



Legacy

The legacy of Professor Li-Xin Dai: Organometallic and asymmetric catalysis

Tao Tu,^{2,*} Yong-Gui Zhou,^{3,*} Yong Tang,^{1,*} Boliang Lou,^{4,*} and Shu-Li You^{1,*}

Prof. Li-Xin Dai will always be remembered for his development of organometallic chemistry and asymmetric synthesis, especially for the refining and synthesis of aureomycin, organoboron chemistry, and the development of novel chiral ligands for transition-metal-catalyzed asymmetric reactions. In addition to making significant contributions to science, Prof. Dai has also made a profound impact as an esteemed educator and mentor, imparting his knowledge and work ethic to future generations of chemists and fostering fruitful collaborations with his colleagues.

Above image: Prof. Dai won the first Chinese Chemical Society Lifetime Achievement Award (2018)





Prof. Li-Xin Dai as a child

Prof. Li-Xin Dai was born on November 13, 1924 in Beijing. His grandfather, Mr. Rubin Dai, was once a renowned industrialist in Shanghai. His father, Mr. Chen-shui Dai, graduated from Peking University and worked as a mining engineer. Prof. Dai completed his early education from Beijing Yuying Primary School in 1936 and Shanghai Sanyu Middle School in 1942, and he was admitted to the Department of Chemistry at Shanghai College (merged into other universities in 1952). In 1943, he transferred to the Department of Chemistry at Zhejiang University, where he graduated in 1947. He then worked in Shanghai Iron and Steel Company and subsequently East China Metallurgical Bureau. In 1953, he joined Shanghai Institute of Organic Chemistry (SIOC), Chinese Academy of Sciences (CAS), serving as assistant professor, associate professor, and full professor. In 1950, Prof. Li-Xin Dai married his wife, Ms. Zhu-Xin Dong, and their daughter Jing Dai was born in 1956.



Prof. Li-Xin Dai married his wife, Zhu-Xin Dong, in 1950

¹State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Lu, Shanghai 200032, China

²Department of Chemistry, Fudan University, Shanghai 200433, China

³State Key Laboratory of Catalysis, Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian, Liaoning 116023, China

⁴Pharmaron Beijing Co., Ltd., No. 6 Taihe Road, BDA, Beijing 100176, China

*Correspondence: taotu@fudan.edu.cn (T.T.), ygzhou@dicp.ac.cn (Y.-G.Z.), tangy@sioc.ac.cn (Y.T.), blou@pharmaron.com (B.L.), slyou@sioc.ac.cn (S.-L.Y.)

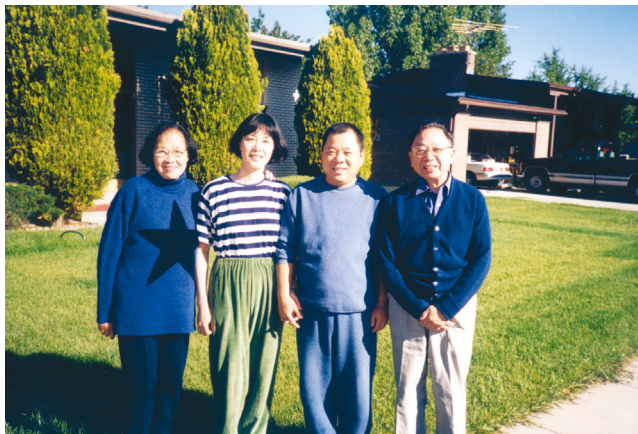
<https://doi.org/10.1016/j.chempr.2024.09.003>



Prof. Li-Xin Dai presenting at the 10th OMCOS conference in Versailles, in 1999

Prof. Li-Xin Dai is one of the pioneers in organometallic chemistry and asymmetric synthesis in China. He was elected as an academician of the CAS in 1993. Throughout his career, he has been recognized with the National Natural Science Award (2nd class) twice (2002 and 2013), the Ho Leung Ho Lee Foundation Prize for Scientific and Technological Innovation (2002), the Chiral Chemistry Life Achievement Award of the Chinese Chemical Society (2014), the Chinese Chemical Society Lifetime Achievement Award (2018), and the Chinese Chemical Society Huang Yao-Zeng Lifetime Achievement Award in Organometallic Chemistry (2018). He published 256 academic papers, edited or translated 15 books, and trained 49 graduate students and postdoctoral fellows. He served as the co-chairman for the 19th IUPAC International Conference on Organometallic Chemistry (2000) and the 7th IUPAC International Conference on Heteroatom Chemistry (2004).

In the 1950s, Prof. Li-Xin Dai participated in the research project of aureomycin chemistry led by Prof. Yao-Zeng Huang, including the extraction, separation,



Prof. Li-Xin Dai and his wife Zhu-Xin Dong, daughter Jing Dai, and son-in-law Yong-Ming Yuan at the home of Jing (Utah)

biological evaluation, and total synthesis of aureomycin.^{1,2} Considering that the absolute configuration of aureomycin had not yet been determined at that time, Prof. Dai proposed the assignment of the absolute configuration through asymmetric synthesis. Eventually, the successful establishment of the extraction process of aureomycin led to the large-scale production of aureomycin via collaboration with the Shanghai Third Pharmaceutical Factory.

After 1958, Prof. Li-Xin Dai spent most of his efforts on the administrative work of science and technology. In the 1960s, he conducted his independent research on hydroboration reactions and the chemistry of carboranes. He investigated the hydroboration reactions of α,β -unsaturated carbonyl compounds and found that the elimination reactions occurred, followed by re-hydroboration, in such systems.³⁻⁵ In 1978, as requested by Prof. Yu Wang, the director of the SIOC at that time, Prof. Dai resumed his role in administrative work, focusing on scientific research management.

In 1984, at the age of 60, Prof. Dai returned to scientific research after retiring from the administrative role. He chose the challenging field of "asymmetric synthesis" and was one of the earliest researchers in this field from China. Recognizing the crucial role of metal coordination in controlling the regioselectivity and stereoselectivity



Prof. Li-Xin Dai and his PhD student, Boliang Lou, in library



Prof. Li-Xin Dai working in his office (2010)

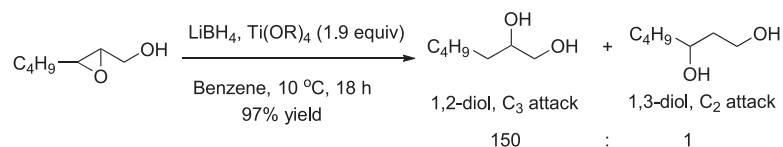
of heteroatoms and unsaturated systems, Prof. Dai has conducted a series of studies to gain insights into how metal coordination affects selectivity, especially for the enantioselectivity of the asymmetric reactions.

“At the age of 60, Prof. Dai returned to scientific research after retiring from the administrative role.”

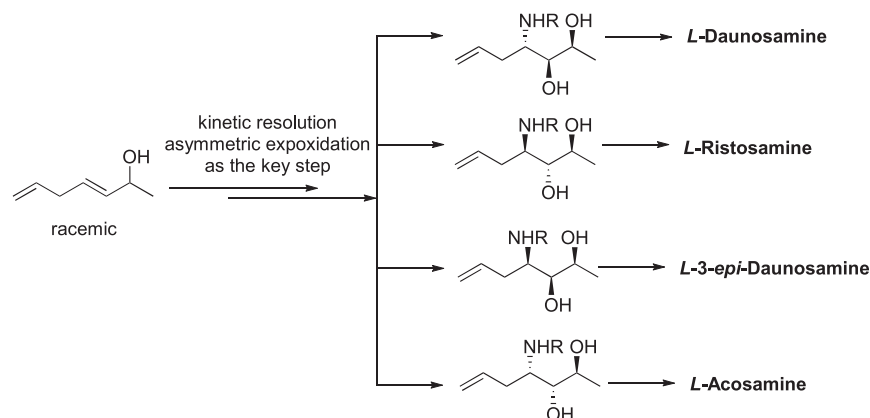
Several representative works from Prof. Dai are listed below:

- (1) Prof. Dai successfully achieved the ring opening reaction of epoxy alcohols with high regio- and stereo-selectivities. The regioselective ring opening of 2,3-epoxide alcohols and acid at the C3 position was enabled by the coordination activation of tetraisopropoxytitanium with regioselectivity greater than 100:1.⁶ Afterward, the hydride ring opening reaction with $\text{LiBH}_4\text{-Ti}(\text{O}^i\text{Pr})_4$ was developed. By combining it with the Sharpless asymmetric epoxidation reaction, the asymmetric synthesis of all members of the natural product 2,3,6-trideoxy-3-aminohexose family was realized for the first time. Various amino sugars and their isomers, like daunosamine, acosamine, ristosamine, and megosamine, were successfully obtained from a single starting material.⁷ These carbohydrates are key components for several important anti-cancer substances such as calicheamicin. He also successfully applied this methodology to the synthesis of chiral drug chloramphenicol and the side chain of anticancer drug taxol. The ring opening reaction of epoxy alcohols with hydride has been indexed in multiple comprehensive books and highlighted in many reviews. This important method for regioselective ring opening of 2,3-epoxide at the C3 position has been extensively applied in the synthesis by many groups.
- (2) Prof. Dai found that the regioselectivity for rhodium-catalyzed hydroboration of styrenes was exactly opposite to that of the classical hydroboration reactions, affording the secondary alcohols with high regioselectivity. The asymmetric reaction could be achieved in excellent enantioselectivity (>90% ee) with catalytic amount of chiral source,⁸ while a stoichiometric chiral source was usually required in the classical asymmetric hydroboration reaction. This work was included in the classic organic chemistry textbook, “Advanced Organic Chemistry” by Jerry March.
- (3) Taking advantage of the coordination ability of palladium with double bonds or heteroatoms in the substrate, Prof. Dai achieved success on remote regioselective control.⁹ Using this strategy, he established a new method for synthesizing optically active morpholine derivatives, with high enantioselectivity

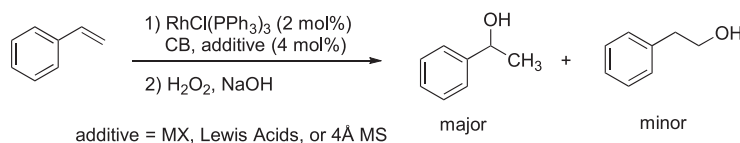
A asymmetric ring opening of epoxy alcohols



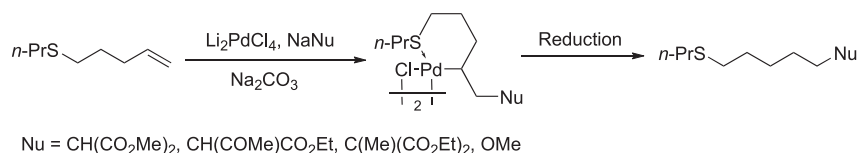
B Asymmetric synthesis of 2,3,6-trideoxy-3-aminohexose



C Rh-catalyzed hydroboration of styrene



D Remote regioselective control



Asymmetric ring opening of epoxy alcohol, asymmetric synthesis of 2,3,6-trideoxy-3-aminohexose, Rh-catalyzed hydroboration of styrene, and remote regioselective control

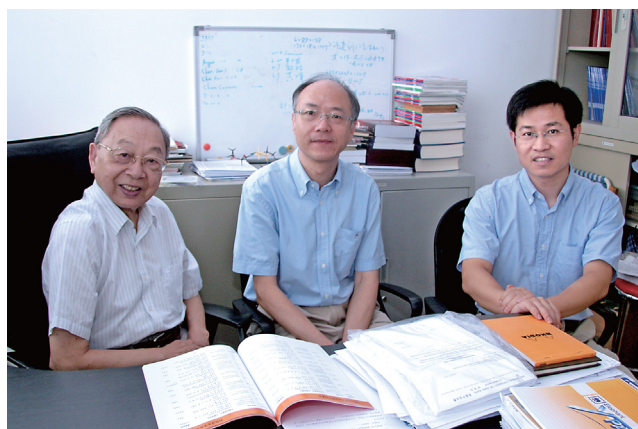
up to 99% ee. By varying the conditions, four different isomers could be obtained with high selectivity, and some of which could make the preparation of chiral drugs such as amorolfine and viloxamine more concisely.¹⁰

- (4) In 1987, Prof. Dai designed and synthesized 1,1'-isoquinoline and its dinuclear complex with chiral palladium compounds, displaying 100% chiral recognition during the coordination process. When racemic 1,1'-isoquinoline reacted with palladium compounds in the *R* configuration, 100% dinuclear complexes in the (*R,R,R*) configuration were obtained via a dynamic kinetic resolution process.¹¹ In the early 1990s, Prof. Dai synthesized a novel chiral ligand with C₂ symmetry, a chiral bidentate ligand named bisoxazoline,¹² at the same time period that chiral bisoxazolines were discovered by other groups. This type of ligand could be applied for asymmetric dihydroxylation of unfunctionalized double bonds, yielding an ee value of up to 70%. The chiral bisoxazoline ligands have been proven to be one of the most widely used and effective ones in asymmetric catalysis nowadays.

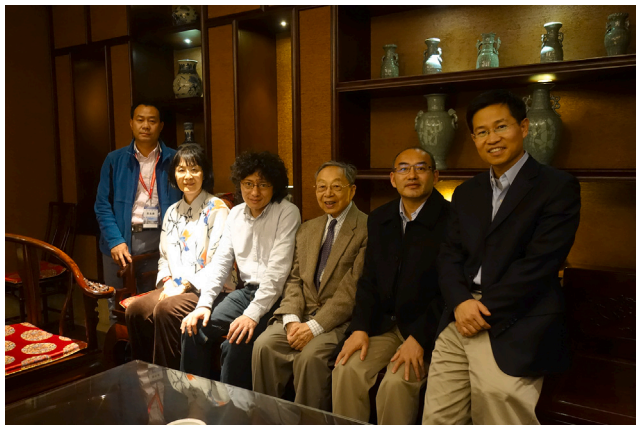


Prof. Li-Xin Dai's students celebrated his birthday in 2018

- (5) Prof. Dai also developed the stereoselective synthesis of vinyl cyclopropanes, vinyl epoxides, and aziridines via the ylide pathway. Furthermore, asymmetric synthesis of alkynyl aziridines was realized by using the chiral sulfonium ylide reagents.¹³ Due to his outstanding contributions in this field, he was invited to write a review on this topic for *Chemical Reviews* in 1997, in collaboration with Prof. V.K. Aggarwal.¹⁴
- (6) Prof. Dai contributed to the synthesis of chiral ferrocenyl ligands and investigation of the role of planar chirality in asymmetric catalysis. He found that central chirality played a role in determining the enantioselectivity and absolute configuration of the product in palladium-catalyzed asymmetric allylic substitution reaction with

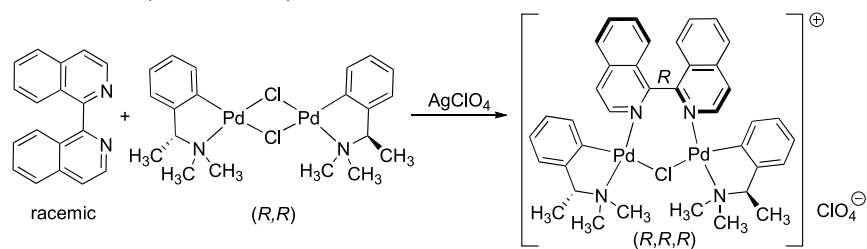


The project of asymmetric catalysis based on chiral *P,N*-ligands won the National Natural Science Award (the second class); Prof. Li-Xin Dai with Xue-Long Hou and Shu-Li You (2013)

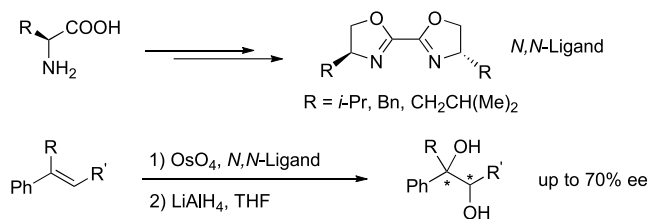


Prof. Li-Xin Dai with Yong-Gui Zhou, Jing Dai, Jin-Quan Yu, Yong Tang, and Shu-Li You in Shanghai in 2016

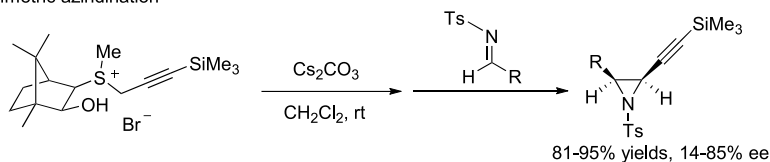
A Chiral 1,1'-isoquinoline Pd complex



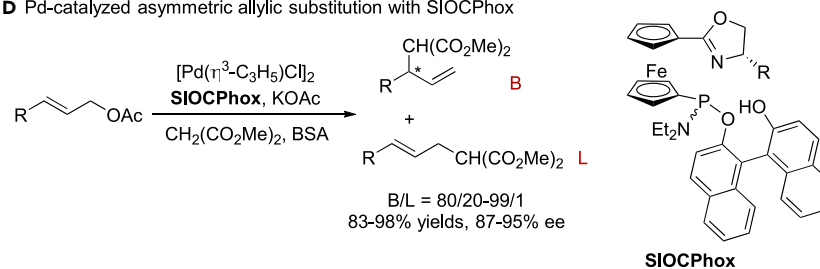
B Synthesis of bisoxazoline ligands and application



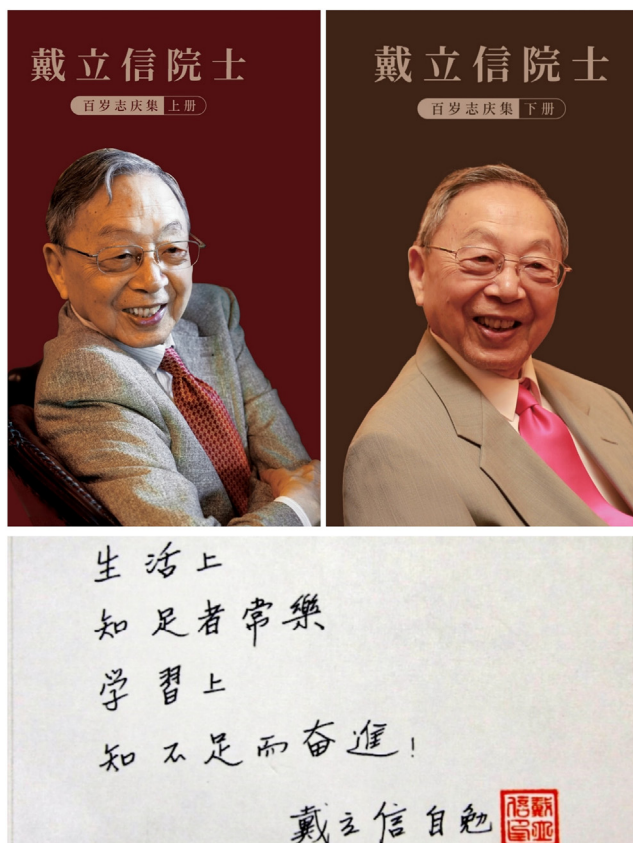
C Asymmetric aziridination



D Pd-catalyzed asymmetric allylic substitution with SIOCPbox



Chiral 1,1'-isoquinoline Pd complex, bisoxazoline ligands, asymmetric synthesis of aziridines, and Pd-catalyzed asymmetric allylic substitution with SIOCPbox



Prof. Li-Xin Dai's motto on scientific research in Chinese

ferrocenyl-oxazoline-type ligands. The matching of planar chirality and central chirality is critical in achieving high enantioselectivity.¹⁵

In addition, the 1,1'-disubstituted ferrocene *P,N*-ligands they synthesized, named SIOCPfox, were found to be highly efficient in palladium-catalyzed asymmetric allylic substitution reactions for the unsymmetrical allyl substrates. Today, this type of novel ligand remains to be one of the most successful ones in palladium catalysis for the unsymmetrical allyl substrates favoring the formation of branch products.¹⁶ Prof. Dai was invited to co-edit a book entitled "Chiral Ferrocenes in Asymmetric Catalysis-Synthesis and Applications," published by Wiley VCH, together with Prof. Xue-Long Hou.

Prof. Dai played a key role in promoting the asymmetric catalysis research field in China. A review article on the emergence of chiral technology, published in *HuaXue TongBao* in 1995, authored by him together with Prof. Xiyan Lu and Prof. Guangmei Zhu, called on China to pay attention to the research of chiral technology, especially asymmetric catalysis.¹⁷ This article has greatly inspired and promoted the development of asymmetric catalysis area in China.

"[Prof. Dai] called on China to pay attention to the research of chiral technology, especially asymmetric catalysis."

Prof. Dai never stopped his passion for science, even at the late stage of his life. For instance, in 2012, Prof. Dai co-edited a comprehensive book, "Organic Chemistry Breakthrough and Perspectives," published by Wiley VCH, with his

colleague, Prof. Kuiling Ding. This book covers topics from total synthesis of natural products, chemical biology, synthetic methodology, and physical organic chemistry, to chemical issues related to urgent needs of human beings. It consists of 21 chapters written by over 100 top scientists from various fields of organic chemistry. In 2020, he co-edited and translated the eighth edition of "Organic Chemistry: Structure and Function," together with Prof. Zhenfeng Xi and Prof. Sanzhong Luo, which received high praise in China.

In addition to his excellence in scientific administration and organic chemistry research, Prof. Dai was also known for making significant contributions to promoting international academic exchange, helping young generations and being a role-model for our scientific community. His famous life motto, "Be content with your life, be insatiable, and forge ahead with your study and research," now is a big inspiration for his students and many others.

"Be content with your life, be insatiable, and forge ahead with your study and research."

DECLARATION OF INTERESTS

Shu-Li You is an advisory board member of *Chem*.

REFERENCES

- Huang, Y., Ni, D., Zong, H., and Dai, L. (1956). Stability of aureomycin at different pH. *Acta Chim. Sinica* 22, 85–92.
- Chen, S., Jin, P., Liu, P., Xu, S., Tong, C., Xu, W., Wang, Y., Huang, Y., Ni, D., Dai, L., Tu, C., Zong, H., Yin, H., Shen, S., and Shan, W. (1956). A report on the fermentation and isolation of aureomycin and the screen of its producing species. *Kexue Tongbao* 7, 73–74.
- Dai, L., and Qian, C. (1963). Hydroboration of α,β -unsaturated aldehydes. *Kexue Tongbao* 14, 56–57.
- Dai, L., and Qian, C. (1965). Hydroboration of functionally substituted olefins I: hydroboration of crotonaldehyde. *Acta Chim. Sinica* 31, 370–376.
- Qian, C., Ye, C., and Dai, L. (1965). Hydroboration of functionally substituted olefins II: hydroboration of α,β -unsaturated aldehydes, ketones and acids. *Acta Chim. Sinica* 31, 376–383.
- Dai, L., Lou, B., Zhang, Y., and Guo, G. (1986). Regioselective titanium mediated reductive opening of 2,3-epoxy alcohols. *Tetrahedron Lett.* 27, 4343–4346.
- Dai, L., Lou, B., and Zhang, Y. (1988). A simple, divergent, asymmetric synthesis of all members of the 2,3,6-trideoxy-3-aminohexose family. *J. Am. Chem. Soc.* 110, 5195–5196.
- Zhang, J., Lou, B., Guo, G., and Dai, L. (1992). Rhodium catalyzed hydroboration: effect on regiochemistry by halides and molecular sieves of the reaction of styrenes. *Acta Chim. Sinica* 50, 910–913.
- Zhang, Y., Shi, X., and Dai, L. (1992). Regiospecific distal carbopalladation of bishomoallylsulfides and β,γ -; γ,δ -unsaturated thioketals. *Acta Chim. Sinica* 50, 726–728.
- Lai, J., Shi, X., Gong, Y., and Dai, L. (1993). Palladium(II)-catalyzed synthesis of optically active tetrahydro-1,4-oxazine derivatives. *J. Org. Chem.* 58, 4775–4777.
- Dai, L., Zhou, Z., Zhang, Y., Ni, C., Zhang, Z., and Zhou, Y. (1987). 1,1'-Bi-isoquinoline: a chiral bidentate N-donor ligand with C_2 -symmetry; formation of optically active complexes with high chiral recognition. *J. Chem. Soc., Chem. Commun.* 1987, 1760–1762.
- Yang, R., Chen, Y., and Dai, L. (1991). The synthesis and application of bidentate N-donor ligands 2,2'-bis(oxazolines). *Acta Chim. Sinica* 49, 1038–1040.
- Li, A., Zhou, Y., Dai, L., Hou, X., Xia, L., and Lin, L. (1997). Asymmetric aziridination over ylides: highly stereoselective synthesis of acetylenyl-N-sulfonylaziridines. *Angew. Chem. Int. Ed. Engl.* 36, 1317–1319.
- Li, A., Dai, L., and Aggarwal, V. (1997). Asymmetric ylide reactions: epoxidation, cyclopropanation, aziridination, olefination, and rearrangement. *Chem. Rev.* 97, 2341–2372.
- Deng, W., You, S., Hou, X., Dai, L., Yu, Y., Xia, W., and Sun, J. (2001). Importance of planar chirality in chiral catalysts with three chiral elements: the role of planar chirality in 2'-substituted 1,1'-P,N-ferrocene ligands on the enantioselectivity in Pd-catalyzed allylic substitution. *J. Am. Chem. Soc.* 123, 6508–6519.
- You, S., Zhu, X., Luo, Y., Hou, X., and Dai, L. (2001). Highly regio- and enantioselective Pd-catalyzed allylic alkylation and amination of monosubstituted allylic acetates with novel ferrocene P,N-ligands. *J. Am. Chem. Soc.* 123, 7471–7472.
- Dai, L., Lu, X., and Zhu, G. (1995). Emergence of chiral technology. *Huaxue Tongbao* 46, 15–22.