Site- and enantioselective oxidation of aliphatic C–H bonds with a general scope, predictable selectivities and in preparatively useful yields, would represent a paradigm shift in the standard logic of organic synthesis. On the other hand, catalytic kinetic resolution (KR) of racemates is one of the most powerful and practical tools to prepare valuable enantiopure targets, which predominantly relies on the manipulation of reactive functional groups. The group of Professor Lei Liu at Shandong University (Jinan, P. R. of China) envisioned that integrating the KR strategy into enantioselective C(sp³)–H oxidation reaction design would advance the development of both research fields (Scheme 1A). Professor Liu said: “During the past three years, we have put into practice this initial idea in achieving base-metal-catalyzed KR of cyclic secondary amines and cyclic ethers through site- and enantiodifferentiating C(sp³)–H oxidation (Scheme 1B; J. Am. Chem. Soc. 2019, 141, 6318–6324; J. Am. Chem. Soc. 2022, 144, 5976–5984; Angew. Chem. Int. Ed. 2021, 60, 176–180; J. Am. Chem. Soc. 2020, 142, 19346–19353).”

According to Professor Liu, chiral organic azides have found dramatically expanded utility in medicine, biology, and materials science. However, catalytic KR to provide optically pure azides has remained elusive, principally owing to two essential features of the azido moiety: (1) its instability, hampering the design of new reactivity with excellent chemoselectivity; and (2) its small size, hampering the achievement of kinetically selective resolution of azides. The general idea of the project is illustrated in Scheme 1A. The KR reaction involves the selective oxidation of the benzylic C–H bond of a cyclic secondary amine or ether to form an azide, followed by dehydrogenation to yield an aldehyde or ketone. The enantiopure product is obtained by kinetic resolution of the racemic mixture.

**Scheme 1** The general idea of the project
Scheme 2 Oxidative KR of cyclic benzylic azides and the origin of effective chiral recognition
of effective chiral recognition. “Existing isolated examples in the literature invariably focused on manipulating the azido moiety through azide–alkyne cycloaddition or extra reactive functional groups preinstalled in substrates, which typically suffer from the use of excess azide substrates, poor chiral recognition, and narrow substrate scope,” remarked Professor Liu, who continued: “Therefore, we decided to explore the KR of organic azides relying on the oxidative reactivity of C(sp³)–H bonds (Scheme 1C).”

“Two main challenges hampered the reaction design (Scheme 1C),” explained Professor Liu. He continued: “First, due to stability issues, selective oxidation of the C(sp³)–H bond adjacent to an azido moiety remains elusive. Second, organic azides lack an effective interaction site to direct the substrate to an ideal location in the transition state, which would result in the chiral discrimination of chemically similar C(sp³)–H bonds of two enantiomers. Accordingly, the project was designed based on the following criteria: (1) given the significance of benzo-fused nitrogen-containing heterocycles in modern pharmacology, we chose a range of racemic benzylic azides bearing such skeletons as substrates; (2) we selected the readily modifiable salen as the prototypical ligand to search for suitable base-metal catalysts; (3) varying the protecting group on the nitrogen moiety was thought to provide an opportunity to tune the oxidative reactivity, site-selectivity, and chiral recognition.”

Careful reaction optimization revealed that when chiral Mn(salen) C1 carrying 2,4-difluorophenyl moieties at C3(3′) sites was used as catalyst, with PhIO as oxidant, oxidative KR of tetrahydroquinoline (THQ)-based organic azides proceeded with excellent site selectivity at the C4–H bond adjacent to the azido moiety over the C2–H bond α to the amide motif, affording the corresponding azines as oxidized products (Scheme 2A). Structurally diverse optically pure THQ-based organic azides were isolated in good yields with excellent ee (s = 20–91). When chiral Mn(salen) C2 was used as catalyst, oxidative KR of indoline-based organic azides proceeded with similar site-selectivity at the C3–H bond, furnishing 2-aminobenzonitriles as oxidized products together with recovered optically pure azides featuring excellent selectivity factors (s = 36–95) (Scheme 2A). Control experiments were performed to explore the substituent effect of different acyl groups on THQ-based azides (Scheme 2B). “An interesting trend was observed: the substrate reactivity towards oxidation was gradually enhanced as the number of methyl groups at the α-position of the carbonyl moiety increased, indicating that such an unconventional trend might originate from the non-covalent interaction between the carbonyl moiety’s α-alkyl group and the Mn(salen) catalyst,” said Professor Liu. He continued: “The deuteration effect of the N-acyl moiety of indoline-based substrates also suggested that the C(sp³)–H bond at the α-position of the carbonyl motif is crucial to the oxidizing reactivity (Scheme 2C). Density functional theory (DFT) calculations were performed for the stereo-determining hydrogen atom transfer process, which suggested that the triplet state was the ground state, and the effective chiral recognition arises from additional CH···F hydrogen bonding interaction between the tBu group of the (R)-enantiomer and the 2,4-difluorophenyl moiety of catalyst C1 in 3TS.” Professor Liu concluded: “Inspired by the interesting and promising non-covalent interaction leading to effective chiral recognition, further efforts on oxidative KR of simple acyclic organic azides and other valuable chiral compounds, that are difficult to access by existing methods, are ongoing.”
About the authors

**Lei Liu** was born in Zibo, Shandong (P. R. of China). He received his B.S. from Lanzhou University (P. R. of China) in 2003. After completing his M.S. program with Professor Rui Wang at the same university, he went to Pittsburgh (USA) in 2006 and pursued graduate studies under the guidance of Professor Paul Floreancig at the University of Pittsburgh. After earning his Ph.D. in 2011, he took a postdoctoral position in the laboratory of Professor Yoshito Kishi at Harvard University (USA). In June 2012, he began his independent career as a professor in the School of Pharmaceutical Sciences of Shandong University (P. R. of China). Since August 2015, he has been a professor in the School of Chemistry and Chemical Engineering of Shandong University (P. R. of China). His research interests lie in the development of selective oxidation methodology and its application in medicinal chemistry.

**Pengbo Ye** was born in Sichuan (P. R. of China). He received his B.S. in pharmacy from Shandong University (P. R. of China) in 2017. Then he received his M.S. in 2020 under the supervision of Prof. Lei Liu at Shandong University (P. R. of China). His research focuses on oxidative kinetic resolution through asymmetric oxidation of carbon–hydrogen bonds. Now, he is a chemical engineer working at the Petrochemical Research Institute, CNPC. His main research interests are propylene polymerization catalysts and polypropylene products.

**Aili Feng** was born in Dezhou, Shandong (P. R. of China). She received her B.S. in chemistry from Liaocheng University (P. R. of China) in 2018. She obtained her M.S. in physical chemistry from Shandong University (P. R. of China) in 2021, where she performed theoretical research with Prof. Rongxiu Zhu. Then she began her Ph.D. studies at Shandong University (P. R. of China), where she works on theoretical investigations of transition-metal-catalyzed organic reactions under the mentorship of Prof. Dongju Zhang.

**Lin Wang** was born in Shandong, P. R. of China. She received her B.S. in pharmacy from Shandong University of Traditional Chinese Medicine (P. R. of China) in 2017. She completed her M.S. studies with Prof. Wei Li at the same university in 2020. She focused on oxidative kinetic resolution of organic azides as an exchange student at Shandong University (P. R. of China) under the direction of Prof. Lei Liu from 2018–2020. Now she is an analytical scientist working at Shandong Bainuo Pharmaceutical Co., Ltd.

**Min Cao** was born in Shandong, P. R. of China. She received her B.S. in chemistry from Hubei University (P. R. of China) in 2015. After completing her M.S. program with Prof. Lei Liu at Shandong University (P. R. of China) in 2019, she continued her Ph.D. studies in the same research group, where she is developing base-metal-catalyzed asymmetric oxidation of carbon–hydrogen bonds.

**Rongxiu Zhu** was born in Linyi, Shandong (P. R. of China). She received her Ph.D. degree from Shandong University (P. R. of China) in 2007 under the supervision of Prof. Chengbu Liu and Prof. Dongju Zhang. In 2011, she went to Texas A&M University (USA) as a one-year visiting scholar with Prof. Steven E Wheeler. Currently, she is an associate professor in Shandong University, and her research interests are focused on elucidating the reaction mechanism and origins of selectivities in transition-metal-catalyzed, organocatalyzed and photocatalyzed reactions by DFT calculations.