SCIENCE CHINA
Chemistry

•ARTICLES•

February 2021 Vol.64 No.2: 232–237
https://doi.org/10.1007/s11426-020-9873-6

# Construction of three stereocenters *via* hydrogenative desymmetrization of 2,2,5-trisubstituted cyclohexane-1,3-diones

Yi-Xuan Ding[1,2], Zhou-Hao Zhu[1,2], Han Wang[1], Chang-Bin Yu[1*] & Yong-Gui Zhou[1,3*]

[1]*State Key Laboratory of Catalysis, Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, China;*
[2]*University of Chinese Academy of Sciences, Beijing 100049, China;*
[3]*State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China*

Received August 15, 2020; accepted September 14, 2020; published online December 11, 2020

A Ru-catalyzed hydrogenative desymmetrization of 2,2,5-trisubstituted cyclohexane-1,3-diones was developed for construction of three stereocenters including two coherent and discontiguous chiral centers and a chiral quaternary carbon with excellent enantio- and diastereoselectivities. Stereodivergent synthesis of four stereoisomers could be conducted with high enantioselectivities. The desymmetrization could be achieved at gram scale without loss of reactivity and optical purity, and a formal synthesis of bioactive molecule (−)-isocelorbicol was completed.

**desymmetrization, hydrogenation, 1, 3-cyclohexanediones, three stereocenters, chiral quaternary carbon**

**Citation:** Ding YX, Zhu ZH, Wang H, Yu CB, Zhou YG. Construction of three stereocenters *via* hydrogenative desymmetrization of 2,2,5-trisubstituted cyclohexane-1,3-diones. *Sci China Chem*, 2021, 64: 232–237, https://doi.org/10.1007/s11426-020-9873-6

## 1 Introduction

Desymmetrization is represented as a powerful synthetic tool for converting *meso* and prochiral substrates into chiral organic molecules [1], often with multiple stereocenters or a chiral quaternary carbon. Recently, desymmetrization of prochiral cyclic diketones, which is emerging as one of the useful building blocks in synthetic organic chemistry, has been diffusely applied to aldol reaction [2], Michael addition [3], Schmidt reaction [4], Diels-Alder reaction [5], retro-Claisen reaction [6] and so on [7]. Among these asymmetric reactions, desymmetrization has been important to the formation of multiple stereocenters or the construction of fully substituted stereocenters.

Stereoselective reduction of one of the diketone moiety is also a useful approach to conduct the enantioselective desymmetrization of cyclic diketones. Most of previous attempts usually focused on the construction of two consecutive stereo-centers with a quaternary carbon *via* mono-reduction of cyclic 1,3-diketones. Enzyme [8], Corey-Bakshi-Shibata reagent (CBS) [9] and transition metals [10] could all help to catalyze the desymmetrization of cyclic symmetric 1,3-diketones with two different substituents at the prochiral carbon (Scheme 1(a)). Recently, our group [11] reported stereoselective reduction of prochiral diketones with Noyori catalyst [12] to build two discontiguous stereocenters *via* remote control (Scheme 1(b)). McIntosh and Zhang's group [13] applied ruthenium catalysts to the hydrogenative desymmetrization of cyclic *meso*-epoxy diketones independently, offering the chiral epoxy hydroxy ketones with three contiguous stereocenters (Scheme 1(c)). To sum up, by using the desymmetrisation methodology, the construction of two consecutive chiral centers, two discontiguous stereocenters, or three coherent stereocenters has been successfully developed. We wondered whether all the goals above can be achieved through substrate design.

*Corresponding authors (email: cbyu@dicp.ac.cn; ygzhou@dicp.ac.cn)

Herein, we report the ruthenium-catalyzed hydrogenative desymmetrization of 2,2,5-trisubstituted 1,3-cyclohexanediones to construct three stereocenters containing two discrete stereocenters and a chiral quaternary carbon stereocenter. Moreover, stereodivergent syntheses of four stereoisomers could be conveniently accessed by combination of substrates and chiral ruthenium catalysts (Scheme 1 (d)).

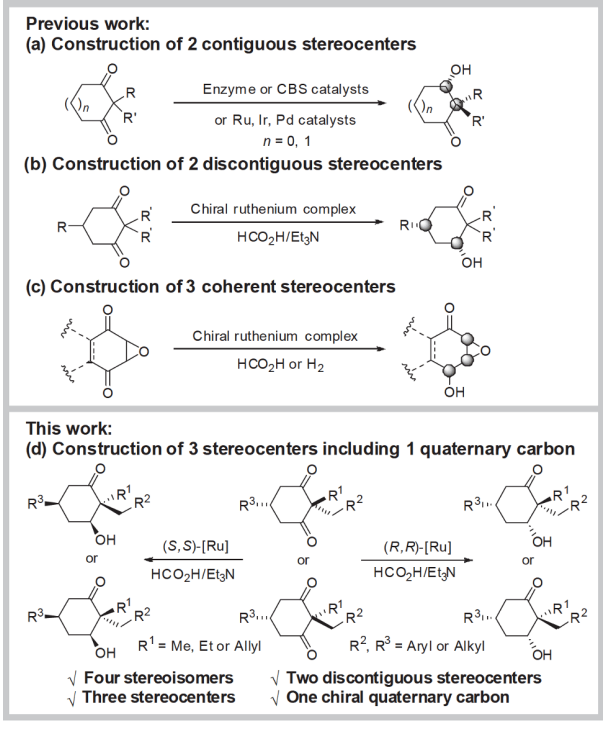
## 2 Experimental

Under the nitrogen atmosphere, a mixture of 2,2-disubstituted 5-phenylcyclohexane-1,3-diones (0.2 mmol) and RuCl[(*R*,*R*)-Tsdpen](*p*-cymene) catalyst (2.5 mg, 0.004 mmol) in an azeotrope of formic acid, triethylamine (5:2, 67 μL, 0.8 mmol) and ethyl acetate (1.0 mL) was stirred at 40 °C for 4 h in which carbon dioxide was released once an hour. After the reaction completion, the volatile was removed under the reduced pressure; the crude residue was directly purified by silica gel column chromatography to afford the desired reductive products. The optical purity was determined by chiral HPLC analysis.

## 3 Results and discussion

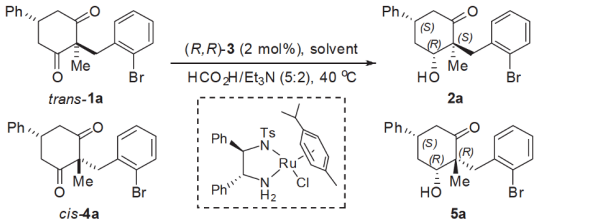
At our outset, we chose *trans* 2-(2-bromobenzyl)-2-methyl-5-phenylcyclohexane-1,3-dione *trans*-**1a** bearing a prochiral quaternary carbon center as the model substrate [7d]. In the presence of 2 mol% RuCl[(*R*,*R*)-Tsdpen](*p*-cymene) catalyst **3** and 4.0 equivalent amount of azeotrope of formic acid and triethylamine at 40 °C in tetrahydrofuran under an argon atmosphere, we indeed observed the desirable reductive product **2a** after 4 h in full conversion with 99.3% ee (Table 1, entry 1). Subsequently, solvent optimization demonstrated that dimethylformamide, dichloromethane, ethyl acetate and ethanol could afford excellent conversions and enantioselectivities (entries 2–5). When isopropanol was used as solvent, the conversion declined to 57% (entry 6). Considering the low toxicity and operational convenience, ethyl acetate was chosen as the solvent for further optimization. Moreover, the results were not affected when decreasing the dosage of reductant to 2 equivalents (entry 7). Gratifyingly, we found that both enantioseletivity and reactivity could maintain at 0.2 mmol scale in 96% yield and with 99.5% ee (entry 8), and determined entry 8 as optimal conditions. Then, *cis* isomer of 2,2,5-trisubstituted cyclohexane-1,3-dione *cis*-**4a** was also tried under the above optimal condition (entry 9). To our delight, excellent 99% ee and 95% isolated yield could be still obtained.

Having optimized the reaction, we proceeded to investigate the substrate scope and functional group tolerance (Scheme 2). The reaction was found to tolerate an array of functional groups on the aromatic ring of the 2-position substituents, including both electron-donating and -withdrawing substituents in all of the *ortho*-, *meta*- and *para*-



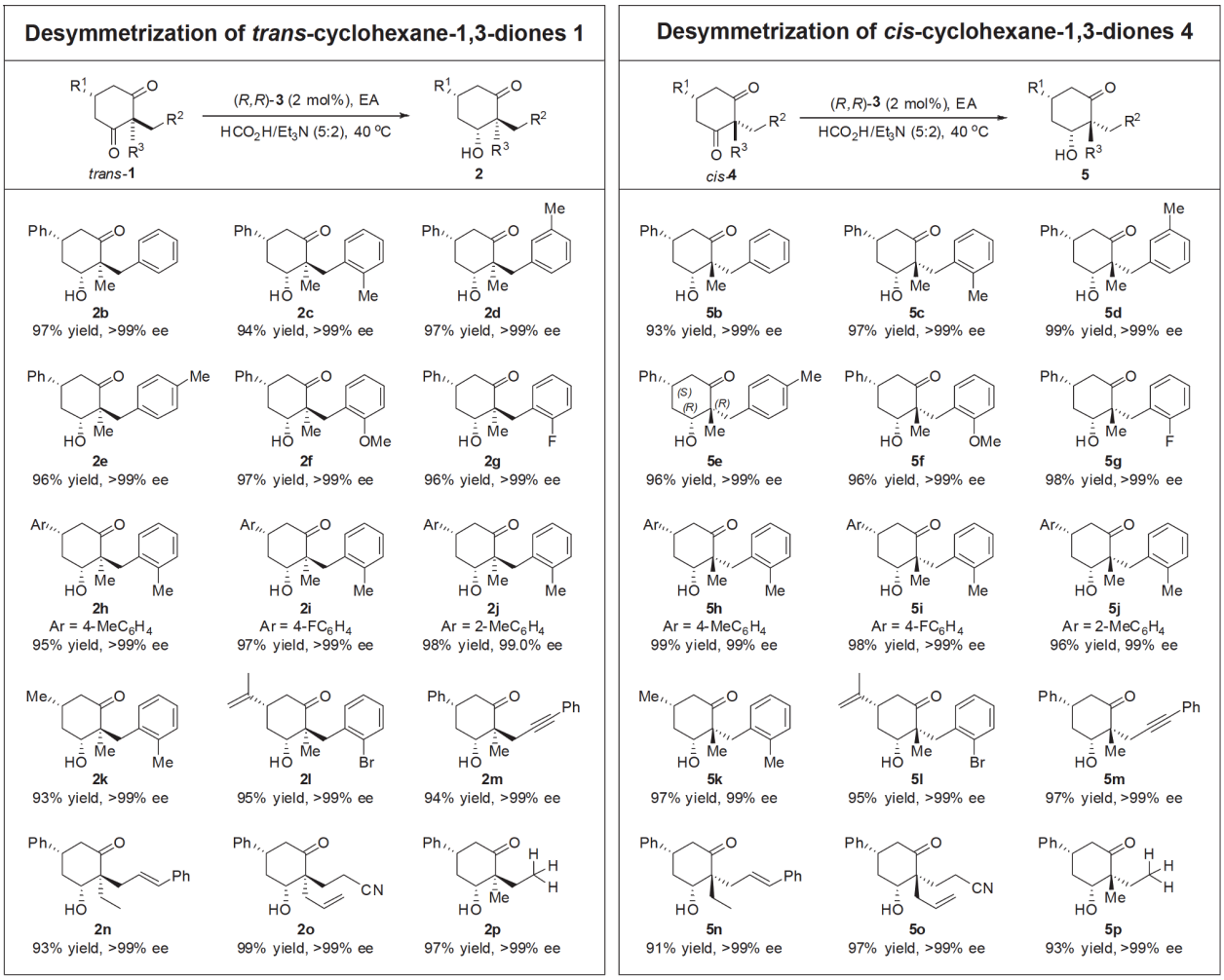

**Scheme 1** Mono-reduction of cyclic 1,3-diketones.

**Table 1** Optimization of the reaction conditions




| Entry[a] | Substrate | Solvent | Conv. (%)[b] | ee (%)[c] |
|---|---|---|---|---|
| 1 | *trans*-**1a** | THF | >95 | 99.3 |
| 2 | *trans*-**1a** | DMF | >95 | 99.5 |
| 3 | *trans*-**1a** | DCM | >95 | 99.6 |
| 4 | *trans*-**1a** | EA | >95 | 99.6 |
| 5 | *trans*-**1a** | EtOH | >95 | 99.5 |
| 6 | *trans*-**1a** | $^{i}$PrOH | 57 | 99.2 |
| 7[d] | *trans*-**1a** | EA | >95 | 99.6 |
| 8[e] | *trans*-**1a** | EA | >95 (96)[f] | 99.5 |
| 9[e] | *cis*-**4a** | EA | >95 (95)[f] | 99.9 |

a) Conditions: **1a** (0.15 mmol), (*R*,*R*)-**3** (2.0 mol%), $HCO_2H/Et_3N$ (4 equiv.), solvent (1.0 mL), 40 °C, 4 h, dr>20:1. THF: tetrahydrofuran, DMF: *N*,*N*-dimethylformamide, DCM: dichloromethane, EA: ethyl acetate. b) Determined by NMR. c) Determined by HPLC. d) 2 Equivalent amount of $HCO_2H/Et_3N$ was used. e) 0.20 mmol scale. f) Isolated yields.



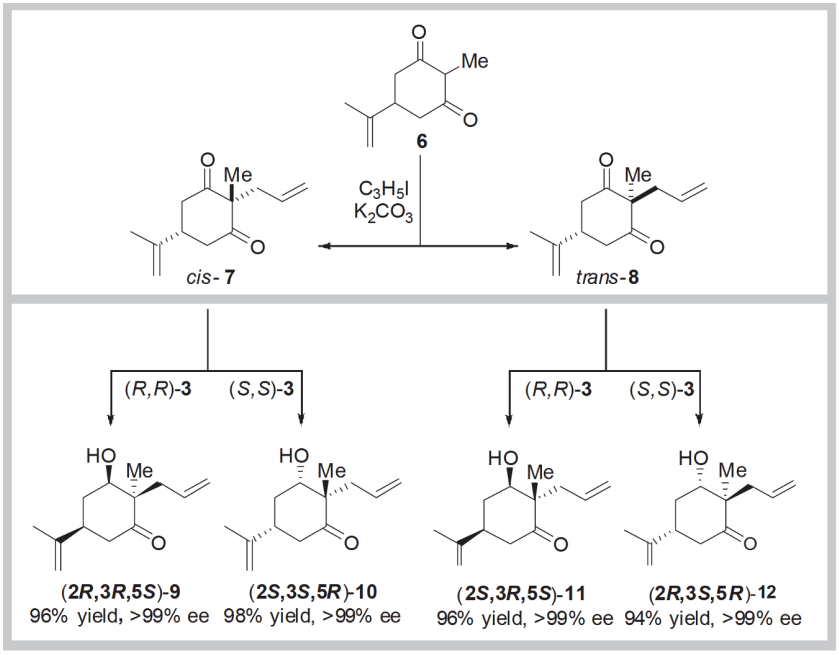

**Scheme 2** Substrate scope of *trans*- and *cis*-2,2,5-trisubstituted cyclohexane-1,3-diones.

positions (**2a**–**2g**). Next, we switched focus on the diverse 5-position substituents of 1,3-cyclohexanediones. The corresponding *para*-fluoro, *para*-methyl and *ortho*-methyl substituted on the aromatic ring at 5-position delivered the desirable products **2h**–**2j** in excellent yields, enantio- and diastereoselectivities. Presumably due to steric hindrance, substrate **2j** required longer reaction time to obtain 98% yield. Diketones with an alkyl group at 5-position were also suitable reaction partners (**2k**, **2l**). Functional groups such as phenylpropargyl (**2m**), cinnamyl (**2n**) and cyanoethyl (**2o**) could be tolerated without erosion of enatioselectivity and reactivity. Notably, the excellent results could still be acquired when there were two substituents virtually equal in size at the 2-position, such as Me and Et (**2p**).

Next, the transfer hydrogenative desymmetrization of a series of *cis* isomers of diketones *cis*-**4** (16 examples) was achieved, giving the desirable products with excellent yields, diastereoseletivities and enantioselectivities regardless of the steric and electronic effect and functional groups.

To determine the absolute configuration of the products, we were fortunate to get single crystals of the products (−)-**2a** and (−)-**5e**. After X-ray crystallographic analysis, the absolute configurations of (−)-**2a** and (−)-**5e** were assigned as (2*S*,3*R*,5*S*)-**2a** and (2*R*,3*R*,5*S*)-**5e**, respectively. We discovered that the configuration of the hydroxyl group was remotely controlled by the 5-phenyl and had nothing to do with the substituents at the 2-position. However, the reaction rate of the *cis* substrate was higher than that of the *trans*, possibly due to the different steric hindrance of the substituents.

We then set out to establish the availability of the stereodivergent access to four stereoisomers **9**, **10**, **11** and **12** (Scheme 3) from the same readily available starting material **6**. Under the optimized condition, the reactions of *cis*-**7** and *trans*-**8** proceeded smoothly, affording four stereoisomers of **9**, **10**, **11** and **12** in high yields with >99% ee and >20:1 dr. The identity and configuration of diastereomers **10** and **12** were confirmed in comparison with the known data in the literature [14]. To our delight, the synthetic utilization of **10** was demonstrated in the formal synthesis of (−)-iso-



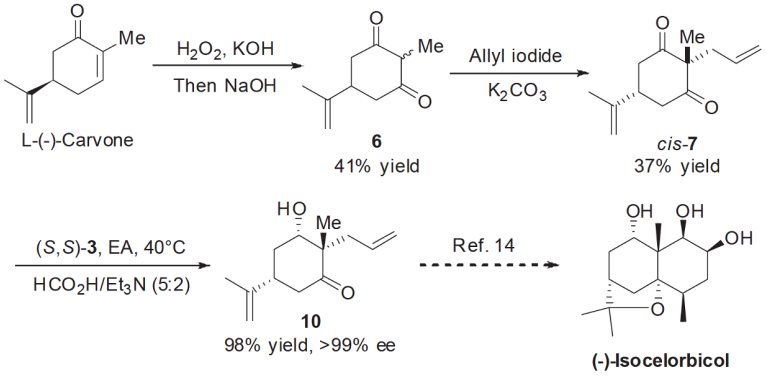

**Scheme 3** The stereodivergent synthesis of four stereoisomers.

celorbicol [14], which was found in many plants of the family *Celastraceae*, as shown in Scheme 4. The key intermediate hydroxyl ketone **10** could be obtained by transfer hydrogenative desymmetrization of diketone **7** which was acquired from (−)-Carvone through epoxidation, hydrolysis and alkylation [15].

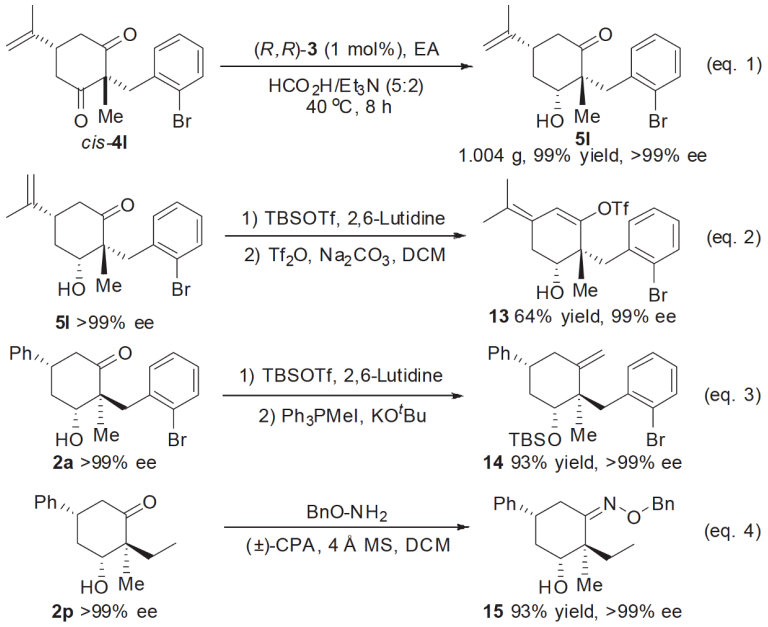
This desymmetrization reaction could be scaled up smoothly at gram scale without any loss of enantioselectivity and reactivity (Scheme 5, eq. (1)). Meanwhile, the utility of hydroxyl cyclohexanone products as building blocks for further elaboration was demonstrated in Scheme 5. We first tried to protect the hydroxy groups in **5l** with *tert*-butyldimethylsilyl (TBS) and completed the conversion of carbonyl to vinyl triflate subsequently based on a related procedure reported by Weix *et al*. [16]. Fortuitously, the more stable conjugated olefin **13** was obtained (eq. (2)), which probably underwent an isomerization. Furthermore, the protection of **2a** with TBS and Wittig olefination [10d] afforded terminal olefin **14** in 93% yields (eq. (3)). In addition, chiral oxime ether **15** could be obtained with 93% yield by reaction of **2p** and *O*-benzyl-hydroxylamine [17] in the presence of phosphoric acid (eq. (4)).

## 4 Conclusions

In conclusion, we successfully realized the construction of three stereocenters in one step, in which two discontiguous chiral centers and a chiral quaternary carbon were presented. This method, totally scalable and operationally simple, allowed the hydrogenative desymmetrization of *cis* and *trans* 2,2,5-trisubstituted cyclohexane-1,3-diones with a diverse




**Scheme 4** Formal synthesis of (−)-isocelorbicol.




**Scheme 5** Gram scale experiment and elaborations.

scope of functional groups showing excellent yields and perfect enantioselectivities. Moreover, stereodivergent syntheses of four stereoisomers were accessed by combination of substrates and chiral ruthenium catalysts. Using the above methodology as the key step, a formal synthesis of the natural product (−)-isocelorbicol was achieved. Derivatizations of the reductive product hydroxyl cyclohexanones were also demonstrated, showcasing the synthetic versatility of the constructed products.

**Acknowledgements** This work was supported by the National Natural Science Foundation of China (21532006, 21690074) and Chinese Academy of Sciences (XDB17020300, SSW-SLH035).

**Conflict of interest** The authors declare no conflict of interest.

**Supporting information** The supporting information is available online at http://chem.scichina.com and http://link.springer.com/journal/11426. The supporting materials are published as submitted, without typesetting or editing. The responsibility for scientific accuracy and content remains entirely with the authors.

1 For selected reviews on desymmetrization, see: (a) Willis MC. *J Chem Soc Perkin Trans 1*, 1999, 1: 1765; (b) García-Urdiales E, Alfonso I, Gotor V. *Chem Rev*, 2005, 105: 313–354; (c) Borissov A, Davies TQ, Ellis SR, Fleming TA, Richardson MSW, Dixon DJ. *Chem Soc Rev*, 2016, 45: 5474–5540; (d) Zeng XP, Cao ZY, Wang YH, Zhou F, Zhou J. *Chem Rev*, 2016, 116: 7330–7396

2 (a) Wadamoto M, Phillips EM, Reynolds TE, Scheidt KA. *J Am Chem Soc*, 2007, 129: 10098–10099; (b) Mori K, Katoh T, Suzuki T, Noji T, Yamanaka M, Akiyama T. *Angew Chem Int Ed*, 2009, 48: 9652–9654; (c) Phillips EM, Wadamoto M, Scheidt KA. *Synthesis*, 2009, 4: 687–690; (d) Ou J, Wong WT, Chiu P. *Org Biomol Chem*, 2012, 10: 5971–5978; (e) Cuadros S, Dell'Amico L, Melchiorre P. *Angew Chem Int Ed*, 2017, 56: 11875–11879

3 (a) Burns AR, Madec AGE, Low DW, Roy ID, Lam HW. *Chem Sci*, 2015, 6: 3550–3555; (b) Feng J, Lin L, Yu K, Liu X, Feng X. *Adv Synth Catal*, 2015, 357: 1305–1310

4 Yang M, Zhao YM, Zhang SY, Tu YQ, Zhang FM. *Chem Asian J*, 2011, 6: 1344–1347

5 Shi LM, Dong WW, Tao HY, Dong XQ, Wang CJ. *Org Lett*, 2017, 19: 4532–4535

6 (a) Grogan G, Graf J, Jones A, Parsons S, Turner NJ, Flitsch SL. *Angew Chem Int Ed*, 2001, 40: 1111–1114; (b) Hill CL, Hung LC, Smith DJ, Verma CS, Grogan G. *Adv Synth Catal*, 2007, 349: 1353–1360

7 (a) Phillips EM, Roberts JM, Scheidt KA. *Org Lett*, 2010, 12: 2830–2833; (b) Reddi Y, Sunoj RB. *Org Lett*, 2012, 14: 2810–2813; (c) Yao L, Zhu Q, Wei L, Wang ZF, Wang CJ. *Angew Chem Int Ed*, 2016, 55: 5829–5833; (d) Zhu C, Wang D, Zhao Y, Sun WY, Shi Z. *J Am Chem Soc*, 2017, 139: 16486–16489; (e) Schneider LM, Schmiedel VM, Pecchioli T, Lentz D, Merten C, Christmann M. *Org Lett*, 2017, 19: 2310–2313; (f) Cai J, Wei Q, Hu XD, Zhang Y, Li W, Cong H, Liu W, Liu WB. *Synthesis*, 2018, 50: 1661–1666; (g) Zhu T, Liu Y, Smetankova M, Zhuo S, Mou C, Chai H, Jin Z, Chi YR. *Angew Chem Int Ed*, 2019, 58: 15778–15782; (h) Donthoju A, Magham LR, Singh N, Manjula N, Chegondi R. *J Org Chem*, 2019, 84: 15735–15744

8 (a) Brooks DW, Mazdiyasni H, Chakrabarti S. *Tetrahedron Lett*, 1984, 25: 1241–1244; (b) Brooks DW, Mazdiyasni H, Grothaus PG. *J Org Chem*, 1987, 52: 3223–3232; (c) Wei ZL, Li ZY, Lin GQ. *Tetrahedron-Asymmetry*, 2001, 12: 229–233; (d) Iwamoto M, Kawada H, Tanaka T, Nakada M. *Tetrahedron Lett*, 2003, 44: 7239–7243

9 (a) Corey EJ, Helal CJ. *Angew Chem Int Ed*, 1998, 37: 1986–2012; (b) Shimizu M, Yamada S, Fujita Y, Kobayashi F. *Tetrahedron-Asymmetry*, 2000, 11: 3883–3886; (c) Yeung , Chein RJ, Corey EJ. *J Am Chem Soc*, 2007, 129: 10346–10347

10 (a) Shi B, Merten S, Wong DKY, Chu JCK, Liu LL, Lam SK, Jäger A, Wong WT, Chiu P, Metz P. *Adv Synth Catal*, 2009, 351: 3128–3132; (b) Kuang L, Liu LL, Chiu P. *Chem Eur J*, 2015, 21: 14287–14291; (c) Gong Q, Wen J, Zhang X. *Chem Sci*, 2019, 10: 6350–6353; (d) Yu CB, Wang HD, Song B, Shen HQ, Fan HJ, Zhou YG. *Sci China Chem*, 2020, 63: 215–221; (e) Wang H, Zhao Y, Ding YX, Yu CB, Zhou YG. *Asian J Org Chem*, 2020, 9: 753–756

11 Yu CB, Song B, Chen MW, Shen HQ, Zhou YG. *Org Lett*, 2019, 21:

9401–9404
12 (a) Kitamura M, Ohkuma T, Inoue S, Sayo N, Kumobayashi H, Akutagawa S, Ohta T, Takaya H, Noyori R. *J Am Chem Soc*, 1988, 110: 629–631; (b) Fujii A, Hashiguchi S, Uematsu N, Ikariya T, Noyori R. *J Am Chem Soc*, 1996, 118: 2521–2522; (c) Noyori R, Ohkuma T. *Angew Chem Int Ed*, 2001, 40: 40–73; (d) Wu Y, Geng Z, Bai J, Zhang Y. *Chin J Chem*, 2011, 29: 1467–1472; (e) Cotman AE, Cahard D, Mohar B. *Angew Chem Int Ed*, 2016, 55: 5294–5298
13 (a) Clay DR, Rosenberg AG, McIntosh MC. *Tetrahedron-Asymmetry*, 2011, 22: 713–716; (b) Hong Y, Chen J, Zhang Z, Liu Y, Zhang W. *Org Lett*, 2016, 18: 2640–2643
14 (a) Huffman JW, Raveendranath PC. *Tetrahedron*, 1987, 43: 5557–5565; (b) Kumaran RS, Mehta G. *Tetrahedron*, 2015, 71: 1718–1731
15 Zhan Y, Zhang XW, Xiong Y, Li BL, Nan FJ. *Org Biomol Chem*, 2016, 14: 747–751
16 Olivares AM, Weix DJ. *J Am Chem Soc*, 2018, 140: 2446–2449
17 Nimmagadda SK, Mallojjala SC, Woztas L, Wheeler SE, Antilla JC. *Angew Chem Int Ed*, 2017, 56: 2454–2458