Asymmetric Catalysis

How to cite:
International Edition: doi.org/10.1002/anie.202009594
German Edition: doi.org/10.1002/ange.202009594

Oxidative Kinetic Resolution of Cyclic Benzylic Ethers

*Shutao Sun, Yingang Ma, Ziqiang Liu, and Lei Liu**

Abstract: *A manganese-catalyzed oxidative kinetic resolution of cyclic benzylic ethers through asymmetric C(sp^3)–H oxidation is reported. The practical approach is applicable to a wide range of 1,3-dihydroisobenzofurans bearing diverse functional groups and substituent patterns at the α position with extremely efficient enantiodiscrimination. The generality of the strategy was further demonstrated by efficient oxidative kinetic resolution of another type of five-membered cyclic benzylic ether, 2,3-dihydrobenzofurans, and six-membered 6H-benzo[c]chromenes. Direct late-stage oxidative kinetic resolution of bioactive molecules that are otherwise difficult to access was further explored.*

Asymmetric oxidation is a powerful and efficient strategy to access valuable optically pure compounds.[1] Significant progress has been made in asymmetric oxidation of reactive functional groups such as alkenes and sulfides. However, enantioselective oxidation of much less reactive aliphatic C–H bonds by nonenzymatic means has remained a daunting challenge.[2] Only a few examples of nonenzymatic asymmetric C–H oxidation have been reported, which typically suffer from moderate enantiocontrol, low substrate conversion, and narrow substrate scope.[3,4] Developing an efficient catalytic asymmetric C–H oxidation with practical value for synthesis would be highly desirable.

Optically pure α-substituted cyclic benzylic ethers are key structural motifs spread across medicinally relevant natural products and synthetic pharmaceuticals. Considerable advances have been made in their asymmetric synthesis through manipulation of prefunctionalized olefins or acetals.[5] However, each method is typically suitable for specific ether skeleton and α-functionality. Given the ready availability of structurally diverse racemic cyclic benzylic ethers, oxidative kinetic resolution (OKR) through enantioselective oxidation of C(sp^3)–H bonds adjacent to ether oxygen would be an attractive strategy to access optically pure ethers with diverse skeletons and α-substituent patterns.[6] Existing KR studies initiated by asymmetric C–H oxidation predominantly focused on secondary alcohols and amines.[7,8] To our knowledge, KR of ethers through asymmetric oxidation of C–H bond adjacent to ether oxygen has never been disclosed to date.[9]

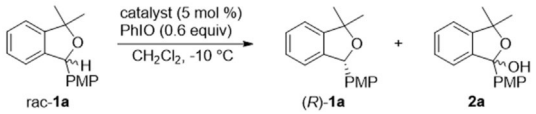
Compared with alcohols and amines, cyclic benzylic ethers lack a strong interaction site with catalyst, which is typically indispensable in asymmetric catalysis to engage both desired reactivity and selectivity by directing substrate to an ideal location in the transition state. Accordingly, chiral discrimination of two ether enantiomers of the racemate would be particularly difficult to achieve. We envisioned that the key to success in OKR of benzylic ethers lies in discovering a chiral catalyst with rigid scaffold whose specificity and catalytic power come from the inflexible fit of the right enantiomer onto the preformed catalyst surface. As part of our ongoing interest in developing practical synthetic methods through sustainable asymmetric C–H oxidation strategy,[8b] we now report a manganese-catalyzed OKR of cyclic benzylic ethers.

α-Substituted 1,3-dihydroisobenzofurans are present in a number of bioactive molecules.[10] Surprisingly, few asymmetric synthetic methods have been established.[11] Therefore, OKR of ether rac-**1a** was initially used as the reference reaction with PhIO as the oxo-transfer agent to search for a suitable chiral catalyst (Table 1). Chiral Mn(salen) **C1** exhibited oxidation catalysis reactivity, though poor enantioselectivity was obtained (entry 1). We envisioned that properly introducing an axial chirality at C3(3′) sites of the basal salen ligand would enhance the ability of Mn(salen) catalyst in differentiating the two enantiomers. Delightedly, promising chiral discrimination was observed when Mn(salen) **C2–C5** bearing binaphthyl groups of axial chirality were employed, and the R_a,*S* Mn(salen) **C4** proved to be optimal (entries 2–5).[3c] Further fine-tuning the binaphthyl moiety identified **C9** to be the superior catalyst (entries 6–10). Temperature and addition manner of oxidant were found to be crucial to achieving an extremely high chiral recognition, and when PhIO (0.6 equiv) was added as six equal portions in 30 min intervals at −40 °C, (*R*)-**1a** was isolated in 49 % yield with 98 % *ee* (K_{rel} = 152.9; entries 11–14).

The scope of OKR of α-substituted 1,3-dihydroisobenzofurans was then investigated (Scheme 1). In general, substrates bearing either electron-donating or electron-withdrawing substituents around the 1,3-dihydroisobenzofuran arene were tolerated, and respective **1a–1g** were recovered in good efficiency with 95–99 % *ee* (Scheme 1 A).[12a] Modification of the geminal C1 disubstitution did not impair the reactivity and enantioselectivity for **1h–1l**. Notably, spirocyclic **1i–1k** with different ring size and substituent pattern were well compatible with oxidation process. Moreover, ether **1l** bearing two stereogenic centers at α positions was competent component with good enantiodiscrimination. A modest *ee* value was observed for **1m** without a C3 substituent probably owing to competitive oxidation of the C_3–H bond. OKR of ethers **1n–1t** bearing a wide range of electronically varied

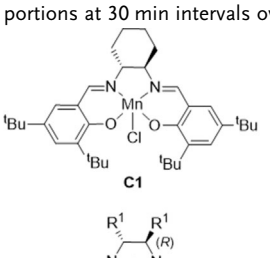
[*] S. Sun, Y. Ma, Z. Liu, Prof. Dr. L. Liu
School of Pharmaceutical Sciences, Shandong University
Jinan 250100 (P. R. China)
E-mail: leiliu@sdu.edu.cn
S. Sun, Prof. Dr. L. Liu
School of School of Chemistry and Chemical Engineering
Shandong University
Jinan 250100 (P. R. China)
Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under:
https://doi.org/10.1002/anie.202009594.

Table 1: Optimization of the reaction conditions.[a]



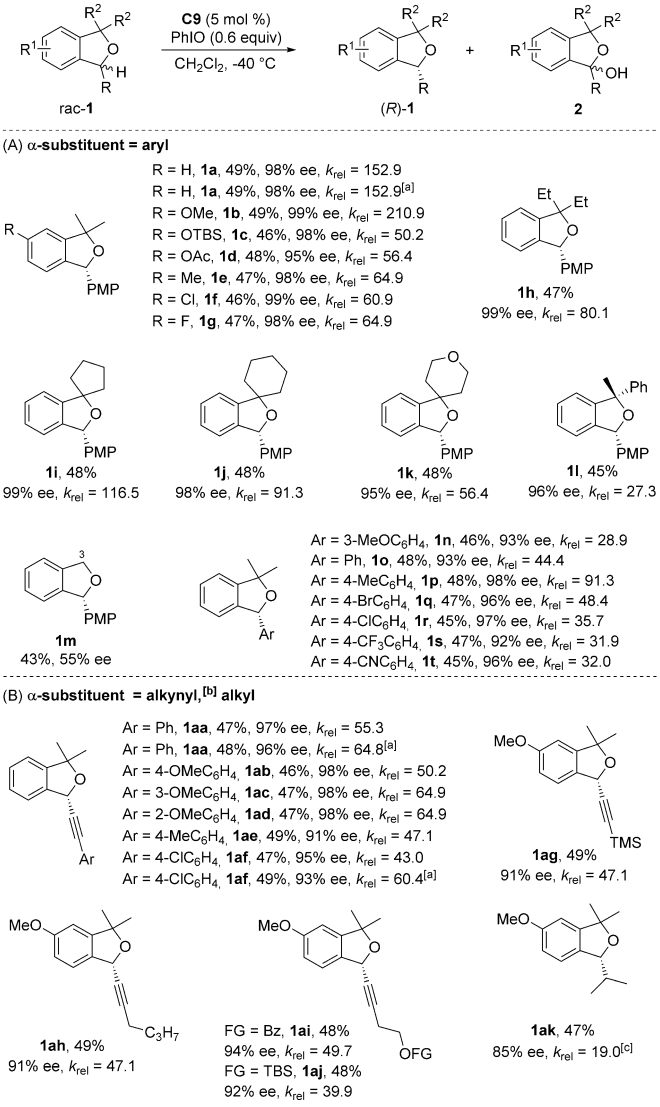
Entry	Catalyst	Conv. [%][b]	*ee* [%][c]	K_{rel}
1	**C1**	30	5	1.3
2	**C2**	38	23	2.7
3	**C3**	41	25	2.7
4	**C4**	37	45	11.7
5	**C5**	40	49	10.5
6	**C6**	39	20	2.3
7	**C7**	36	3	1.1
8	**C8**	42	26	2.7
9	**C9**	38	56	38.9
10	**C10**	37	8	1.4
11[d]	**C9**	46	79	64.1
12[e]	**C9**	32	41	21.7
13[d,f]	**C9**	49	91	117.4
14[d,g]	**C9**	51	98	152.9

[a] Reaction conditions: rac-**1a** (0.1 mmol), catalyst (5 mol%), and PhIO (0.06 mmol) in CH_2Cl_2 (1.0 mL) at −10°C for 2 h, unless otherwise noted. [b] Conversion was calculated from the yield of recovered **1a**. [c] Determined by HPLC analysis on a chiral stationary phase. [d] Reaction at −40°C. [e] Reaction at −60°C. [f] PhIO was added in three portions at 30 min intervals over 1.5 h. [g] PhIO was added in six portions at 30 min intervals over 2.5 h. PMP = 4-MeOC_6H_4.



C4: R^1 = -$(CH_2)_4$-, R^2 = Ph
C5: R^1 = R^2 = Ph
C6: R^1 = -$(CH_2)_4$-, R^2 = 3,5-$(CH_3)_2C_6H_3$
C7: R^1 = -$(CH_2)_4$-, R^2 = 3,5-$(CF_3)_2C_6H_3$
C8: R^1 = -$(CH_2)_4$-, R^2 = 4-$SiMe_3C_6H_4$
C9: R^1 = -$(CH_2)_4$-, R^2 = 4-PhC_6H_4
C10: R^1 = -$(CH_2)_4$-, R^2 = 2-naphthyl

C2: R^1 = -$(CH_2)_4$-, R^2 = Ph
C3: R^1 = R^2 = Ph



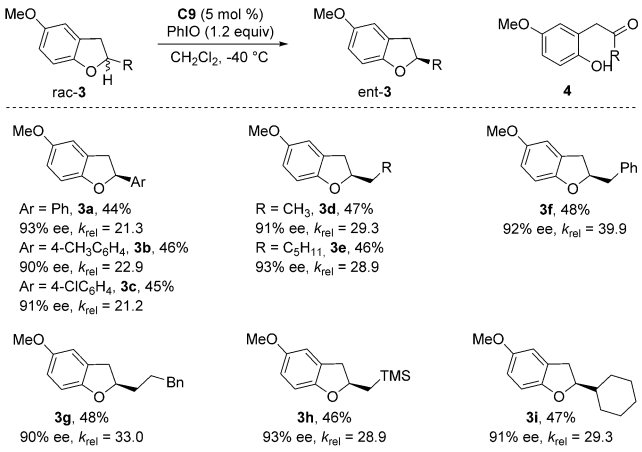
Scheme 1. Scope of the reaction of 1,3-dihydroisobenzofurans. Yields are for recovered **1**. [a] Reaction with 0.5 mmol of rac-**1**. [b] Catalyst **C3** (5 mol%) was used. [c] Catalyst **C9** (5 mol%) was used. Bz = benzoyl, TBS = *tert*-butyldimethylsilyl.

α-aryl groups proceeded smoothly. α-Alkynyl-substituted ethers were also competent components, as demonstrated by effective OKR of aryl acetylenes **1aa**–**1af** and alkyl acetylenes **1ag**–**1aj**.[12b] Commonly encountered functionalities were well tolerated as additional functional handles. Notably, α-alkynyl-substituted 1,3-dihydroisobenzofurans cannot be prepared with existing asymmetric methods. The skeleton **1ak** with an α-alkyl substituent was also tolerated.

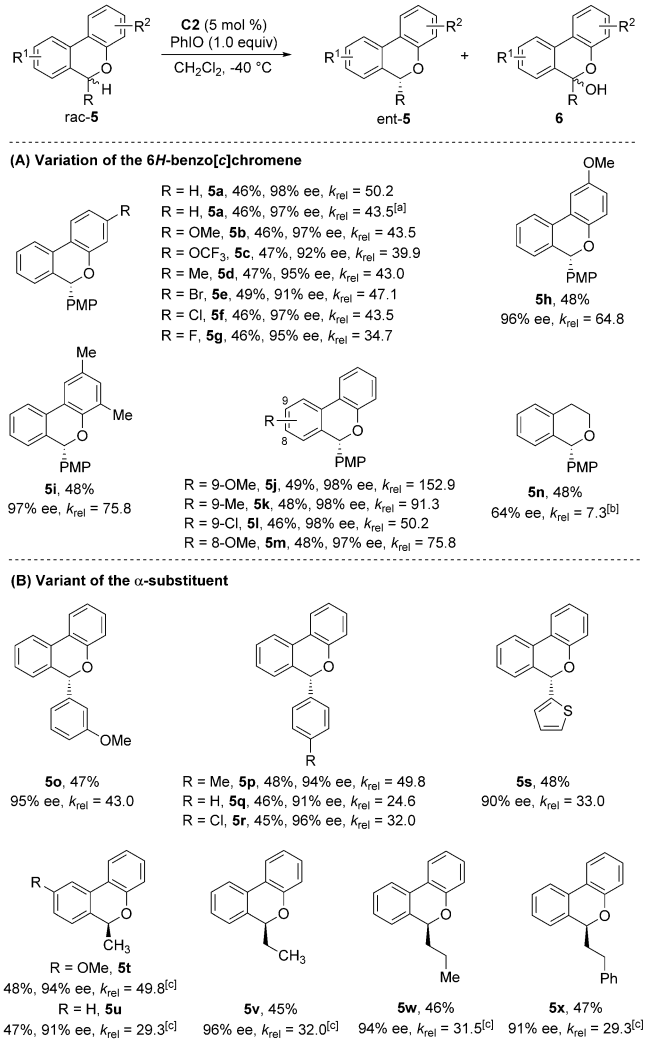
To further demonstrate the generality in asymmetric access to diverse cyclic benzylic ethers, OKR of 2,3-dihydrobenzofurans, the other type of biologically important five-membered skeleton, was next examined (Scheme 2). Ethers **3a**–**3c** bearing electronically varied α-aryl moieties were tolerated. No identifiable oxidized product was detected, which might be ascribed to over-oxidation of phenol **4** by PhIO. 2,3-Dihydrobenzofurans containing diverse α-alkyl substituents were also competent candidates, as demonstrated by isolating enantiopure **3d**–**3i** with good selectivity factors.

Besides five-membered cyclic benzylic ethers, the applicability to six-membered cyclic benzylic ethers was then studied (Scheme 3). In general, substituents on either arene ring of 6*H*-benzo[*c*]chromene skeleton were well-tolerated, and respective **5a**–**5m** were resolved with excellent selectivity factors (34.7–152.9).[12c] OKR of isochroman **5n** proceeded with a modest selectivity factor. Racemic **5o**–**5s** containing a range of electronically varied aryl and heteroaryl moieties at α position participated in OKR process smoothly. α-Alkyl-substituted **5t**–**5x** were also well tolerated.

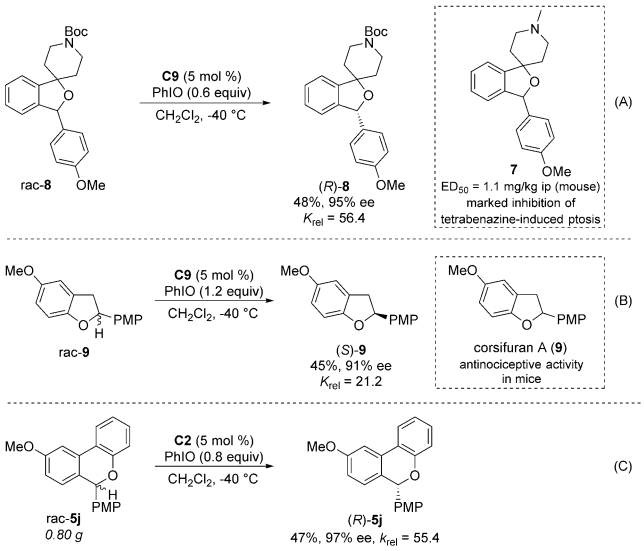
Perhaps the most striking advance of the strategy would be direct late-stage OKR of bioactive molecules that are otherwise difficult to access (Scheme 4). α-PMP-substituted 3*H*-spiro[isobenzofuran-1,4′-piperidine] **7** is a potential therapeutic agent to central nervous system with marked anti-



Scheme 2. Scope of the reaction of 2,3-dihydrobenzofurans. TMS = trimethylsilyl.



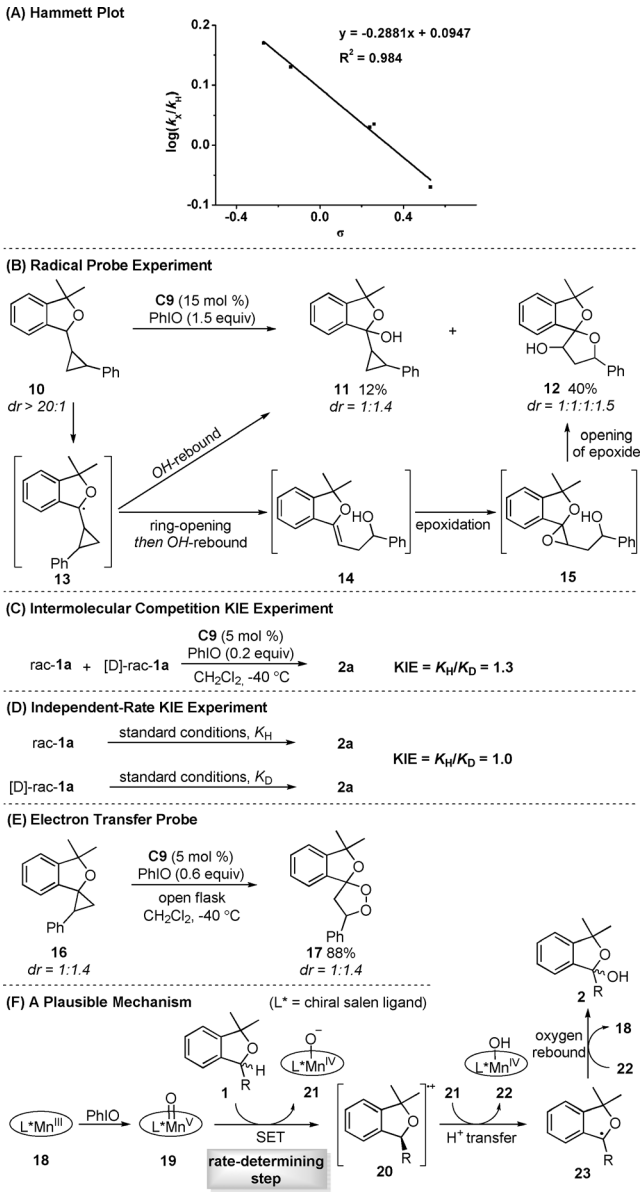
Scheme 3. OKR of α-substituted 6*H*-benzo[*c*]chromenes. [a] Reaction with 0.5 mmol of rac-**5a**. [b] Catalyst **C3** (5 mol%) was used. [c] Catalyst **C9** (5 mol%) was used.



Scheme 4. Synthetic utility and gram-scale reaction study.

tetrabenazine activity (Scheme 4A).[10a] Under standard conditions, rac-**8** underwent OKR process smoothly, and (*R*)-**8** was recovered in 48% yield with 95% *ee* (K_{rel} = 56.4). Corsifuran A (**9**) is isolated from the Mediterranean liverwort *Corsinia coriandrina*, and exhibits promising antinociceptive effect in mice (Scheme 4B).[13] OKR of rac-**9** proceeded, and remaining (*S*)-**9** was isolated in 45% yield with 91% *ee* (K_{rel} = 21.2).[12c] A gram-scale reaction proceeded without obvious loss of selectivity factor, as demonstrated by recovery of (*R*)-**5j** in 47% yield with 97% *ee* (Scheme 4C).

Mechanistic studies were performed to get a preliminary understanding of manganese-catalyzed OKR of cyclic benzylic ethers (Scheme 5). The Hammett plot ($\log(k_X/k_H)$ versus σ) for competitive oxidation of **1o** and respective **1a** and **1p**–**1s** was shown in Scheme 5A.[14] The observed plot displayed linear correlation with a ρ value of −0.288 (R^2 = 0.98). Good linearity suggests that oxidation proceeds through a single mechanism.[15a,b] The quite small negative value of ρ together with the poor correlation with σ^+ (R^2 = 0.92, see the Supporting Information) indicate the absence of obvious charge separation in the transition state.[15c,d,16] Radical clock experiment was next performed (Scheme 5B). Subjecting cyclopropane **10** to asymmetric oxidation conditions provided a mixture of hydroxylated **11** and spirocyclic ether **12**. We envisioned that both **11** and **12** should be generated from carbon-centered radical **13**. In general, there are two plausible mechanisms for converting **10** to **13**, which are 1) one-step hydrogen atom transfer (HAT) and 2) single electron transfer (SET) followed by proton transfer.[17] Competitive and independent deuterium kinetic isotope effect (KIE) studies of rac-**1a** and [D]-rac-**1a** revealed respective KIE of 1.3 and 1.0 (Schemes 5C and D).[18] These values suggested that the C–H bond cleavage should not be involved in the rate-determining step. Given that manganese-catalyzed HAT typically exhibits a high KIE, the HAT pathway might be excluded for this reaction.[17] Instead, it has been reported that manganese-catalyzed C–H oxidation with a KIE around 1.0



Scheme 5. Mechanistic studies.

might proceed through a pathway involving a sequential rate-determining SET followed by a proton transfer.[19] Accordingly, electron transfer probe experiment was next conducted (Scheme 5E).[20] Under standard conditions with flask open to air, cyclopropane **16** was efficiently transformed to endoperoxide **17** in 88% yield. No reaction was observed in the absence of either manganese **C9** or PhIO. The observation indicates that the SET pathway might be viable. Based on above observations, a plausible mechanistic pathway for OKR of ether **1** were suggested (Scheme 5F). Chiral Mn^{III} catalyst **18** is first oxidized by PhIO giving oxoMn^{V} intermediate **19**. Ether **1** underwent single electron oxidation by **19**, giving radical cation **20** and Mn^{IV} **21**. A proton transfer from **20** to **21** furnished benzylic radical **23** and Mn^{IV}–OH **22**. Finally, the rebound of incipient substrate radical **23** to **22** affords hemiacetal **2** and regenerates Mn^{III} **18**. Based on the absolute configuration of recovered 1,3-dihydroisobenzofurans, (*S*)-**1** should be oxidized more preferentially than (*R*)-**1**.

In summary, the first OKR of cyclic benzylic ethers has been established. The practical manganese-catalyzed asymmetric C(sp^3)–H oxidation is applicable to a range of five-membered 1,3-dihydroisobenzofurans and 2,3-dihydrobenzofurans together with six-membered 6*H*-benzo[*c*]chromenes bearing diverse α-substituent patterns with extremely efficient enantiodiscrimination. The direct late-stage OKR of bioactive molecules that are otherwise difficult to access was further investigated. This strategically different approach would unlock opportunities for topologically straightforward synthetic planning for asymmetric access to diversely substituted cyclic benzylic ethers.

Acknowledgements

We gratefully acknowledge the National Science Foundation of China (21722204 and 21971148).

Conflict of interest

The authors declare no conflict of interest.

Keywords: asymmetric C–H oxidation · cyclic benzylic ethers · kinetic resolution · late-stage oxidation · synthetic methods

[1] For selected reviews on catalytic asymmetric oxidation, see: a) H. C. Kolb, M. S. VanNieuwenhze, K. B. Sharpless, *Chem. Rev.* **1994**, *94*, 2483; b) J. F. Larrow, E. N. Jacobsen, *Top. Organomet. Chem.* **2004**, *6*, 123; c) O. A. Wong, Y. Shi, *Chem. Rev.* **2008**, *108*, 3958; d) C.-M. Che, J.-S. Huang, *Chem. Commun.* **2009**, 3996; e) M. J. Schultz, M. S. Sigman, *Tetrahedron* **2006**, *62*, 8227.

[2] a) T. Newhouse, P. S. Baran, *Angew. Chem. Int. Ed.* **2011**, *50*, 3362; *Angew. Chem.* **2011**, *123*, 3422; b) M. Milan, M. Bietti, M. Costas, *Chem. Commun.* **2018**, *54*, 9559.

[3] For the asymmetric oxidation of benzylic C–H bonds, see: a) J. T. Groves, P. Viski, *J. Am. Chem. Soc.* **1989**, *111*, 8537; b) J. F. Larrow, E. N. Jacobsen, *J. Am. Chem. Soc.* **1994**, *116*, 12129; c) K. Hamachi, R. Irie, T. Katsuki, *Tetrahedron Lett.* **1996**, *37*, 4979; d) R. Zhang, W.-Y. Yu, T.-S. Lai, C.-M. Che, *Chem. Commun.* **1999**, 1791; e) H. Srour, P. L. Maux, G. Simonneaux, *Inorg. Chem.* **2012**, *51*, 5850; f) E. P. Talsi, D. G. Samsonenko, R. V. Ottenbacher, K. P. Bryliakov, *ChemCatChem* **2017**, *9*, 4580; g) F. Burg, M. Gicquel, S. Breitenlechner, A. Pöthig, T. Bach, *Angew. Chem. Int. Ed.* **2018**, *57*, 2953; *Angew. Chem.* **2018**, *130*, 3003; h) A. H. Abazid, N. Clamor, B. J. Nachtsheim, *ACS Catal.* **2020**, *10*, 8042.

[4] For C–H oxidation enabling enantioselective desymmetrization, see: a) A. Miyafuji, T. Katsuki, *Tetrahedron* **1998**, *54*, 10339; b) S.-I. Murahashi, S. Noji, T. Hirabayashi, N. Komiya, *Tetrahedron: Asymmetry* **2005**, *16*, 3527; c) J. R. Frost, S. M. Huber, S. Breitenlechner, C. Bannwarth, T. Bach, *Angew. Chem. Int. Ed.* **2015**, *54*, 691; *Angew. Chem.* **2015**, *127*, 701; d) M. Milan, M. Bietti, M. Costas, *ACS Cent. Sci.* **2017**, *3*, 196; e) B. Qiu, D. Xu, Q. Sun, C. Miao, Y.-M. Lee, X.-X. Li, W. Nam, W. Sun, *ACS Catal.* **2018**, *8*, 2479; f) M. Cianfanelli, G. Olivo, M. Milan, R. J. M. K. Gebbink, X. Ribas, M. Bietti, M. Costas, *J. Am. Chem. Soc.* **2020**, *142*, 1584.

[5] a) S. E. Reisman, A. G. Doyle, E. N. Jacobsen, *J. Am. Chem. Soc.* **2008**, *130*, 7198; b) P. N. Moquist, T. Kodama, S. E. Schaus, *Angew. Chem. Int. Ed.* **2010**, *49*, 7096; *Angew. Chem.* **2010**, *122*, 7250; c) P. Maity, H. D. Srinivas, M. P. Watson, *J. Am. Chem. Soc.* **2011**, *133*, 17142; d) V. M. Lombardo, C. D. Thomas, K. A. Scheidt, *Angew. Chem. Int. Ed.* **2013**, *52*, 12910; *Angew. Chem.* **2013**, *125*, 13148; e) C. Zhao, S. B. Chen, D. Seidel, *J. Am. Chem. Soc.* **2016**, *138*, 9053; f) S. Das, L. Liu, Y. Zheng, M. W. Alachraf, W. Thiel, C. K. De, B. List, *J. Am. Chem. Soc.* **2016**, *138*, 9429.

[6] For selected reviews on nonenzymatic KR, see: a) J. M. Keith, J. F. Larrow, E. N. Jacobsen, *Adv. Synth. Catal.* **2001**, *343*, 5; b) M. Breuer, K. Ditrich, T. Habicher, B. Hauer, M. Keβeler, R. Stürmer, T. Zelinski, *Angew. Chem. Int. Ed.* **2004**, *43*, 788; *Angew. Chem.* **2004**, *116*, 806; c) E. Vedejs, M. Jure, *Angew. Chem. Int. Ed.* **2005**, *44*, 3974; *Angew. Chem.* **2005**, *117*, 4040.

[7] For selected examples of nonenzymatic OKR of secondary alcohols, see: a) S. Hashiguchi, A. Fujii, K.-J. Haack, K. Matsumura, T. Ikariya, R. Noyori, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 288; *Angew. Chem.* **1997**, *109*, 300; b) D. R. Jensen, J. S. Pugsley, M. S. Sigman, *J. Am. Chem. Soc.* **2001**, *123*, 7475; c) E. M. Ferreira, B. M. Stoltz, *J. Am. Chem. Soc.* **2001**, *123*, 7725; d) A. T. Radosevich, C. Musich, F. D. Toste, *J. Am. Chem. Soc.* **2005**, *127*, 1090; e) V. D. Pawar, S. Bettigeri, S.-S. Weng, J.-Q. Kao, C.-T. Chen, *J. Am. Chem. Soc.* **2006**, *128*, 6308; f) S. Arita, T. Koike, Y. Kayaki, T. Ikariya, *Angew. Chem. Int. Ed.* **2008**, *47*, 2447; *Angew. Chem.* **2008**, *120*, 2481; g) K. Murakami, Y. Sasano, M. Tomizawa, M. Shibuya, E. Kwon, Y. Iwabuchi, *J. Am. Chem. Soc.* **2014**, *136*, 17591.

[8] For nonenzymatic dehydrogenative KR of amines, see: a) K. Saito, Y. Shibata, M. Yamanaka, T. Akiyama, *J. Am. Chem. Soc.* **2013**, *135*, 11740; b) R. Lu, L. Cao, H. Guan, L. Liu, *J. Am. Chem. Soc.* **2019**, *141*, 6318.

[9] For a representative example of hydrolytic KR of epoxides, see: M. Tokunaga, J. F. Larrow, F. Kakiuchi, E. N. Jacobsen, *Science* **1997**, *277*, 936.

[10] a) V. J. Bauer, B. J. Duffy, D. Hoffman, S. S. Klioze, R. W. Kosley, Jr., A. R. McFadden, L. L. Martin, H. H. Ong, *J. Med. Chem.* **1976**, *19*, 1315; b) E. G. Maestrup, C. Wiese, D. Schepmann, P. Brust, B. Wünsch, *Bioorg. Med. Chem.* **2011**, *19*, 393.

[11] a) I. Čorić, J. H. Kim, T. Vlaar, M. Patil, W. Thiel, B. List, *Angew. Chem. Int. Ed.* **2013**, *52*, 3490; *Angew. Chem.* **2013**, *125*, 3574; b) N. M. Weldy, A. G. Schafer, C. P. Owens, C. J. Herting, A. Varela-Alvarez, S. Chen, Z. Niemeyer, D. G. Musaev, M. S. Sigman, H. M. L. Davies, S. B. Blakey, *Chem. Sci.* **2016**, *7*, 3142; c) D. Chen, S. R. Chemler, *Org. Lett.* **2018**, *20*, 6453.

[12] a) The absolute configuration of recovered **1a** was determined by X-ray diffraction analysis. b) The absolute configuration of recovered **1aa** was assigned on the basis of CD spectroscopy measurements and theoretical calculations. c) The absolute configuration of recovered **5a** and **9** was assigned by comparing the optical rotation with reported data. See the Supporting Information for details.

[13] A. Tosun, E. K. Akkol, I. Süntar, H. Ö. Kiremit, Y. Asakawa, *Pharm. Biol.* **2013**, *51*, 1008.

[14] a) L. P. Hammett, *Physical Organic Chemistry*, McGraw-Hill, London, **1970**; b) L. P. Hammett, *Chem. Rev.* **1935**, *17*, 125.

[15] a) Y. Nakagawa, N. Mizuno, *Inorg. Chem.* **2007**, *46*, 1727; b) K. Kamata, T. Hirano, R. Ishimoto, N. Mizuno, *Dalton Trans.* **2010**, *39*, 5509; c) M. M. Abu-Omar, J. H. Espenson, *J. Am. Chem. Soc.* **1995**, *117*, 272; d) E. P. Talsi, D. G. Samsonenko, K. P. Bryliakov, *Chem. Eur. J.* **2014**, *20*, 14329.

[16] The Hammett ρ value for reactions involving a radical cation species was reported to be between −1 and 0; see: a) L. T. Burka, *J. Am. Chem. Soc.* **1985**, *107*, 2549; b) Y. Watanabe, T. Iyanagi, S. Dae, *Tetrahedron Lett.* **1980**, *21*, 3683.

[17] W. Nam, Y.-M. Lee, S. Fukuzumi, *Acc. Chem. Res.* **2018**, *51*, 2014.

[18] As suggested by an anonymous referee, competitive KIE studies with several different Mn(salen) catalysts were conducted. See the Supporting Information for details.

[19] J. Jung, S. Kim, Y.-M. Lee, W. Nam, S. Fukuzumi, *Angew. Chem. Int. Ed.* **2016**, *55*, 7450; *Angew. Chem.* **2016**, *128*, 7576.

[20] a) C. Madelaine, Y. Six, O. Buriez, *Angew. Chem. Int. Ed.* **2007**, *46*, 8046; *Angew. Chem.* **2007**, *119*, 8192; b) H. Shimizu, S. Onitsuka, H. Egami, T. Katsuki, *J. Am. Chem. Soc.* **2005**, *127*, 5396.

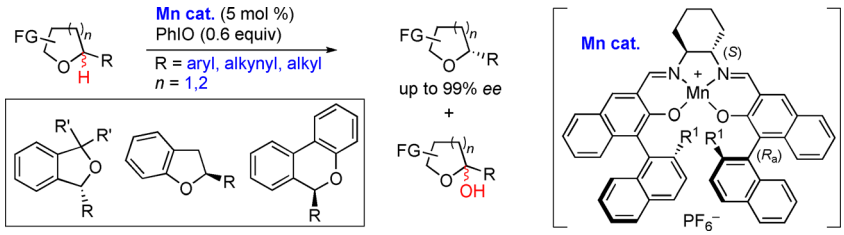
Manuscript received: July 12, 2020
Version of record online: ■■ ■■, ■■■■

Communications

Asymmetric Catalysis

S. Sun, Y. Ma, Z. Liu,
L. Liu* ——————— ■■■■–■■■■

Oxidative Kinetic Resolution of Cyclic Benzylic Ethers



A manganese-catalyzed kinetic resolution through asymmetric C(sp^3)–H oxidation was applied to a wide range of five-membered 1,3-dihydroisobenzofurans and 2,3-dihydrobenzofurans as well as six-membered 6*H*-benzo[*c*]chromenes bearing diverse α-substituents with extremely efficient enantiodiscrimination (see scheme). Late-stage oxidative kinetic resolution of bioactive molecules that are otherwise difficult to access was further demonstrated.