OL | Organic Letters

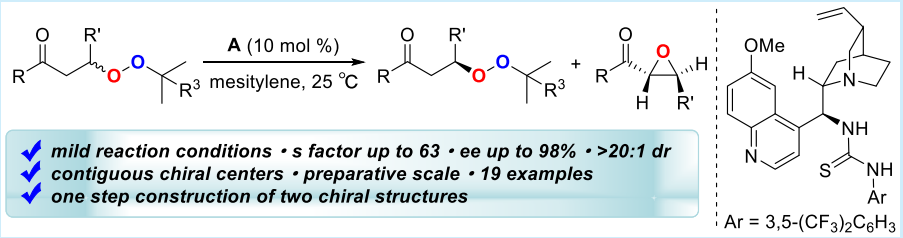
pubs.acs.org/OrgLett Letter

Organocatalytic Enantioselective γ-Elimination: Applications in the Preparation of Chiral Peroxides and Epoxides

Fangli Hu, Zhili Chen, Yu Tan, Da Xu, Shengli Huang, Shiqi Jia, Xiangnan Gong, Wenling Qin,* and Hailong Yan*

Cite This: https://dx.doi.org/10.1021/acs.orglett.0c00295 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

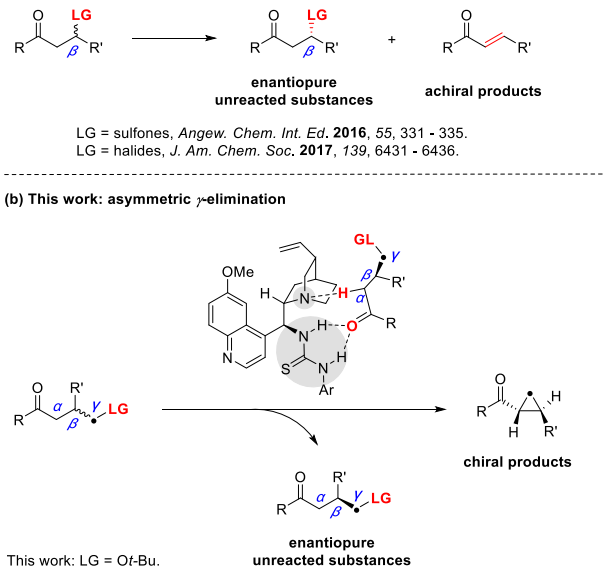


ABSTRACT: An organocatalyzed enantioselective γ-elimination process has been achieved and applied in the kinetic resolution of peroxides to access chiral peroxides and epoxides. The reaction provided a pathway for the preparation of two useful synthetic and biologically important structural motifs through a single-step reaction. A range of substrates has been resolved with a selectivity factor up to 63. The obtained enantioenriched peroxides and epoxides allowed a series of transformations with retained optical purities.

Elimination reactions[1] represent a direct and versatile strategy for the construction of new carbon−carbon[2] or carbon−heteroatom bonds[3] with molecular complexities. Enantioselective elimination processes[4] are of particular interest due to their convenience in accessing valuable chiral compounds, albeit asymmetric elimination approaches have not become a well-established methodology in the organic chemist's toolbox. As a precedent example, enantioselective β-hydride elimination has been achieved to access enantioenriched allenes by using Pd(II)−chiral ligands as the catalytic system.[5] As shown in Scheme 1a, our group has developed some organocatalytic enantioselective β-elimination reactions based on β-functionalized ketones to access chiral sulfones and compounds with contiguous halides bearing stereocenters via kinetic resolution.[6] Despite these achievements, an inherent drawback of kinetic resolution based on β-elimination is that the products of the β-elimination reaction are usually achiral substances. Theoretically, by extending the distance between the leaving group and the carbonyl to carry out a γ-elimination,[7] followed by an α-H sponge in the presence of chiral catalyst, the enantioselective cyclization can be realized to give an enantioenriched three-membered ring[8] as the product, and the chiral substrate can be recovered (Scheme 1b). To our surprise, this strategy has never been reported, probably because the large distance between the leaving group and the carbonyl functionality increased the difficulty of stereocontrol.

In our efforts to develop enantioselective elimination processes, we were encouraged to design a new reaction

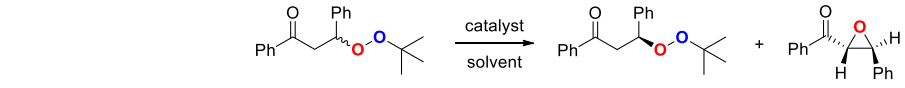
Scheme 1. Previous Work and Our Strategy

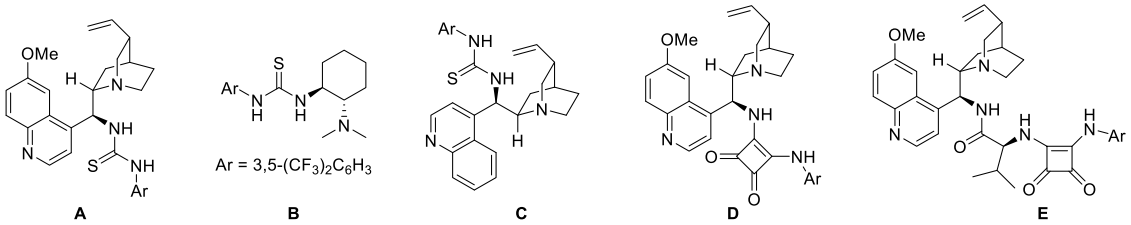


Received: January 21, 2020

https://dx.doi.org/10.1021/acs.orglett.0c00295
Org. Lett. XXXX, XXX, XXX−XXX

Table 1. Optimization of Reaction Conditions[a]





entry	cat.	solvent	concentration (M) (T (°C))	ee (**1a**) (%)[b]	ee (**2a**) (%)[b]	conv. (%)[c]	s[d]
1	**A**	toluene	0.1 (25)	90	82	52	31
2	**B**	toluene	0.1 (25)	64	87	42	28
3	**C**	toluene	0.1 (25)	−32	−83	28	15
4	**D**	toluene	0.1 (25)	51	87	37	24
5	**E**	toluene	0.1 (25)	9	39	19	2
6	**A**	*m*-xylene	0.1 (25)	75	86	47	30
7	**A**	*p*-xylene	0.1 (25)	55	90	38	33
8	**A**	mesitylene	0.1 (25)	83	86	49	34
9	**A**	CH_2Cl_2	0.1 (25)	50	89	36	28
10	**A**	$CHCl_3$	0.1 (25)	30	91	25	28
11	**A**	ethyl acetate	0.1 (25)	32	84	28	16
12	**A**	THF	0.1 (25)	6	78	7	9
13	**A**	acetone	0.1 (25)	27	80	25	12
14	**A**	mesitylene	0.2 (25)	96	78	55	31
15	**A**	mesitylene	0.13 (25)	92	81	53	31
16	A	**mesitylene**	**0.07 (25)**	**94**	**84**	**53**	**40**
17	**A**	mesitylene	0.05 (25)	72	88	45	34
18	**A**	mesitylene	0.07 (0)	13	85	13	14
19	**A**	mesitylene	0.07 (15)	63	87	42	27
20	**A**	mesitylene	0.07 (35)	77	71	52	13

[a]Reaction conditions: (±)-**1a** (0.1 mmol) and catalyst (10 mol %) in solvent for 47 h. [b]ee value was determined by HPLC analysis on a chiral stationary phase. [c]Conversion = $(ee^{1a})/(ee^{1a} + ee^{2a})$. [d]Selectivity factor was calculated by the method of Fiaud: $s = \ln[(1 - \text{conv.})(1 - ee^{1a})]/\ln[(1 - \text{conv.})(1 + ee^{1a})]$.

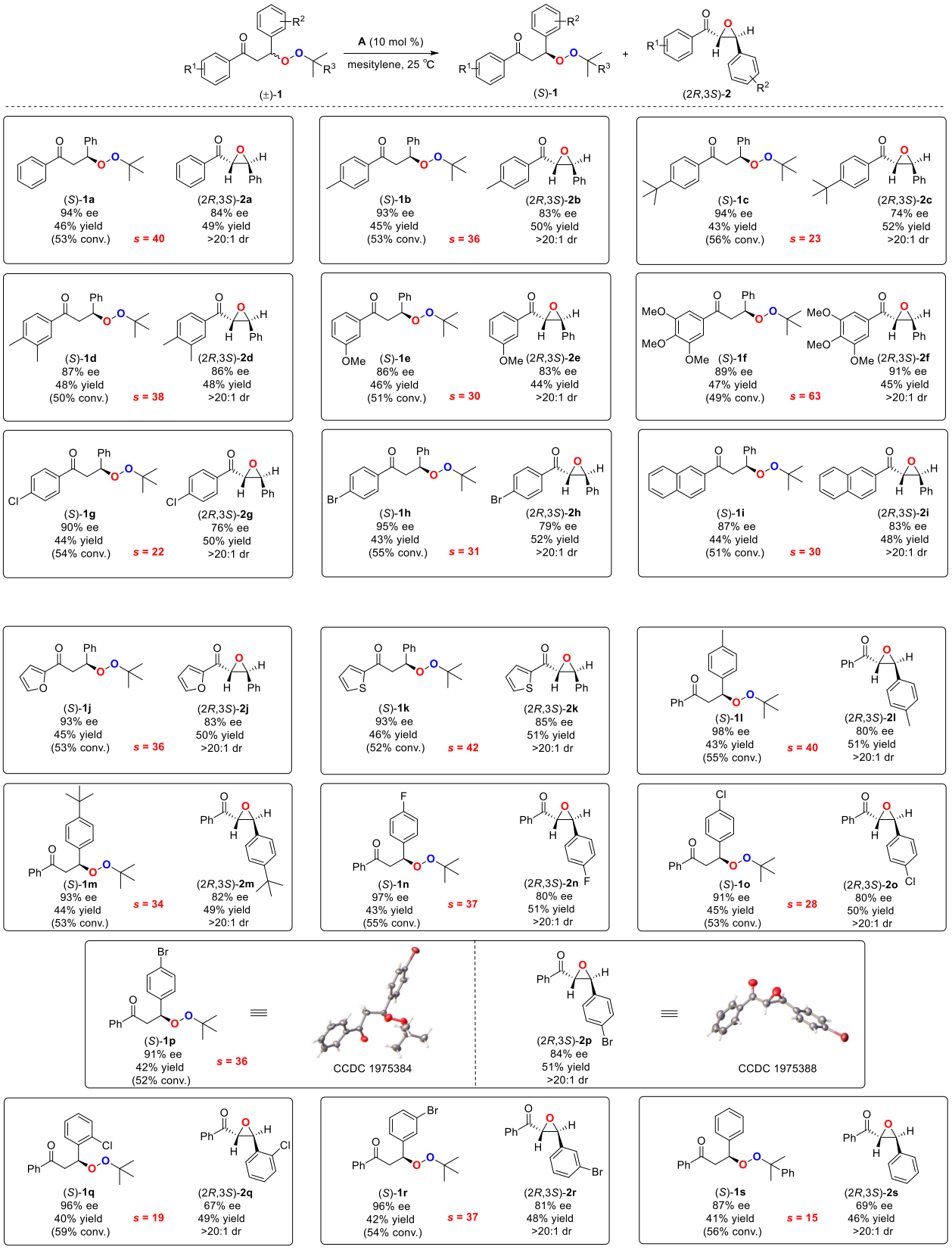
model involving γ-elimination with a Brønsted base organocatalyst. In 2011, Li[9] reported an iron-catalyzed direct carbonylation−peroxidation of alkenes to access peroxides, which was demonstrated to undergo an epoxidation process to furnish the corresponding epoxides in the presence of an organo-base catalyst.[9a] We envisioned that a chiral organocatalyst might be used to carry out the reaction enantioselectivity, in which a kinetic resolution procedure for preparing two kinds of chiral molecules based on γ-elimination could be realized.

Both peroxide and epoxide motifs exist in a large number of biologically interesting natural products as well as drugs[10] and were considered to be responsible for their bioactivities, such as anticancer,[11] antiparasite,[12] antibacterial,[13] and antiaging activities. In the past decades, tremendous progress has been made in the asymmetric preparation of chiral epoxides.[14] Meanwhile, direct enantioselective peroxidation processes have received considerable attention, and pioneering works have been reported by Deng,[15] Nakamura,[16] Li,[17] and Dussault.[18] Despite these achievements, the enantioselective approaches toward the preparation of chiral peroxides and epoxides in one single step still remain unexplored. We reported herein the first organocatalyzed[19] enantioselective kinetic resolution approach to access chiral peroxides via an enantioselective γ-elimination process and afford chiral epoxides as valuable products.

We began our study by using racemic peroxide **1a** as the substrate in the presence of quinine-derived thiourea catalyst **A** in toluene. To our delight, the reaction proceeded smoothly in 52% conversion, and the epoxide (2*R*,3*S*)-**2a** was obtained with 82% ee and the chiral peroxide (*S*)-**1a** was recovered with 90% ee (Table 1, entry 1). Next, the Takemoto catalyst (catalyst **B**) was tested under the same reaction conditions. The enantiopurity of the epoxide was increased, albeit the ee value of substrate was decreased (Table 1, entry 2). Cinchonine-derived thiourea catalyst **C** was not able to increase the enantiopurity of the product and the substrate, thus giving the lower s value for this resolution reaction based on γ-elimination (s = 15, Table 1, entry 3). To improve the performance of this resolution process, we further evaluated quinine-derived squaramide catalysts **D** and **E**. Disappointingly, both catalysts turned out to be inferior for enantiocontrol (Table 1, entries 4 and 5). After the optimal catalyst was identified, we evaluated a series of solvents (Table1, entries 6−13), and mesitylene was demonstrated to be the best solvent for this enantioselective γ-elimination reaction (s = 34, Table 1, entry 8). The further evaluation of the concentration (Table 1, entries 14−17) and temperature (Table 1, entries 18−20)

https://dx.doi.org/10.1021/acs.orglett.0c00295
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 2. Substrate Scope[a]



[a]Reaction conditions: (±)-**1** (0.1 mmol), **A** (10 mol %) in mesitylene (1.5 mL) at 25 °C. See the SI for the reaction time. The ee value was determined by HPLC analysis on a chiral stationary phase. Yield of isolated product. Conversion = $(ee^1)/(ee^1 + ee^2)$. The diastereomeric ratio (dr) was determined by the ^{1}H NMR analysis of the crude reaction mixture. The selectivity factor was calculated by the method of Fiaud: $s = \ln[(1 - \text{conv.})(1 - ee^1)]/\ln[(1 - \text{conv.})(1 + ee^1)]$.

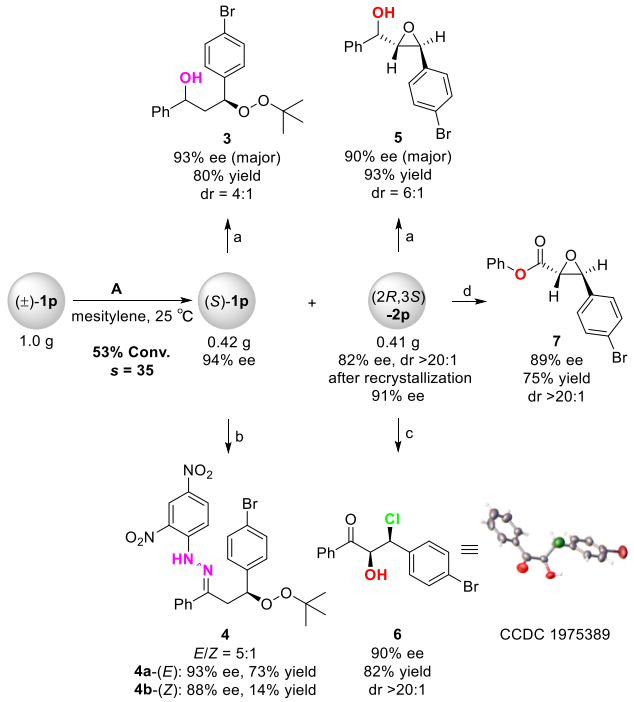
https://dx.doi.org/10.1021/acs.orglett.0c00295
Org. Lett. XXXX, XXX, XXX−XXX

suggested that the highest *s* value could be obtained under the following reaction conditions: 0.1 mmol substrates and 10 mol % catalyst **A** in mesitylene (1.5 mL) at 25 °C for 47 h.

With the optimized reaction conditions in hand (Table 1, entry 16), we investigated the substrate scope of the established kinetic resolution of peroxides through an enantioselective γ-elimination reaction (Scheme 2). The peroxides were obtained from the corresponding olefins, aldehydes, and *t*-BuOOH or cumyl hydroperoxide under the catalysis of *n*-Bu_4NBr; the detailed procedures are shown in the SI. Substrates with electron-donating R^1 groups at the phenyl ring allowed the enantioselective γ-elimination to give chiral peroxides (*S*)-**1b**–**f** with high *s* values and with up to 94% ee; the corresponding epoxides (2*R*,3*S*)-**2b**–**f** were also obtained with good enantioselectivities. *para*-Chloride-substituted substrate racemic **1g** was tolerated in our reaction system, and chiral peroxide (*S*)-**1g** was recovered in 44% yield with 90% ee. Epoxide (2*R*,3*S*)-**2g** was formed with a moderate ee value. Similarly, *para*-bromo-substituted substrate **1h** also afforded a good selectivity with an *s* value of 31. By substituting the phenyl ring with naphthalene, 2-furan, or 2-thiophene, peroxides **1i**–**k** were also efficiently resolved with high enantioselectivities (*s* value up to 42). After the investigation of the R^1 group of peroxides, we determined the substrate scope with different R^2 groups. Substrates with electron-donating R^2 groups resulted in chiral peroxides (*S*)-**1l** (methyl) and (*S*)-**1m** (*tert*-butyl), respectively, with 98% ee and 93% ee, and epoxides (2*R*,3*S*)-**2l** and (2*R*,3*S*)-**2m** were obtained with good enantioselectivities as well. Using halides such as fluoride, chloride, and bromide as R^2 groups located in the para position of phenyl ring, corresponding substrates were suitable for the resolution to give enantioenriched peroxides (*S*)-**1n**–**p** (up to 97% ee) and epoxides (2*R*,3*S*)-**2n**–**p** (up to 84% ee), and selectivity factors as high as 37 were obtained. The absolute configurations of (*S*)-**1p** and (2*R*,3*S*)-**2p** were determined by X-ray crystallography, and others were analogously assigned. When R^2 was an *ortho*-chloro or *meta*-bromo group on the phenyl ring, chiral peroxides (*S*)-**1q** and (*S*)-**1r** were recovered after an enantioselective γ-elimination process with promising results (96% ee and up to 42% yield), and epoxides (2*R*,3*S*)-**2q**-**r** were obtained with up to 81% ee. After substituting the *tert*-butyl peroxide group with a dimethyl phenyl group, the corresponding substrate could also be resolved to give chiral peroxide (*S*)-**1s** in 41% yield with 87% ee. Nevertheless, the reactions were not successful with α-ester peroxide and alkyl ketone peroxides under standard reaction conditions.

After the substrate scope of the reaction was investigated, we planned to further demonstrate the synthetic potential of our reaction. First, a gram-scale reaction was carried out to prepare (*S*)-**1p** and (2*R*,3*S*)-**2p** under the optimal reaction conditions, and the chemical yield and enantioselectivity showed almost no variation (Scheme 3). Next, a few functional transformations of chiral substrates and products were conducted. As expected, the enantioenriched peroxide (*S*)-**1p** could be converted into the corresponding peroxide **3** in 80% yield with good stereoselectivity (93% ee and 4:1 dr) by sodium borohydride. Upon the treatment of (*S*)-**1p** with 2,4-dinitrophenyl hydrazine in methanol at 40 °C for 6 h, product **4a** was formed as the major product in 73% yield with 93% ee value. Moreover, the utility of the epoxide from this γ-elimination-based kinetic resolution was also explored. Epoxide (2*R*,3*S*)-**2p** was sufficiently transformed into alcohol **5** and ester **7** through a reductive and oxidative process, respectively;

Scheme 3. Gram-Scale Preparation and Synthetic Applications[a]

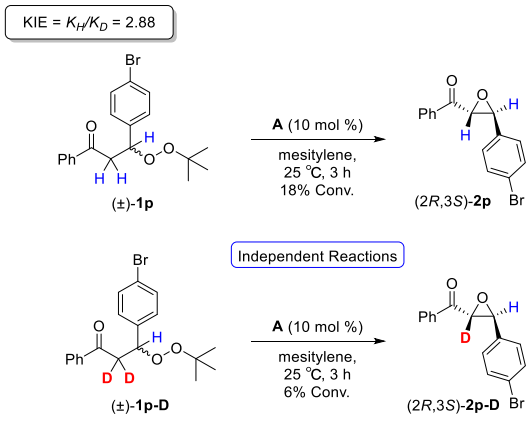


[a]For reaction conditions, see the SI.

both products were obtained in good yield with high ee. Treating epoxide (2*R*,3*S*)-**2p** with $SnCl_4$ afforded a chlorinated open-chain product **6** instead of a cyclized adduct, as reported.[20] The absolute configuration of product **6** was assigned through X-ray crystallography.

In an attempt to gain some insights into the mechanism of this enantioselective γ-elimination transformation, we measured the independent initial rates of parallel reactions with substrates (±)-**1p** and α-proton-deuterated substrate (±)-**1p-D** under the standard reaction conditions (Scheme 4). The primary intermolecular kinetic isotopic effect (KIE)[21] was calculated to be 2.88, indicating that the deprotonation of the α-proton of the carbonyl group was probably involved in the rate-determining step.

Scheme 4. Kinetic Isotopic Effect Experiment[a]



[a]For reaction conditions, see the SI.

https://dx.doi.org/10.1021/acs.orglett.0c00295
Org. Lett. XXXX, XXX, XXX−XXX

In summary, we established the first organocatalytic kinetic resolution of peroxides through enantioselective γ-elimination to afford chiral peroxides and epoxides. Both substances are important building blocks in synthetic chemistry and play reliable roles in numerous bioactive natural products as well as medicines. This methodology provided a single-step reaction for the preparation of two kinds of valuable chiral compounds. This asymmetric γ-elimination-based resolution process was tolerant of a range of peroxides with high selectivity factors, and the obtained products allowed a variety of further transformations while retaining optical purity. Furthermore, the KIE study suggested that the deprotonation of the α-proton of the carbonyl group determined the rate of this enantioselective γ-elimination process.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00295.

Experimental procedure and characterization data for all of the products (PDF)

Accession Codes

CCDC 1975384 and 1975388−1975389 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Authors

Wenling Qin − *Chongqing Key Laboratory of Natural Product Synthesis and Drug Research, School of Pharmaceutical Sciences, Chongqing University, Chongqing 401331, P. R. China;* orcid.org/0000-0002-5654-5785; Email: wenling.qin@cqu.edu.cn

Hailong Yan − *Chongqing Key Laboratory of Natural Product Synthesis and Drug Research, School of Pharmaceutical Sciences, Chongqing University, Chongqing 401331, P. R. China;* orcid.org/0000-0003-3378-0237; Email: yhl198151@cqu.edu.cn

Authors

Fangli Hu − *Chongqing Key Laboratory of Natural Product Synthesis and Drug Research, School of Pharmaceutical Sciences, Chongqing University, Chongqing 401331, P. R. China*

Zhili Chen − *Chongqing Key Laboratory of Natural Product Synthesis and Drug Research, School of Pharmaceutical Sciences, Chongqing University, Chongqing 401331, P. R. China*

Yu Tan − *Chongqing Key Laboratory of Natural Product Synthesis and Drug Research, School of Pharmaceutical Sciences, Chongqing University, Chongqing 401331, P. R. China*

Da Xu − *Chongqing Key Laboratory of Natural Product Synthesis and Drug Research, School of Pharmaceutical Sciences, Chongqing University, Chongqing 401331, P. R. China*

Shengli Huang − *Chongqing Key Laboratory of Natural Product Synthesis and Drug Research, School of Pharmaceutical Sciences, Chongqing University, Chongqing 401331, P. R. China*

Shiqi Jia − *Chongqing Key Laboratory of Natural Product Synthesis and Drug Research, School of Pharmaceutical Sciences, Chongqing University, Chongqing 401331, P. R. China*

Xiangnan Gong − *Analytical and Testing Center of Chongqing University, Chongqing University, Chongqing 401331, P. R. China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c00295

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This study was supported by the Scientific Research Foundation of China (grant nos. 21772018, 21922101, and 21901026).

■ REFERENCES

(1) (a) Fumagalli, G.; Stanton, S.; Bower, J. F. Recent Methodologies that Exploit C-C Single-Bond Cleavage of Strained Ring Systems by Transition Metal Complexes. *Chem. Rev.* **2017**, *117*, 9404−9432. (b) Chu, T.; Nikonov, G. I. Oxidative Addition and Reductive Elimination at Main-Group Element Centers. *Chem. Rev.* **2018**, *118*, 3608−3680.

(2) (a) Huang, Y.; Hayashi, T. Rhodium-Catalyzed Asymmetric Arylation/Defluorination of 1-(Trifluoromethyl)alkenes Forming Enantioenriched 1,1-Difluoroalkenes. *J. Am. Chem. Soc.* **2016**, *138*, 12340−12343. (b) Liao, G.; Li, B.; Chen, H.-M.; Yao, Q.-J.; Xia, Y.-N.; Luo, J.; Shi, B.-F. Pd-Catalyzed Atroposelective C-H Allylation through β-O Elimination: Diverse Synthesis of Axially Chiral Biaryls. *Angew. Chem., Int. Ed.* **2018**, *57*, 17151−17155.

(3) (a) Liu, D.; Kozmin, S. A. Catalytic Enantioselective Isomerization of Silacyclopentene Oxides: New Strategy for Stereocontrolled Assembly of Acyclic Polyols. *Angew. Chem., Int. Ed.* **2001**, *40*, 4757−4759. (b) Igawa, K.; Yoshihiro, D.; Abe, Y.; Tomooka, K. Enantioselective Synthesis of Silacyclopentanes. *Angew. Chem., Int. Ed.* **2016**, *55*, 5814−5818.

(4) (a) Matsuda, T.; Shigeno, M.; Makino, M.; Murakami, M. Enantioselective C-C Bond Cleavage Creating Chiral Quaternary Carbon Centers. *Org. Lett.* **2006**, *8*, 3379−3381. (b) Barth, R.; Roush, W. R. Enantioselective Synthesis of α-Methylene-β-Hydroxy Carboxylic Acid Derivatives via a Diastereoselective Aldol/β-Elimination Sequence: Application to the C(15)-C(21) Fragment of Tedanolide C. *Org. Lett.* **2010**, *12*, 2342−2345.

(5) (a) Bissember, A. C.; Levina, A.; Fu, G. C. A Mild, Palladium-Catalyzed Method for the Dehydrohalogenation of Alkyl Bromides: Synthetic and Mechanistic Studies. *J. Am. Chem. Soc.* **2012**, *134*, 14232−14237. (b) Wan, B.; Ma, S. Enantioselective Decarboxylative Amination: Synthesis of Axially Chiral Allenyl Amines. *Angew. Chem., Int. Ed.* **2013**, *52*, 441−445. (c) Crouch, I. T.; Neff, R. K.; Frantz, D. E. Pd-Catalyzed Asymmetric β-Hydride Elimination en Route to Chiral Allenes. *J. Am. Chem. Soc.* **2013**, *135*, 4970−4973.

(6) (a) Li, L.; Liu, Y.; Peng, Y.; Yu, L.; Wu, X.; Yan, H. Kinetic Resolution of β-Sulfonyl Ketones through Enantioselective β-Elimination using a Cation-Binding Polyether Catalyst. *Angew. Chem., Int. Ed.* **2016**, *55*, 331−335. (b) Liu, Y.; Qin, W.; Yan, H. Efficient Enrichment of Chiral β-Sulfonyl Ketones through Asymmetric β-Elimination. *Synlett* **2016**, *27*, 2756−2760. (c) Tan, Y.; Luo, S.; Li, D.; Zhang, N.; Jia, S.; Liu, Y.; Qin, W.; Song, C. E.; Yan, H. Enantioselective Synthesis of *anti-syn*-Trihalides and *anti-syn-anti*-Tetrahalides via Asymmetric β-Elimination. *J. Am. Chem. Soc.* **2017**, *139*, 6431−6436.

(7) Glasspoole, B. W.; Crudden, C. M. Cross-coupling between a racemic secondary alkyl halide and an alkyl borane to produce an enantioenriched alkyl-alkyl product is one of the final substrate combinations to succumb to the synthetically powerful Suzuki-Miyaura methodology. *Nat. Chem.* **2011**, *3*, 912−913.

(8) For a thematically similar strategy for the formation of cyclopropanes, see: (a) Payne, G. B. Cyclopropanes from Reactions of Ethyl (Dimethylsulfuranylidene)acetate with α,β-Unsaturated

Compounds. *J. Org. Chem.* **1967**, *32*, 3351−3355. (b) Kunz, R. K.; MacMillan, D. W. C. Enantioselective Organocatalytic Cyclopropanations. The Identification of a New Class of Iminium Catalyst Based upon Directed Electrostatic Activation. *J. Am. Chem. Soc.* **2005**, *127*, 3240−3241. (c) Zhao, Y.-H.; Zhao, G.; Cao, W.-G. Organocatalytic asymmetric cyclopropanation of α,β-unsaturated aldehydes with arsonium ylides. Tetrahedron. *Tetrahedron: Asymmetry* **2007**, *18*, 2462−2467. (d) Cheng, Y.; An, J.; Lu, L.-Q.; Luo, L.; Wang, Z.-Y.; Chen, J.-R.; Xiao, W.-J. Asymmetric Cyclopropanation of β,γ-Unsaturated α-Ketoesters with Stabilized Sulfur Ylides Catalyzed by C_2-Symmetric Ureas. *J. Org. Chem.* **2011**, *76*, 281−284.

(9) (a) Liu, W.; Li, Y.; Liu, K.; Li, Z. Iron-Catalyzed Carbonylation-Peroxidation of Alkenes with Aldehydes and Hydroperoxides. *J. Am. Chem. Soc.* **2011**, *133*, 10756−10759. (b) Liu, K.; Li, Y.; Zheng, X.; Liu, W.; Li, Z. Synthesis of α-ester-β-keto peroxides via iron-catalyzed carbonylation-peroxidation of α,β-unsaturated esters. *Tetrahedron* **2012**, *68*, 10333−10337. (c) Liu, K.; Li, Y.; Liu, W.; Zheng, X.; Zong, Z.; Li, Z. Efficient and Selective Synthesis of α,β-Epoxy-γ-Butyrolactones from 2-Peroxy-1,4-Dicarbonyl Compounds. *Chem. - Asian J.* **2013**, *8*, 359−363. (d) Lv, L.; Shen, B.; Li, Z. Total Synthesis of (±)-Clavilactones A, B, and Proposed D through Iron-Catalyzed Carbonylation-Peroxidation of Olefin. *Angew. Chem., Int. Ed.* **2014**, *53*, 4164−4167. (e) Zong, Z.; Lu, S.; Wang, W.; Li, Z. Iron-catalyzed alkoxycarbonylation-peroxidation of alkenes with carbazates and T-Hydro. *Tetrahedron Lett.* **2015**, *56*, 6719−6721. (f) Zong, Z.; Bai, X.; Lu, S.; Li, Z. A general method for synthesis of *cis*-dicarbonyl epoxides through DBU/LiBr-cocatalyzed cyclization of α,β-dicarbonyl peroxides. *Tetrahedron Lett.* **2016**, *57*, 3827−3831. (g) Chen, Y.; Chen, Y.; Lu, S.; Li, Z. Copper-catalyzed three-component phosphorylation-peroxidation of alkenes. *Org. Chem. Front.* **2018**, *5*, 972−976. (h) Xu, R.; Li, Z. Ag-catalyzed sulfonylation-peroxidation of alkenes with sulfonyl hydrazides and T-Hydro. *Tetrahedron Lett.* **2018**, *59*, 3942−3945.

(10) (a) Chung, L. W.; Hayashi, S.; Lundberg, M.; Nakatsu, T.; Kato, H.; Morokuma, K. Mechanism of Efficient Firefly Bioluminescence via Adiabatic Transition State and Seam of Sloped Conical Intersection. *J. Am. Chem. Soc.* **2008**, *130*, 12880−12881. (b) Kildgaard, S.; de Medeiros, L. S.; Phillips, E.; Gotfredsen, C. H.; Frisvad, J. C.; Nielsen, K. F.; Abreu, L. M.; Larsen, T. O. Cyclopiamines C and D: Epoxide Spiroindolinone Alkaloids from *Penicillium* sp. CML 3020. *J. Nat. Prod.* **2018**, *81*, 785−790. (c) Liu, F.; Wang, Y.-N.; Li, Y.; Ma, S.-G.; Qu, J.; Liu, Y.-B.; Niu, C.-S.; Tang, Z.-H.; Li, Y.-H.; Li, L.; Yu, S.-S. Minor Nortriterpenoids from the Twigs and Leaves of *Rhododendron latoucheae*. *J. Nat. Prod.* **2018**, *81*, 1721−1733. (d) Ernouf, G.; Wilt, I. K.; Zahim, S.; Wuest, W. M. Epoxy Isonitriles, A Unique Class of Antibiotics: Synthesis of Their Metabolites and Biological Investigations. *ChemBioChem* **2018**, *19*, 2448−2452.

(11) (a) Dembitsky, V. M. Bioactive peroxides as potential therapeutic agents. *Eur. J. Med. Chem.* **2008**, *43*, 223−251. (b) Pompeo, M. M.; Cheah, J. H.; Movassaghi, M. Total Synthesis and Anti-Cancer Activity of All Known Communesin Alkaloids and Related Derivatives. *J. Am. Chem. Soc.* **2019**, *141*, 14411−14420.

(12) (a) Hamada, Y.; Tokuhara, H.; Masuyama, A.; Nojima, M.; Kim, H.-S.; Ono, K.; Ogura, N.; Wataya, Y. Synthesis and Notable Antimalarial Activity of Acyclic Peroxides, 1-(Alkyldioxy)-1-(methyldioxy)cyclododecanes. *J. Med. Chem.* **2002**, *45*, 1374−1378. (b) Gemma, S.; Kunjir, S.; Sanna Coccone, S.; Brindisi, M.; Moretti, V.; Brogi, S.; Novellino, E.; Basilico, N.; Parapini, S.; Taramelli, D.; Campiani, G.; Butini, S. Synthesis and Antiplasmodial Activity of Bicyclic Dioxanes as Simplified Dihydroplakortin Analogues. *J. Med. Chem.* **2011**, *54*, 5949−5953.

(13) (a) Liang, S.; Wei, Q.; Xue, J.; Sun, Y.; Chen, Z.; Kuang, H.; Wang, Q. Chemical composition and biological activities of essential oil from *Filifolium sibiricum* (L.) Kitam. *Nat. Prod. Res.* **2016**, *30*, 2861−2863. (b) Farkasovska, J.; Bugarova, V.; Godocikova, J.; Majtan, V.; Majtan, J. The role of hydrogen peroxide in the antibacterial activity of different floral honeys. *Eur. Food Res. Technol.* **2019**, *245*, 2739−2744.

(14) (a) Xia, Q.-H.; Ge, H.-Q.; Ye, C.-P.; Liu, Z.-M.; Su, K.-X. Advances in Homogeneous and Heterogeneous Catalytic Asymmetric Epoxidation. *Chem. Rev.* **2005**, *105*, 1603−1662. (b) Wang, X.; Reisinger, C. M.; List, B. Catalytic Asymmetric Epoxidation of Cyclic Enones. *J. Am. Chem. Soc.* **2008**, *130*, 6070−6071. (c) Zhao, Z.; Bagdi, P. R.; Yang, S.; Liu, J.; Xu, W.; Fang, X. Stereodivergent Access to Enantioenriched Epoxy Alcohols with Three Stereogenic Centers via Ruthenium-Catalyzed Transfer Hydrogenation. *Org. Lett.* **2019**, *21*, 5491−5494.

(15) (a) Lu, X.; Liu, Y.; Sun, B.; Cindric, B.; Deng, L. Catalytic Enantioselective Peroxidation of α,β-Unsaturated Ketones. *J. Am. Chem. Soc.* **2008**, *130*, 8134−8135. (b) Sun, B.-F.; Hong, R.; Kang, Y.-B.; Deng, L. Asymmetric Total Synthesis of (−)-Plicatic Acid via a Highly Enantioselective and Diastereoselective Nucleophilic Epoxidation of Acyclic Trisubstitued Olefins. *J. Am. Chem. Soc.* **2009**, *131*, 10384−10385. (c) Liu, Y.; Provencher, B. A.; Bartelson, K. J.; Deng, L. Highly enantioselective asymmetric Darzens reactions with a phase transfer catalyst. *Chem. Sci.* **2011**, *2*, 1301−1304. (d) Lu, X.; Deng, L. Catalytic Asymmetric Peroxidation of α,β-Unsaturated Nitroalkenes by a Bifunctional Organic Catalyst. *Org. Lett.* **2014**, *16*, 2358−2361. (e) Hu, L.; Lu, X.; Deng, L. Catalytic Enantioselective Peroxidation of α,β-Unsaturated Aldehydes for the Asymmetric Synthesis of Biologically Important Chiral Endoperoxides. *J. Am. Chem. Soc.* **2015**, *137*, 8400−8403.

(16) Nakamura, S.; Takahashi, S. Organocatalytic Enantioselective Peroxidation of Ketimines Derived from Isatins. *Org. Lett.* **2015**, *17*, 2590−2593.

(17) Guo, W.; Liu, Y.; Li, C. Asymmetric Catalytic 1,2-Hydroperoxidation of Isatin-Derived Ketimine with Hydrogen Peroxide in the Crowding Environment of PEGs. *Org. Lett.* **2017**, *19*, 1044−1047.

(18) (a) Dussault, P. H.; Trullinger, T. K.; Cho-shultz, S. Chiral Silyl Ketene Acetals from Thioesters: Reaction with Acetals and Peroxyacetals to Form 3-Alkoxy- and 3-Peroxyalkanoates. *Tetrahedron* **2000**, *56*, 9213−9220. (b) Dussault, P. H.; Trullinger, T. K.; Noor-e-Ain, F. Opening of Substituted Oxetanes with H_2O_2 and Alkyl Hydroperoxides: Stereoselective Approach to 3-Peroxyalcohols and 1,2,4-Trioxepanes. *Org. Lett.* **2002**, *4*, 4591−4593. (c) Xu, C.; Raible, J. M.; Dussault, P. H. Total Synthesis of Peroxyacarnoates A and D: Metal-Mediated Couplings as a Convergent Approach to Polyunsaturated Peroxides. *Org. Lett.* **2005**, *7*, 2509−2511. (d) Dai, P.; Trullinger, T. K.; Liu, X.; Dussault, P. H. Asymmetric Synthesis of 1,2-Dioxolane-3-acetic Acids: Synthesis and Configurational Assignment of Plakinic Acid A. *J. Org. Chem.* **2006**, *71*, 2283−2292.

(19) (a) Bae, H. Y.; Sim, J. H.; Lee, J.-W.; List, B.; Song, C. E. Organocatalytic Enantioselective Decarboxylative Aldol Reaction of Malonic Acid Half Thioesters with Aldehydes. *Angew. Chem., Int. Ed.* **2013**, *52*, 12143−12147. (b) Bae, H. Y.; Kim, M. J.; Sim, J. H.; Song, C. E. Direct Catalytic Asymmetric Mannich Reaction with Dithiomalonates as Excellent Mannich Donors: Organocatalytic Synthesis of (*R*)-Sitagliptin. *Angew. Chem., Int. Ed.* **2016**, *55*, 10825−10829. (c) Jiang, X.-L.; Liu, S.-J.; Gu, Y. Q.; Mei, G.-J.; Shi, F. Catalytic Asymmetric [4 + 1] Cyclization of *ortho*-Quinone Methides with 3-Chlorooxindoles. *Adv. Synth. Catal.* **2017**, *359*, 3341−3346. (d) Chen, Z.-C.; Chen, Z.; Du, W.; Chen, Y.-C. Transformations of Modified Morita-Baylis-Hillman Adducts from Isatins Catalyzed by Lewis Bases. *Chem. Rec.* **2019**, *19*, 1−16. (e) Ma, C.; Jiang, F.; Sheng, F.-T.; Jiao, Y.; Mei, G.-J.; Shi, F. Design and Catalytic Asymmetric Construction of Axially Chiral 3,3′-Bisindole Skeletons. *Angew. Chem., Int. Ed.* **2019**, *58*, 3014−3020.

(20) (a) Ahmed, N.; Pathe, G. K.; Jheeta, S. $SnCl_4$ or $TiCl_4$: highly efficient catalysts for the detetrahydropyranylation and demethoxymethylation of phenolic ethers and sequential one-pot asymmetric synthesis of 3-aryl-2-hydroxy-2,3-dihydroindan-1-ones from chalcone epoxides. *RSC Adv.* **2015**, *5*, 63095−63103. (b) Waheed, M.; Ahmed, N. Pd/Indanone-Based Ligands: An Efficient Catalyst System for Ullmann-Type, Suzuki-Miyaura, and Mizoroki-Heck Cross-Coupling Reactions with Aryl Tosylates and Aryl Halides. *Synthesis* **2017**, *49*, 4372−4382.

https://dx.doi.org/10.1021/acs.orglett.0c00295
Org. Lett. XXXX, XXX, XXX−XXX

(21) (a) Giagou, T.; Meyer, M. P. Kinetic Isotope Effects in Asymmetric Reactions. *Chem. - Eur. J.* **2010**, *16*, 10616−10628. (b) Simmons, E. M.; Hartwig, J. F. On the Interpretation of Deuterium Kinetic Isotope Effects in C-H Bond Functionalizations by Transition-Metal Complexes. *Angew. Chem., Int. Ed.* **2012**, *51*, 3066−3072.

https://dx.doi.org/10.1021/acs.orglett.0c00295
Org. Lett. XXXX, XXX, XXX−XXX