Design and Synthesis of Organic Molecules for Catalysis

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Education

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The field of molecular catalysis has been an attractive area of research for realizing efficient and new transformations in the synthesis of functional molecules. The design of chiral molecular catalysts has been recognized as one of the most valuable strategies; therefore, a great deal of effort has been dedicated to the developments. In general, "metals" have been frequently used as the activation centers, and conformationally rigid catalyst frameworks have been preferably components for the catalyst design. To develop a new type of molecular catalysis, we have focused on the use of non-metal elements as activation centers and have incorporated non-covalent interactions as organizing forces in the molecular design of catalysts. This approach had not received much attention until recently. We hope that our approach will open a new frontier in chiral organic molecules to chiral molecular science from chiral molecular chemistry.

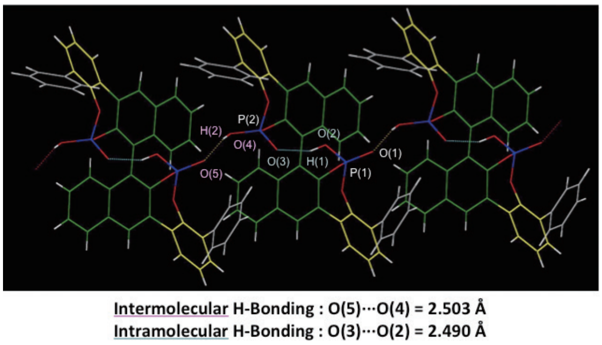

Figure 1. Hydrogen bonding network in chiral bis-phosphoric acid catalyst derived from (*R*)-3,3'-di(2-hydroxy-3 -arylphenyl)binaphthol. Hydrogen bond acts as activation unit for the substrate in asymmetric reaction space and controls atropisomeric behavior in naphthyl–phenyl axis.

Selected Publications

- T. P. Yoon and E. N. Jacobsen, *Science* **299**, 1691–1693 (2003).
- N. Momiyama and H. Yamamoto, "Brønsted Acid Catalysis of Achiral Enamine for Regio- and Enantioselective Nitroso Aldol Synthesis," *J. Am. Chem. Soc.* **127**, 1080–1081 (2005).
- N. Momiyama, T. Konno, Y. Furiya, T. Iwamoto and M. Terada, "Design of Chiral Bis-Phosphoric Acid Catalyst Derived from (*R*)-3,3'-Di(2-hydroxy-3-arylphenyl)binaphthol: Catalytic Enantioselective Diels–Alder Reaction of α,β-Unsaturated Aldehydes with Amidodienes," *J. Am. Chem. Soc.* **133**, 19294–19297 (2011).
- N. Momiyama, H. Tabuse, H. Noda, M. Yamanaka, T. Fujinami, K. Yamanishi, A. Izumiseki, K. Funayama, F. Egawa, S. Okada, H. Adachi and M. Terada, "Molecular Design of a Chiral Brønsted Acid with Two Different Acidic Sites: Regio-, Diastereo-, and Enantioselective Hetero-Diels–Alder Reaction of Azopyridinecarboxylate with Amidodienes Catalyzed by Chiral Carboxylic Acid–Monophosphoric Acid," *J. Am. Chem. Soc.* **138**, 11353–11359 (2016).
- S. Oishi, T. Fujinami, Y. Masui, T. Suuki, M. Kato, N. Ohtsuka and N. Momiyama, "Three-Center-Four-Electron Halogen Bond Enables Non-Metallic Complex Catalysis for Mukaiyama-Mannich-Type Reaction," *iScience* **25**, 105220 (2022).

1. Design of Perfluorohalogenated Arenes

Halogens form attractive non-covalent interactions between terminal halogen atoms in compounds of the type R—X (X = Cl, Br, I) and Lewis bases. This non-covalent interaction is known as either halogen bonding or σ-hole bonding, which occurs when “R” is a highly electronegative substituent, such as perfluorinated alkyl or aryl substituents. Based on the electrophilic feature of the halogen atom, we have investigated two types of perfluorohalogenated arenes in their design and synthesis: Perfluorohalogenated styrenes and naphthalenes, aimed at creating functional molecules.[1,2]

The Wittig reaction of perfluorohalobenzaldehydes was systematically studied to synthesize 2,3,5,6-tetrafluoro-4-halostyrenes (TFXSs), functional monomers bearing halogen bond donor sites.[1] The reaction proceeded efficiently in tetrahydrofuran using 1,1,3,3-tetramethylguanidine as the organic base. Correlation analysis quantitatively identified three key factors necessary for obtaining TFXS in reasonable yields. This approach not only advances the study of halogen bond-based functional molecules but also introduces digitalization as a promising strategy in small molecule synthesis.

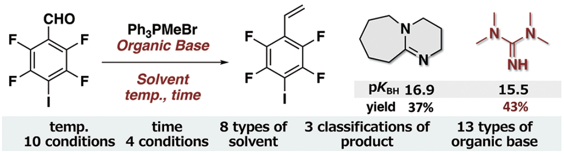

Figure 2. Synthesis of perfluoroiodinated styrenes as halogen bond donor site-introduced functional monomers.

Perfluorohalogenated naphthalenes (PFXNaPs) are unique small molecules with great potential to exhibit a new type of σ-hole and π-hole bonding, owing to the incorporation of multiple F atoms onto the naphthalene ring. We developed a synthetic protocol for PFXNaPs, conduct crystal engineering investigations, and explored the intermolecular interactions of PFXNaPs through π-hole and σ-hole bondings.[2] We successfully synthesized PFXNaPs using Mg amide-mediated halogenation reactions of electron-deficient F_7 and F_6 naphthalenes, achieving good to excellent yields. Crystal structure analyses of 3,6-I_2F_6 naphthalene unveiled intermolecular π-hole stacking between two C atoms in the naphthalene ring, in cooperation with the σ-hole bonding of two I atoms. This mode of intermolecular interaction has not been classified in previous reports. Computational studies show that the π-hole bonding in PFXNaPs is substantially enhanced compared to corresponding benzene molecules without diminishing the σ-hole bonding. The unique stacked interaction in PFXNaPs is primarily governed by electrostatic interaction and dispersion correction energies, with the contribution of C···C contacts being 10 times greater than that in benzene analogs. The results enable further applications of PFXNaPs in the fields of perfluorohalogenated arenes and organic crystalline materials.

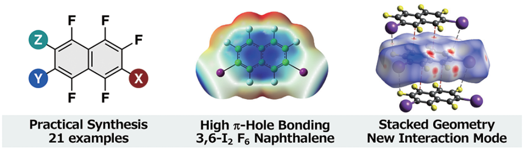

Figure 3. Synthesis and feature of perfluorohalogenated naphthalenes as potential crystalline materials.

2. Design of Halenium Complexes

In the filed of perfluorohalogenated arenes, the two-center-two-electron (2c2e) bond is a key feature. Similarly, halogen(I), generally X^+ (X = I, Br, Cl), acts as a strong halogen bond donor site. In contrast to the 2c2e halogen bond, halogen(I) simultaneously interacts with two Lewis bases. This bond is recognized as a three-center-four-electron (3c4e) halogen bond. Importantly, successful examples have consistently required the use of stoichiometric amounts of 3c4e complexes. Despite the utility of the 3c4e halogen bond in synthetic chemistry, its potential for non-metallic complex catalysis had not yet been thoroughly investigated until our report.[3,4]

We discovered that the 3c4e halogen bond can serve as a new driving force for catalysis.[3] By integrating halogen(I) (X^+: I^+ or Br^+), the bis-pyridyl ligand *NN*, and a non-nucleophilic counter anion Y, we developed non-metallic complex catalysts, [*N*···X···*N*]Ys, that exhibited outstanding activity and facilitated the Mukaiyama–Mannich-type reaction of *N*-heteroaromatics with parts-per-million-level catalyst loading. NMR titration experiments, CSI-MS, computations, and UV-vis spectroscopic studies suggest that the robust catalytic activity of [*N*···X···*N*]Y can be attributed to the unique ability of the 3c4e X-bond for binding chloride: i) the covalent nature transforms the $[N\cdots X\cdots N]^+$ complexation to sp^2 CH as a hydrogen-bonding donor site, and ii) the noncovalent property allows for the dissociation of $[N\cdots X\cdots N]^+$ for the formation of $[Cl\cdots X\cdots Cl]^-$. This study introduces the application of 3c4e X-bonds in catalysis *via* halogen(I) complexes.

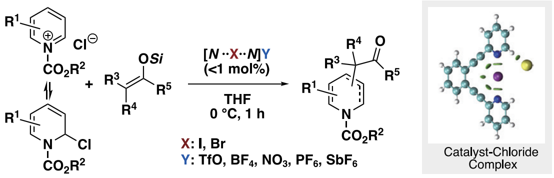

Figure 4. Halenium complex catalysis *via* three-center-four-electron halogen bond enables non-metallic complex catalysis for Mukaiyama-Mannich-type reaction.

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3) S. Oishi, T. Fujinami, Y. Masui, T. Suzuki, M. Kato, N. Ohtsuka and N. Momiyama, *iScience* **25**, 105220 (2022).

4) S. Oishi, T. Fujinami, Y. Masui, T. Suzuki, M. Kato, N. Ohtsuka and N. Momiyama, *STAR Protocols* **4**, 102140 (2023).