

Chemical and physical properties of organic molecules depend not only on their chemical structure, i.e., functional groups and their connectivities but also on their conformations. The molecular properties are governed by their dominant conformations which mask unique chemical events from a rare conformation. I developed conformational manipulation utilizing molecular confinement in a cavity of a molecular coordination cage to disclose the hidden properties and rare chemical events. The confinement effect enabled site- and stereoselective reactions, switching of physical properties of molecules, and molecular activation. This methodology provides a new mechanism to control organic reactions which is difficult to be achieved by other conventional methods. A new system to widen a target scope and enhance the confinement effect has also been developed.

1. Folding of flexible, linear precursors for selective reactions

Conformational fixing of a flexible, linear precursor is desired for site- and stereoselective reactions. The coordination cage with electron-deficient panel ligands provides sticky walls for electron-rich moieties of the substrate. The adequate utilization of the pinning on the walls renders conformational fixing of flexible substrates. This approach realized the precise recognition of chemically indistinguishable alkene moieties, rendering the site-selective functionalization of linear diterpenoids (*J. Am. Chem. Soc.* 2019). The strategy “folding of linear substrates in a confined cavity” was also applied for cyclization reactions. By using the cage, stereo- and site-selective thermal cyclization of diterpenoids and oligo arylalkynes were achieved (to be presented in the 101st CSJ meeting). Importantly, these kinds of selectivity are difficult to be achieved by the conventional design of a reactant or a molecular catalyst, because the whole shape of the target molecule is needed to be recognized.

2. Activation of amides by non-covalent twisting

For the past few decades, organic chemists have explored the enhanced reactivity of strained molecules. In general, strain in the molecules is synthetically invoked by using a rigid cyclic backbone or bulky substituents. Highly reactive twisted amides have also been synthesized by the same strategy. However, the switching of the unactivated planar amides into the reactive twisted amides through non-covalent manipulation remained challenging. The manipulation by confinement realized the amide activation by twisting (*Nat. Chem.* 2020). The octahedral coordination cage accommodated benzanilide derivatives in a *cis*-twisted conformation. The twist around the amide bond (up to 34°) enhanced hydrolysis under the basic conditions. The reaction proceeded with up to 14-fold acceleration compared with that in bulk solution.

3. Molecular manipulation by capping the portals of the cage

A new strategy to provide additional recognition sites at the cage's portals for more effective confinement has also been developed (*J. Am. Chem. Soc.* 2020). Attaching of tripodal anions on triangular portals of the octahedral cage afforded strong interactions with the guest molecules at the portals. The capping of the portals by the anion enabled the accommodation of even cationic substrates in the cationic coordination cage. The cap was also found to disturb the tumbling of the guest inside the cavity. This strategy will be applied for further controlled reactions in the cavity.