

Hydrogen bonding networks are ubiquitous in biological systems and play a key role in controlling the conformational dynamics and allosteric interactions of enzymes. Yet in small organometallic catalysts, hydrogen bonding rarely controls ligand binding to the metal center. In this work, a hydrogen bonding network within a well-defined organometallic catalyst works in concert with cation–dipole interactions to gate substrate access to the active site. An ammine ligand acts as one cofactor, templating a hydrogen bonding network within a pendent crown ether and preventing the binding of strong donor ligands, such as nitriles, to the nickel center. Sodium ions are the second cofactor, disrupting hydrogen bonding to enable switchable ligand substitution reactions. Thermodynamic analyses provide insight into the energetic requirements of the different supramolecular interactions that enable substrate gating. The dual cofactor approach enables switchable catalytic hydroamination of crotononitrile. Systematic comparisons of catalysts with varying structural features provide support for the critical role of the dual cofactors in achieving on/off catalysis with substrates containing strongly donating functional groups that might otherwise interfere with switchable catalysts.