TKK Science Award in Chemical Science

New Privileged Chiral Ligand for Catalytic Asymmetric Reactions

By YAN Fusheng (Staff Reporter)

CAS Member Prof. FENG Xiaoming, distinguished chemist from College of Chemistry, Sichuan University

The 2020 TKK Science Award in Chemical Science went to CAS Member Prof. FENG Xiaoming for his important contributions to chirality science, particularly the discovery of a new type of privileged chiral ligands termed *N*, *N*´-dioxide that has found widespread applications in asymmetric catalytic reactions.

The term chiral, from the Greek for 'hand', refers to anything which can't be superimposed on its own mirror image; that is, just like the relationship between one's right hand and left hand that, no matter how you shift or rotate, you can't exactly superimpose one onto the other. So, whenever something is not superimposable on its own mirror image, we call it chiral, or it has chirality or 'handedness'.

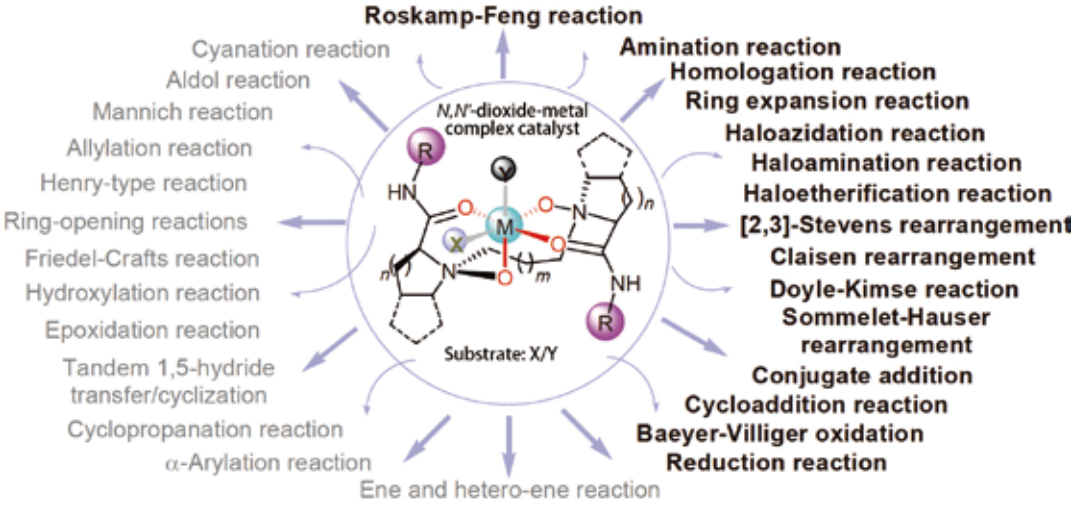
Chirality is a fundamental property of nature. For example, the spiral Milky Way is chiral, gloves and shoes are chiral, snail shells are chiral (some individuals have shells that spiral in a right-handed direction, others have left-handed shells), and most biological molecules including glucose, amino acids and nucleic acids are also chiral, and even light can be chiral.

Chirality plays important roles in life sciences, pharmacy and materials science. Notably, the importance of chirality, or handedness, in drug development got noticed in a devastating way. Back in the 1950s, a drug named Thalidomide was widely prescribed to pregnant women to relieve the morning sickness. It was later discovered that Thalidomide is a chiral molecule and while the left-handed molecule was effective, the right-handed one was highly toxic, causing thousands of children around the world born with severe defects.

This tragedy, however, greatly stimulated intensive research into chiral molecules, as well as new ways of producing chiral compounds with high enantioselectivity, *i.e.* producing compounds with one particular handedness.

To efficiently obtain chiral molecules, chemists resort to asymmetric catalysis, which has now become one of the most active research areas in chemistry. In particular, metal-catalyzed asymmetric reactions have attracted much attention in recent years. These chiral metal catalysts usually consist of a central metal ion and a surrounding chiral ligand. The central metal ion is catalytically active and the surrounding chiral ligand, acting as a chiral environment, controls the enantioselectivity of the catalytic reactions.

Though numerous chiral ligands, as well as chiral catalysts, have been reported in the last two decades, only a handful of them, rooted in very few core structures,



Representative asymmetric reactions catalyzed by chiral *N,N'*-dioxide-metal complexes, in which many new or challenging reactions are shown in black bold. (Image by FENG's Lab)

can be truly regarded as 'privileged chiral ligands', or 'privileged chiral catalysts' that are catalytically proficient and of good enantioselectivity over a wide range of different reactions. Interestingly, almost all of these privileged chiral ligands/catalysts share relatively rigid conformations, and, by default, having a chiral ligand of rigid conformation was considered as a prerequisite to be a privileged chiral ligand/catalyst.

Jumping outside of the box, FENG and co-workers developed a new type of privileged chiral ligands, termed *N, N´*-dioxide, that is conformationally flexible. Its flexible conformation can be mainly attributed to a variable length alkyl chain that acts as a linker to hold two chiral 'palms' together. Upon coordination with a metal ion, the chiral metal complex forms a chiral 'pocket', which is flexible and thereby allows substrate of different sizes to fit inside the pocket.

By coordinating with over 20 different types of metal ions, these versatile chiral ligands, with varying side chain, linker or backbone, provide an arsenal of chiral metal complexes that can be tuned to catalyze a plethora of asymmetric reactions, including many new and challenging reactions, with high enantioselectivity. For example, the first asymmetric Roskamp reaction was achieved with a *N, N´*-dioxide/Sc(III) complex at low catalyst loading, which updates the comment about β-keto esters in text of *Organic Chemistry*, Oxford, and the reaction is amended as "Roskamp-Feng reaction" in Elsevier's *Organic Synthesis Based on Name Reactions*. These new methods of asymmetric reactions enable the efficient synthesis of several biologically active drugs and natural products.

Notably, this new family of chiral ligands/catalysts have many advantageous properties, including wide substrate generality, excellent enantioselectivity and activity, cheap and available materials, mild reaction temperature, relative insensitivity to moisture, operational simplicity, and facile preparative-scale applications.

The discovery of these new *N, N´*-dioxides also updates a new guideline to the rational design of other privileged chiral ligands/catalysts. "The future of the *N*-oxide family of catalysts in asymmetric transformation and discrimination is promising," says Prof. FENG in *Accounts of Chemical Research*, a high-impacting review journal. Now, the chiral *N, N´*-dioxides, referred to as 'Feng ligands', are commercially available from Sigma-Aldrich and have been successfully adopted by many research groups and companies.

FENG and his coworkers would keep on their quest for a profound understanding of the relationship between the structure of "privileged" catalyst and their catalytic features in reactions. "The broader objective is to identify general design principles, which will allow scientists to approach the ideal goal of perfect chemical reactions via rational design of both novel catalysts and other functional molecules, resulting in 100% selectivity, 100% yield, and without unwanted waste products," says the group on their lab's website.