocyclic enones and the integration of OYEs with other catalytic disciplines have been rarely investigated.[18] Herein, we developed an aqueous chemoenzymatic two-step one-pot cascade reaction for the direct synthesis of enantioenriched tertiary α-aryl cycloketones from readily available 2-iodocycloenones. In this process, the aryl groups were installed through Suzuki–Miyaura coupling (SMC) catalyzed by an immobilized Pd catalyst (DON@Pd), and subsequently, the acidic α-H-containing stereocenters were constructed by OYE-catalyzed AH of α-aryl endocyclic enones (Scheme 1d).

To test the feasibility of this strategy, 2-phenylcyclohexenone (**1a**) synthesized by SMC reaction of 2-iodocyclohexenone and phenylboronic acid,[19] was selected as a model substrate. For the AH reaction, we evaluated three different OYEs (*Ts*OYE from *Thermus scotoductus*, OYE1 from *Saccharomyces pastorianus* and YqjM from *Bacillus subtilisin*) in form of freeze-dried *Escherichia coli* cells overexpressing these enzymes. All reactions were carried out under the following conditions: substrates (5 mM), NADPH (15 mM), in a Tris-HCl buffer solution (10 mL, pH 7.5) at 30 °C, using DMF (v/v 10%) as cosolvent to overcome the poor substrate solubility in water. Unfortunately, **1a** was not transformed by *Ts*OYE and OYE1, only YqjM could produce (*R*)-2-phenylcyclohexanone (**2a**) in extremely low yield (9%), albeit with high stereoselectivity (Table 1, entries 1–3). The *R* configuration of **2a** was determined by optical rotation compared with the literature data.[20] Although the yield and the ee value were further increased when the reaction was conducted under diluted conditions, it was still far from satisfactory (Table 1, entries 4 and 5). Subsequent experiments revealed a significant cosolvent effect on the catalytic performance of YqjM. Water-miscible DME and acetone led to no conversion (Table 1, entries 6 and 7), DMSO and THF caused decreases in the enantioselectivity of the AH (Table 1, entries 8 and 9). Water-immiscible isooctane and ionic liquids (ILs) significantly improved the yield and enantioselectivity of the reaction (Table 1, entries 11–13). The best result was obtained with [BMIm][NTf_2] (20% v/v) as cosolvent (Table 1, entry 14), which was attributed to its better biocompatibility and extraction ability.[21] In this biphasic system, the substrate was partitioned into the IL phase, which served as substrate reservoir and product sink,[22] thereby preventing the interaction between the substrate/cosolvent and the YqjM. However, a further increase to 1 : 1 (v/v) [BMIm][NTf_2] proved to be harmful to YqjM (Table 1, entry 15). The effect of cosolvents on relative enzyme activity was also evaluated, and the results were summarized as shown in Fig. S1.† The water-miscible solvents (DMF, DME, DMSO, THF and acetone) had a severely deleterious effect on enzyme activity, while the water-immiscible solvents (*n*-hexane, isooctane and ILs) were more biocompatible, especially [BMIm][NTf_2], which was consistent with the reaction results.

According to literature,[17a] the type of cofactor and recycling system can cause remarkable variation of yields and stereoselectivities. This effect was also examined in our reactions (Table 1, entries 16–18). Using NADPH gave better results than using NADH. With catalytic amounts of NADPH, the recycling system of glucose dehydrogenase (GDH)/glucose (Glu) pair achieved 79% yield and 97% ee (Table 1, entry 18). Furthermore, recombinant cells co-expressing the enzymes of YqjM and GDH (YqjM-RBS-GDH) were constructed to avoid

Table 1 Optimization studies of OYEs-catalyzed AH of 2-phenylcyclohexenone[a]



1a **(*R*)-2a**

Entry	Cosolvents	Enzymes	Yield[b] (%)	ee[b] (%)
1[c]	DMF (10%)	OYE1	n.d.	—
2	DMF (10%)	*Ts*OYE	n.d.	—
3	DMF (10%)	YqjM	9	85
4[c]	DMF (10%)	YqjM	26	85
5[d]	DMF (10%)	YqjM	42	87
6	DME (10%)	YqjM	n.d.	—
7	Acetone (10%)	YqjM	n.d.	—
8	DMSO (10%)	YqjM	42	60
9	THF (10%)	YqjM	39	59
10	*n*-Hexane (10%)	YqjM	43	92
11	Isooctane (10%)	YqjM	58	94
12	[BMIm][PF_6] (10%)	YqjM	64	95
13	[BMIm][NTf_2] (10%)	YqjM	70	95
14	[BMIm][NTf_2] (20%)	YqjM	76	95
15	[BMIm][NTf_2] (50%)	YqjM	32	67
16[e]	[BMIm][NTf_2] (20%)	YqjM	54	90
17	[BMIm][NTf_2] (20%)	YqjM + FDH	43	82
18	[BMIm][NTf_2] (20%)	YqjM + GDH	79	97
19	[BMIm][NTf_2] (20%)	YqjM-RBS-GDH	89	99
20[f]	[BMIm][NTf_2] (20%)	YqjM-RBS-GDH	86	99

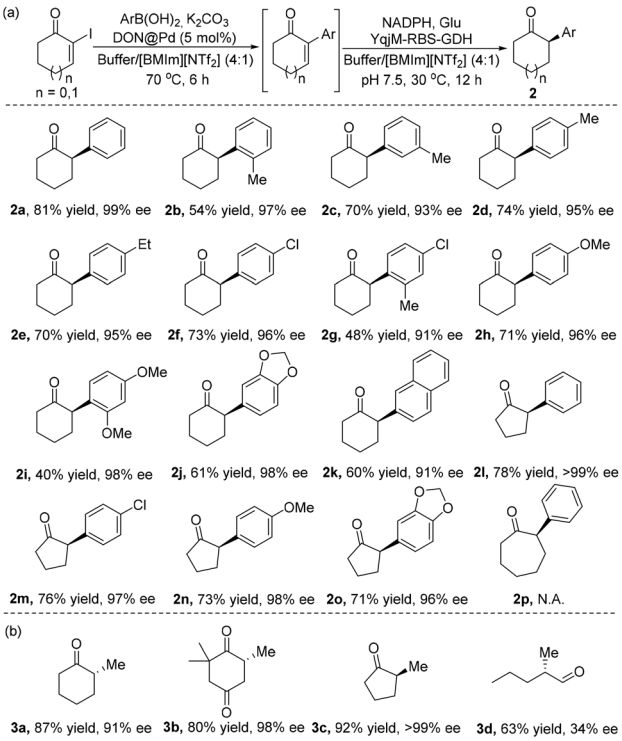
[a] Reactions were carried out at 30 °C in Tris-HCl buffer (pH 7.5) using **1a** (5 mM), OYEs whole-cell lyophilizates (0.2 g), NADPH as hydrogen source. [b] The yields and the values of ee were determined by HPLC. [c] Using **1a** (2 mM). [d] Using **1a** (1 mM). [e] NADH as hydrogen source. [f] Using **1a** (25 mM). n.d. = not determined.

adding extra GDH (Fig. S2†), and they produced **2a** in a higher yield and stereoselectivity (Table 1, entry 19). This result was mainly ascribed to that the two enzymatic transformations occurred within the cell, which enhanced the cofactor regeneration efficiency.[23] Under the optimal solvent system, the substrate concentration could increase to 25 mM with only a slight decrease in yield (Table 1, entry 20).

The integration of SMC and enzymatic hydrogenation in the same reaction medium was explored to realize the two-step one-pot chemoenzymatic cascade synthesis of enantioenriched tertiary α-aryl cycloketones. Preliminary experiments revealed that the direct combination of the two steps caused incomplete bioreduction (only 41% overall yield), which was ascribed to the inhibition of enzyme by the residual boronic acid.[5a] Because the heterogeneous Pd/C could not convert boronic acid completely, especially in the case of using recycled catalyst. While the homogeneous catalysts, such as $Pd(PPh_3)_4$ and $Pd(OAc)_2/PPh_3$, could make the coupling reaction proceed more thoroughly, the metal cation and phosphine ligand were also inhibitors of the enzyme.[24] To solve this problem, an immobilized-Pd catalyst was fabricated using our previously reported dendritic organosilica nanoparticles as carrier (DON@Pd, the particle size and the loading amount of Pd were calculated to be 1.8 nm and 5 wt%, respectively) (Fig. S3–S5†).[25] The wrinkle structure with high specific surface area is conductive to the formation of ultrasmall and high dispersed Pd nanoparticles. After a simple optimization of the reaction conditions (Table S1†), the obtained DON@Pd produced **1a** in almost quantitative yield. Fortunately, its combination with YqjM in a biphasic system where Pd-catalyzed C–C formation was performed in the IL phase, and enzymatic C=C AH was performed in the buffer phase, could produce the final product **2a** in 81% yield and 99% ee. It should be mentioned that the yield of cascade synthesis was higher than that of stepwise synthesis (63%).

After the optimized reaction protocol for the chemoenzymatic asymmetric synthesis of tertiary α-aryl cyclohexanones was established, the substrate scope of the reaction was surveyed. As indicated in Scheme 2a, substrates containing electron-donating and electron-withdrawing substituents were converted into the corresponding target products (**2a–k**) in moderate to high yields (40–81%) and excellent enantioselectivities (91–99% ee). The *ortho*-substituents of the aryl groups caused much slower reaction rates and lower yields due to the increased steric bulk (**2b**, **2g** and **2i**). In addition, the five- and seven-membered ring substrates were also investigated. The tertiary α-aryl cyclopentanones (**2l–o**) were also obtained in good yield (71–78%) and excellent enantioselectivities (96–99% ee). However, α-phenyl cycloheptenone (**2p**) could not be converted, which may be due to that the substrate specificity of YqjM is generally limited to small molecules.[26] The enzymatic AH of α-alkyl enones in this biphasic system was also evaluated (**3a–d**), achieving improved yields and increased substrate concentrations compared to the previous reported results (Scheme 2b and Table S2†).

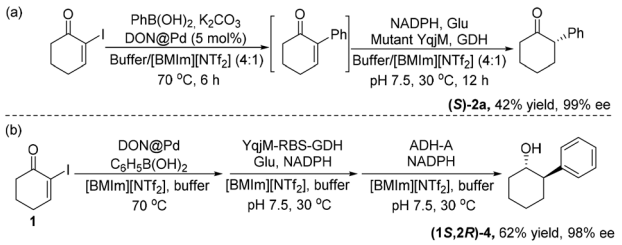
As shown in previous reports,[27] the stereoselectivity of the YqjM strongly depends on the substrate and is hardly predictable. We also observed a striking switch of stereopreference in



Scheme 2 (a) Chemoenzymatic asymmetric synthesis of tertiary α-aryl cycloanones and (b) enzymatic asymmetric hydrogenation of α-alkyl enones.

the reduction of α-phenyl and α-methyl cyclohexenones (**2a** and **3a**). In order to rationalize this phenomenon, induced docking experiments were performed based on the crystal structure of YqjM. In the process of YqjM-catalyzed hydrogenation, H-bonding formed between His167 and C=O bond of the substrate is essential for the activation of C=C bond (Fig. S6–S8†).[28] Ala-60 and Ile-69 build up the entrance of the active site cavity forming a deep and small pocket on the bottom, which can accommodate the methyl group of **3a**, but cannot accept the sterically hindered phenyl ring of **2a** (Fig. S6 and S7†), thus forcing **2a** to turn around and to bind in the opposite orientation. In addition, the reorientation by 180° of **2a** in the active site resulted in a strong π–π interaction between the phenyl ring of **2a** and the imidazole ring of His167 (Fig. S7†), in which the distance between the two planes is about 3.3–3.7 Å (Fig. S9†). The effective H-bond and π–π interactions bring the substrate closer to the active center of the enzyme, which is responsible for the high level of enantio-induction.

The access to enantiocomplementary products is highly valuable for manufacturing drugs since the two mirror-image forms of a chiral molecule usually exhibit different pharmacological activities. Site-directed mutation was performed to develop an enantiocomplementary variant of YqjM for obtaining the opposite enantiomer products. We envisioned that widening the active pocket to accommodate the sterically hindered phenyl group might be a viable solution. After careful screening of the amino acids around the active pocket, a



Scheme 3 (a) Chemoenzymatic asymmetric synthesis of (*S*)-**2a** and (b) three-step one-pot chemoenzymatic asymmetric synthesis of chiral α-aryl cycloalkanol.

double amino acid mutation (Gly-60 and Gly-69 were installed in place of Ala-60 and Ile-69, respectively) was found to induce complete reversal of the enantioselectivity of YqjM (Fig. S8†). After a slight optimization of the reaction conditions, (*S*)-**2a** was produced by the mutant YqjM through the above developed chemoenzymatic process with 42% yield and 99% ee (Scheme 3a).

To expand the applicability of the chemoenzymatic protocol, a three-step one-pot cascade reaction was developed for asymmetric synthesis of chiral α-aryl cycloalkanols *via* the combination of this process with AH of C═O bond catalyzed by alcohol dehydrogenase from *Rhodococcus ruber* (ADH-A).[29] Without any purification of intermediates, enantioenriched (1*S*,2*R*)-2-phenylcyclohexan-1-ol (**4**) was directly produced from 2-iodocyclohexenone in 62% yield and 98% ee (Scheme 3b).

Finally, the recyclability of the both types of catalysts was investigated by the model reaction of chemoenzymatic production of (*R*)-**2a** under the optimal conditions. The DON@Pd could be recovered by centrifugal separation before enzymatic AH, and its high catalytic performance was completely sustained for 5 cycles with no significant leaching and aggregation of Pd NPs (Fig. S10 and S11†). However, the recovery of the catalytically active cells was difficult due to significant cell lysis observed under these reaction conditions. To solve this problem, the two enzymes (YqjM and GDH) were purified and co-immobilized on DONs (for details see ESI†). Under optimized immobilization conditions, the maximum enzyme loading was 230 mg $g_{support}^{-1}$ (Fig. S12†). Compared with the whole cells, the co-immobilized catalyst exhibited obviously higher stabilities to organic solvents, temperatures and pH, as well as higher storage stability (Fig. S13–S16†). While the whole cells were almost inactivated after recycled 5 times (Fig. S17†), the co-immobilized enzymes used 5 times still maintained a moderate activity, producing (*R*)-**2a** in 52% yield and 93% ee (Fig. S18†).

Conclusions

In conclusion, an aqueous chemoenzymatic approach for asymmetric synthesis of enantioenriched tertiary α-aryl cycloketones has been developed for the first time. The transformation relies on the sequential cascade reaction combining Pd-catalyzed SMC and YqjM-catalyzed AH of α-aryl endocyclic enones. This process can be expanded to synthesize chiral α-aryl cycloalkanols bearing two contiguous stereocenters by combining ADH-catalyzed AH of C═O bond. An enantiocomplementary variant of the YqjM was also obtained by site-directed mutation. This concept, which integrates the versatile reactivity of chemocatalysis and the exquisite selectivity of biocatalysis, is a green, reliable alternative and supplement to the existing approaches for the asymmetric synthesis of chiral molecules.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work supported by the National Natural Science Foundation of China (21901058, 21878068 and 22078081), the Science and Technology Research Project of Hebei Higher Education (ZD2019045), the Natural Science Foundation of Hebei Province (B2017202056 and B2019202216), the Natural Science Foundation of Tianjin City (20JCYBJC00530) and the Foundation of Tianjin Key Laboratory of Brine Chemical Engineering and Resource Eco-utilization (Tianjin University of Science and Technology), People's Republic of China (BCERE202001).

Notes and references

1 N. Turner and L. Humphreys, *Biocatalysis in Organic Synthesis: The Retrosynthesis Approach*, Royal Society of Chemistry, Cambridge, 2018.
2 K. Chen and F. Arnold, *Nat. Catal.*, 2020, **3**, 203–213.
3 (*a*) N. Schmidt, E. Eger and W. Kroutil, *ACS Catal.*, 2016, **6**, 4286–4311; (*b*) U. Bornscheuer, *Philos. Trans. R. Soc., A*, 2017, **376**, 20170063.
4 For selected reviews of chemoenzymatic cascade catalysis, see: (*a*) X. Huang, M. Cao and H. Zhao, *Curr. Opin. Chem. Biol.*, 2020, **55**, 161–170; (*b*) R. Ye, J. Zhao, B. Wickemeyer, F. Toste and G. A. Somorjai, *Nat. Catal.*, 2018, **1**, 318–325; (*c*) J. Schrittwieser, S. Velikogne, M. Hall and W. Kroutil, *Chem. Rev.*, 2018, **118**, 270–348; (*d*) M. Honig, P. Söndermann, N. Turner and E. Carreira, *Angew. Chem., Int. Ed.*, 2017, **56**, 8942–8973; (*e*) O. Verho and J. Bäckvall, *J. Am. Chem. Soc.*, 2015, **137**, 3996–4009; (*f*) Y. Liu, P. Liu, S. Gao, Z. Wang, P. Luan, J. González-Sabín and Y. Jiang, *Chem. Eng. J.*, 2020, 127659.
5 For selected papers for aqueous chemoenzymatic cascade reactions see: (*a*) E. Burda, W. Hummel and H. Gröger, *Angew. Chem., Int. Ed.*, 2008, **47**, 9551–9554; (*b*) H. Sato, W. Hummel and H. Gröger, *Angew. Chem., Int. Ed.*, 2015, **54**, 4488–4492; (*c*) N. Ríos-Lombardía, C. Vidal, E. Liardo, F. Morís, J. García-Álvarez and J. González-Sabín, *Angew. Chem., Int. Ed.*, 2016, **55**, 8691–8695; (*d*) J. Schrittwieser, F. Coccia, S. Coccia, B. Grischek, W. Kroutil, N. d'Alessandro and F. Hollmann, *Green Chem.*, 2013, **15**, 3318–3331; (*e*) J. Xu, M. Arkin, Y. Peng, W. Xu, H. Yu, X. Lin and Q. Wu,

Green Chem., 2019, **21**, 1907–1911; (*f*) M. Rodríguez-álvarez, N. Ríos-Lombardía, S. Schumacher, D. Pérez-Iglesias, F. Morís, V. Cadierno, J. García-Álvarez and J. González-Sabín, *ACS Catal.*, 2017, **7**, 7753–7759; (*g*) M. Cortes-Clerget, N. Akporji, J. Zhou, F. Gao, P. Guo, M. Parmentier, F. Gallou, J. Berthon and B. Lipshutz, *Nat. Commun.*, 2019, **10**, 2169; (*h*) S. Cosgrove, M. Thompson, S. Ahmed, F. Parmeggiani and N. Turner, *Angew. Chem.*, 2020, **59**, 18156–18160.

6 (*a*) S. Schmidt, K. Castiglione and R. Kourist, *Chem. – Eur. J.*, 2018, **24**, 1755–1768; (*b*) F. Rudroff, M. Mihovilovic, H. Gröger, R. Snajdrova, H. Iding and U. Bornscheuer, *Nat. Catal.*, 2018, **1**, 12–22.

7 (*a*) Y. Hao, X. Hu, Y. Zhou, J. Zhou and J. Yu, *ACS Catal.*, 2020, **10**, 955–993; (*b*) Y. Xu, T. Su, Z. Huang and G. Dong, *Angew. Chem., Int. Ed.*, 2016, **55**, 2559–2563.

8 (*a*) X. Huang, W. Oh and J. Zhou, *Angew. Chem., Int. Ed.*, 2018, **57**, 7673–7677; (*b*) R. Liu, B. Li, J. Lu, C. Shen, J. Gao and Y. Jia, *J. Am. Chem. Soc.*, 2016, **138**, 5198–5201.

9 Z. Huang, L. Lim, Z. Chen, Y. Li, F. Zhou, H. Su and J. Zhou, *Angew. Chem., Int. Ed.*, 2013, **52**, 4906–4911.

10 (*a*) H. Cheol and H. Yamamoto, *J. Am. Chem. Soc.*, 2008, **130**, 9246–9247; (*b*) S. Nakamura, M. Kaneeda, K. Ishihara and H. Yamamoto, *J. Am. Chem. Soc.*, 2000, **122**, 8120–8130.

11 Y. Shen, B. Wang and Y. Shi, *Angew. Chem., Int. Ed.*, 2006, **45**, 1429–1432.

12 For a review of AH of enones, see: H. Hagiwara, *Nat. Prod. Commun.*, 2018, **13**, 489–499.

13 For selected AH of acyclic enones, see: (*a*) J. Yang, M. Fonseca, N. Vignola and B. List, *Angew. Chem., Int. Ed.*, 2005, **44**, 108–110; (*b*) S. Lu and C. Bolm, *Angew. Chem.*, 2008, **120**, 9052–9055; (*c*) W. Lu, Y. Chen and X. Hou, *Angew. Chem.*, 2008, **120**, 10287–10290; (*d*) W. Lu, Y. Hen and X. Hon, *Adv. Synth. Catal.*, 2010, **352**, 103–107; (*e*) J. Margalef, X. Caldentey, E. Karlsson, M. Coll, J. Mazuela, O. Pàmies, M. Diéguez and M. Pericàs, *Chem. – Eur. J.*, 2014, **20**, 12201–12214.

14 For selected AH of exocyclic enones, see: (*a*) F. Tian, D. Yao, Y. Liu, F. Xie and W. Zhang, *Adv. Synth. Catal.*, 2010, **352**, 1841–1845; (*b*) X. Wang, Z. Han, Z. Wang and K. Ding, *Angew. Chem., Int. Ed.*, 2012, **51**, 936–940; (*c*) Y. Liu, I. Gridnev and W. Zhang, *Angew. Chem.*, 2014, **126**, 1932–1936; (*d*) X. Liu, Z. Han, Z. Wang and K. Ding, *Angew. Chem., Int. Ed.*, 2014, **53**, 1978–1982; (*e*) Z. Zheng, Y. Cao, Q. Chong, Z. Han, J. Ding, C. Luo, Z. Wang, D. Zhu, Q. Zhou and K. Ding, *J. Am. Chem. Soc.*, 2018, **140**, 10374–10381.

15 For selected AH of endocyclic enones, see: (*a*) D. Dobbs, K. Vanhessche, E. Brazi, V. Rautenstrauch, J. Lenoir, J. Genêt, J. Wiles and S. Bergens, *Angew. Chem., Int. Ed.*, 2000, **39**, 1992–1995; (*b*) J. Tuttle, S. Ouellet and D. W. MacMillan, *J. Am. Chem. Soc.*, 2006, **128**, 12662–12663; (*c*) T. Ohshima, H. Tadaoka, K. Hori, N. Sayo and K. Mashima, *Chem. – Eur. J.*, 2008, **14**, 2060–2066; (*d*) E. Szabados, N. Györffy, A. Tungler, J. Balla and L. Könczö, *React. Kinet. Catal. Lett.*, 2014, **111**, 107–114.

16 (*a*) M. Reetz, *Angew. Chem., Int. Ed.*, 2011, **50**, 138–174; (*b*) A. Scholtissek, D. Tischler, A. Westphal, W. van Berkel and C. Paul, *Catalysts*, 2017, **7**, 130; (*c*) H. Toogood and N. Scrutton, *ACS Catal.*, 2018, **8**, 3532–3549.

17 (*a*) M. Hall, C. Stueckler, H. Ehammer, E. Pointner, G. Oberdorfer, K. Gruber, B. Hauer, R. Stuermer, W. Kroutil, P. Macheroux and K. Faber, *Adv. Synth. Catal.*, 2008, **350**, 411; (*b*) S. Padhi, D. Bougioukou and J. Stewart, *J. Am. Chem. Soc.*, 2009, **131**, 3271.

18 (*a*) Y. Wang, M. Bartlett, C. Denard, J. Hartwig and H. Zhao, *ACS Catal.*, 2017, **7**, 2548; (*b*) Z. Litman, Y. Wang, H. Zhao and J. Hartwig, *Nature*, 2018, **560**, 355; (*c*) B. Kosjek, F. J. Fleitz, P. G. Dormer, J. T. Kuethe and P. N. Devine, *Tetrahedron: Asymmetry*, 2008, **19**, 1403–1406.

19 F. Felpin, *J. Org. Chem.*, 2005, **70**, 8575–8578.

20 The *R* configuration of **2a** was determined by optical rotation compared with the literature data. The optical rotation of the product **2a** is $[\alpha]_D^{22}$ = +108.9 (*c* 0.45, $CHCl_3$, 99% ee) [Lit. $[\alpha]_D^{22}$ = +102 (*c* 0.45, $CHCl_3$, 93% ee)], see: C. Cheon, O. Kanno and F. Toste, *J. Am. Chem. Soc.*, 2011, **133**, 13248–13251.

21 (*a*) B. Gauchot, W. Kroutil and A. Schmitzer, *Chem. – Eur. J.*, 2010, **16**, 6748–6751; (*b*) F. van Rantwijk, R. Lau and R. Sheldon, *Trends Biotechnol.*, 2003, **21**, 131–138; (*c*) R. Sheldon, R. Lau, M. Sorgedrager, F. van Rantwijk and K. Seddon, *Green Chem.*, 2002, **4**, 147–151; (*d*) U. Kragl, M. Eckstein and N. Kaftzik, *Curr. Opin. Biotechnol.*, 2002, **13**, 565–571; (*e*) Q. Liu, M. Janssen, F. van Rantwijk and R. Sheldon, *Green Chem.*, 2005, **7**, 39–42.

22 (*a*) C. Risi, F. Zhao and D. Castagnolo, *ACS Catal.*, 2019, **9**, 7264–7269; (*b*) V. Nosek and J. Míšek, *Angew. Chem.*, 2018, **130**, 9997–10000; (*c*) N. Scalacci, G. Black, G. Mattedi, N. Brown, N. Turner and D. Castagnolo, *ACS Catal.*, 2017, **7**, 1295–1300.

23 X. Zhou, R. Zhang, Y. Xu, H. Liang and J. Jiang, *Process Biochem.*, 2015, **50**, 1807–1813.

24 P. Schaaf, T. Bayer, M. Koley, M. Schnurch, U. Bornscheuer, F. Rudroff and M. Mihovilovic, *Chem. Commun.*, 2018, **54**, 12978–12981.

25 (*a*) J. Gao, W. Kong, L. Zhou, Y. He, L. Ma, Y. Wang, L. Yin and Y. Jiang, *Chem. Eng. J.*, 2017, **309**, 70–79; (*b*) L. Gao, Z. Wang, Y. Liu, P. Liu, S. Gao, J. Gao and Y. Jiang, *Chem. Commun.*, 2020, **56**, 13547–13550.

26 D. Mansell, H. Toogood, J. Waller, J. Hughes, C. Levy, J. Gardiner and N. Scrutton, *ACS Catal.*, 2013, **3**, 370–379.

27 (*a*) D. Bougioukou, S. Kille, A. Taglieber and M. Reetz, *Adv. Synth. Catal.*, 2009, **351**, 3287–3305; (*b*) G. Oberdorfer, G. Steinkellner, C. Stueckler, K. Faber and K. Gruber, *ChemCatChem*, 2011, **3**, 1562–1566; (*c*) T. Classen, J. Pietruszka and S. Schuback, *ChemCatChem*, 2013, **5**, 711–713; (*d*) G. Oberdorfer, K. Gruber, K. Faber and M. Hall, *Synlett*, 2012, 1857–1864.

28 K. Kitzing, T. Fitzpatrick, C. Wilken, J. Sawa, G. Bourenkov, P. Macheroux and T. Clausen, *J. Biochem.*, 2005, **280**, 27904–27913.

29 M. Karabec, A. Lyskowski, K. Tauber, G. Steinkellner, W. Kroutil, G. Grogan and K. Gruber, *Chem. Commun.*, 2010, **46**, 6314–6316.

