Organocatalytic Stereoselective Cyanosilylation of Small Ketones

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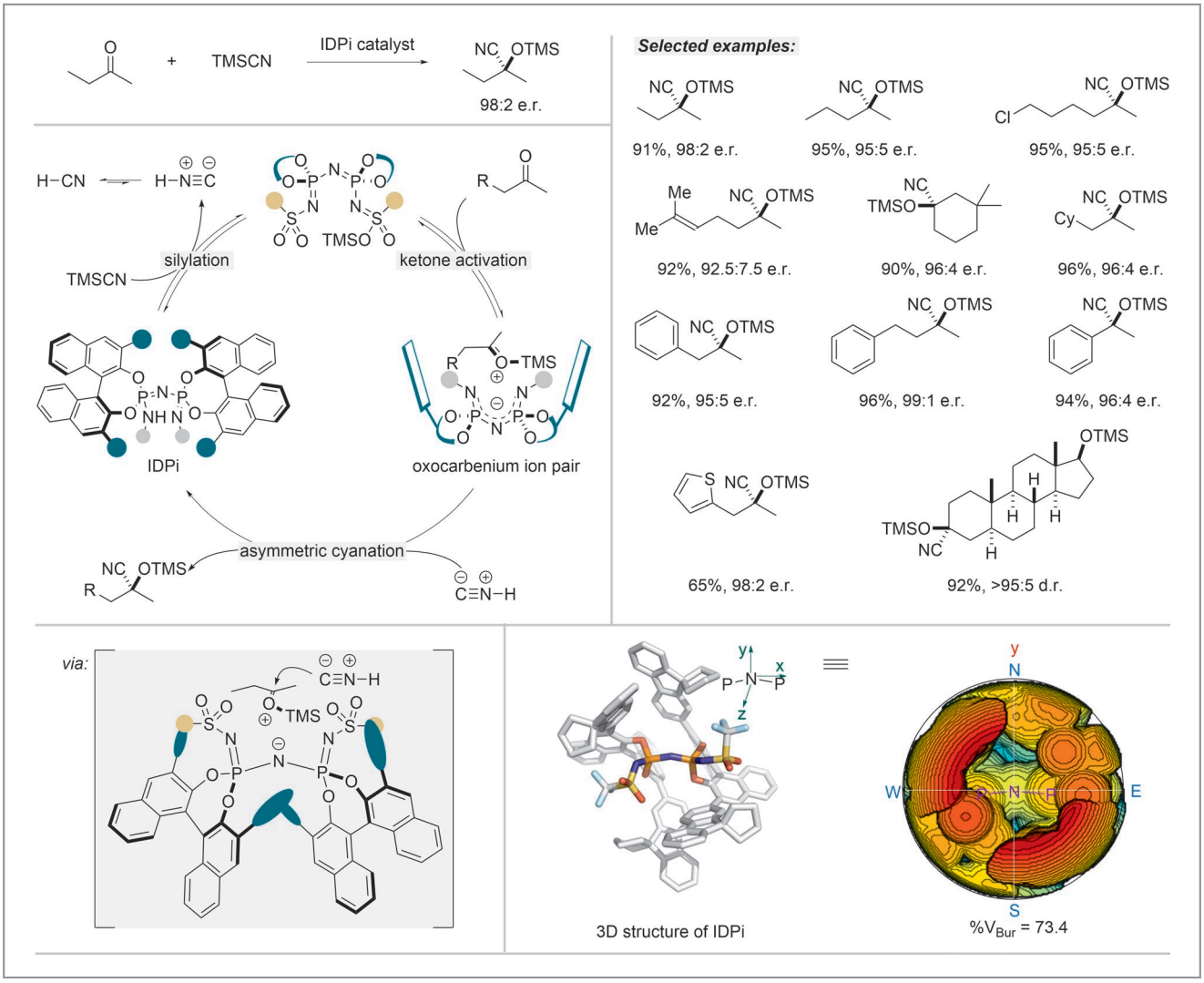
The asymmetric cyanosilylation of carbonyl compounds is a highly versatile approach to build C–C bonds, enabling access to silyl-cyanohydrins, which are important building blocks with wide applications in the pharmaceutical and chemical industry. In past decades, the enantioselective cyanosilylation reaction has been thoroughly studied and many fascinating methodologies have been established.[1] Nevertheless, the enantiofacial discrimination of dialkyl ketones is difficult to control with chiral catalysts, due to the limited steric and electronic differences of the two substituents, and constitutes a long-standing challenge in organic synthesis. In particular, asymmetric reactions involving 2-butanone, which carries a methyl and an ethyl group on the carbonyl group, typically can only be catalyzed by enzymes following the 'lock-and-key principle'. Recently, the research group of Professor Benjamin List at the Max-Planck-Institute für Kohlenforschung (Germa-



Scheme 1 Organic acid-catalyzed asymmetric cyanosilylation of ketones

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ny) has designed and employed a sterically confined organic superacidic imidodiphosphorimidate (IDPi) catalyst to successfully accomplish the asymmetric cyanosilylation of 2-butanone with an enantiomeric ratio of 98:2 (Scheme 1). "This particular reaction has already been studied with various catalysts, including engineered enzymes, metal complexes, and organocatalysts, which all proved to be competent catalysts, albeit furnishing the desired product with insufficient selectivity," said Professor List.

"In the past five years, IDPi-based catalysis has been employed to solve challenging problems in the field of asymmetric catalysis, such as activation of inert olefins,[2] single aldolizations of acetaldehyde enolates,[3] transformation of a non-classical carbocation,[4] and organocatalytic reactions with (sub)ppm-level catalyst loading.[5] While addressing these synthetic challenges, we are also keen to seek better ways to differentiate extremely challenging enantiofaces, including those of 2-butanone. Here we were encouraged from previous results on Diels–Alder reaction and intramolecular Friedel–Crafts reaction involving the differentiation of methyl and ethyl groups,[6,7]" said Professor List.

To probe the mechanism of this new synthetic application of IDPi catalysis, the authors of the title *Nature* article first performed the reaction under the catalysis of a less acidic chiral disulfonimide (DSI) catalyst. The reaction exclusively provided the corresponding silyl enol ether, and no silylcyanohydrin was detected. "This result suggests the decisive role of strong acidity in the chemoselectivity of this reaction," explained the first author Dr. Hui Zhou, who continued: "We performed NMR studies and captured the formation of silyl enol ethers in the initial stage of the reaction. Subsequently, a key control experiment between the silyl enol ether and in situ generated (iso)hydrocyanic acid further confirmed the surprising existence of the enol silane under the reaction conditions."

Professor Gui-Juan Cheng and co-workers at the Chinese University of Hong Kong (China) performed DFT calculations to support the experimental observations. "Results of structural analysis showed that the IDPi catalyst has a confined structure with a buried volume of up to 73.4%, and its central skeleton and substituents form a narrow chiral pocket, which efficiently differentiates the transition state structures. Our calculations suggest that varying the substituents of the catalyst can influence the shape, size, embedded volume and steric hindrance, thereby providing enzyme-like pockets to specifically recognize different types of substrates such as aliphatic ketones and aromatic ketones," explained Professor Cheng.

Based on the experimental, NMR and theoretical results, the authors proposed a plausible mechanism as follows: 1. a silylium-based active catalyst is generated from the reaction of the pre-catalyst IDPi and TMSCN with the release of isohydrocyanic acid; 2. activation of the ketone leads to the formation of an oxycarbonium ion pair intermediate; 3. addition of isohydrocyanic acid furnishes the target product and regenerates the catalyst. "We hope that our research will stimulate further research on confinement control in selective catalysis," concluded Professor List.

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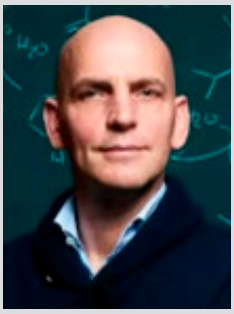
About the authors

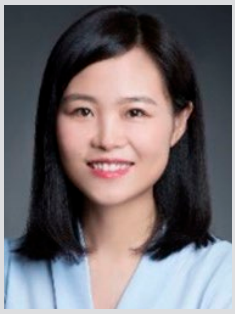


Prof. B. List

Benjamin List was born in 1968 in Frankfurt, Germany. He graduated from Freie University Berlin (Germany) in 1993 and received his Ph.D. (1997) from the University of Frankfurt (Germany). After postdoctoral studies (1997–1998) as a Feodor Lynen Fellow of the Alexander von Humboldt foundation at The Scripps Research Institute (USA), he became a Tenure Track Assistant Professor there in January 1999. Subsequently, he developed the first proline-catalyzed asymmetric intermolecular aldol-, Mannich-, Michael-, and α-amination reactions. In 2003 he moved to the Max-Planck-Institut für Kohlenforschung (Germany), where he has been a director since 2005. From 2012 until 2014 he was the managing director of the institute. He has served as an honorary professor at the University of Cologne (Germany) since 2004, and as a specially appointed professor at Hokkaido University (Japan) since 2020. His research interests are new catalysis concepts and chemical synthesis in general. He has pioneered and contributed several concepts including aminocatalysis, enamine catalysis, and asymmetric counteranion-directed catalysis (ACDC). His accomplishments have been recognized by several awards including the Otto Bayer Prize (2012), the Mukaiyama Award (2013), the Cope Scholar Award (2014), the Gottfried Wilhelm Leibniz Prize (2016), member of the German National Academy of Sciences Leopoldina (2018), Nobel Prize in Chemistry (2021), and Herbert C. Brown Award (2022).

Dr. H. Zhou

Hui Zhou was born in Ezhou city, Hubei (P. R. of China). She obtained her Ph.D. in 2016 from Lanzhou Institute of Chemical Physics (LICP), Chinese Academy of Sciences (CAS, China) under the supervision of Prof. Gaoxi Jiang and Prof. Chungu Xia. After a short time staying in Prof. Xin Cui's lab as a postdoctoral fellow at Mississippi State University (USA), she moved to the Max-Planck-Institut für Kohlenforschung (Mülheim an der Ruhr, Germany) and worked as a postdoctoral fellow under the supervision of Prof. Benjamin List. Currently her research focuses on asymmetric organocatalysis. She has received prizes such as the Ph.D. National Scholarship (2015, Ministry of Education of China), and a Post-doctoral Fellowship (2017, Max-Planck Society).

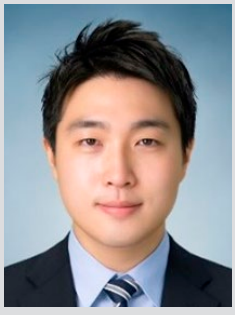


Prof. G. J. Cheng

Gui-Juan Cheng received her Ph.D. from Peking University (P. R. of China) in 2015 under the supervision of Prof. Yun-Dong Wu and Prof. Xinhao Zhang. She then worked in Prof. Walter Thiel's research group at Max-Planck-Institut für Kohlenforschung (Germany) as a postdoctoral fellow. Dr. Cheng began her independent career as an assistant professor at the Chinese University of Hong Kong (Shenzhen, P. R. of China) in 2018. The research program of her laboratory has been focused on mechanistic studies of organic and enzymatic reactions and the mechanism-based development of organic and biocatalytic reactions.

Dr. Y. Zhou

Yu Zhou obtained his Ph.D. in chemistry at The Hong Kong University of Science and Technology (HKUST, P. R. of China) in 2018 under the supervision of Professor Zhenyang Lin. During that time, he carried out computational studies on the reaction mechanism of transition-metal catalysts, especially copper catalysts. Currently, he is the associate research fellow at the Chinese University of Hong Kong, Shenzhen (CUHKSZ, P. R. of China). His research interest is focused on theoretical studies of electronic structures and reaction mechanisms of organocatalysts and metalloenzymes.



Dr. H.-Y. Bae

Han-Yong Bae was born in the Republic of Korea. He received his Ph.D. from Sungkyunkwan University (2015, SKKU, Korea), conducting studies on biomimetic Brønsted base catalyzed asymmetric organocatalysis under the supervision of Professor Choong Eui Song. After completing his graduate studies, he moved to Germany and pursued postdoctoral research with Professor Benjamin List at the Max-Planck-Institut für Kohlenforschung. He developed a new highly active silylium Lewis acid mediated organocatalytic asymmetric Mukaiyama aldol reaction (approaching sub-ppm-level asymmetric organocatalysis). In 2019, Han-Yong was appointed as an Assistant Professor at

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Ulsan National Institute of Science and Technology (UNIST, Korea), and shortly thereafter, moved to SKKU as an Assistant Professor (tenure track). His current research interests are exploiting fundamental homogeneous catalysis as a tool for further multidisciplinary and practical applications in the synthesis of biologically relevant molecules, materials science, and biological science.

Dr. M. Leutzsch

Markus Leutzsch received his M.Sc. in chemistry from Leipzig University (Germany) in 2011. He then moved to the Max-Planck-Institut für Kohlenforschung (Mülheim an der Ruhr, Germany) to pursue his doctoral studies in the group of Prof. Benjamin List and the in-house NMR department under the guidance of Dr. Christophe Farés. Thereafter he moved to the University of Cambridge (UK) to work as postdoctoral research associate in the Magnetic Resonance Research Centre lead by Prof. Dame L. F. Gladden, Prof. M. D. Mantle and Prof. A. J. Sederman. He then moved back to the Max-Planck-Institut für Kohlenforschung (Germany) in late 2018 as a senior NMR research scientist. His current research interests include mechanistic investigations of a broad range of catalytic reactions and the spectroscopic characterization of NMR-active transition-metal nuclei.

Y. Li

Yihang Li is currently a graduate student at Max-Planck-Institut für Kohlenforschung (Mülheim an der Ruhr, Germany) in the group of Professor Benjamin List, where his research projects focus on the development of chiral confine super-base catalysts for enantioselective reactions. He is also involved with studies on super-acid catalysis. Before his graduate studies at Max-Planck-Institut für Kohlenforschung, he completed his M.S. in organic chemistry from the Nankai University (P. R. of China) in 2017 under the supervision of Prof. Pingping Tang.

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