Design and Synthesis of Organic Molecules for Catalysis

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Education

2000	B.S. Nagoya University
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Professional Employment

2005	Postdoctoral Fellow, Harvard University
2006	Assistant Professor, Tohoku University
2014	Associate Professor, Institute for Molecular Science Associate Professor, The Graduate University for Advanced Studies

Awards

2003	The Elizabeth R. Norton Prize for Excellence in Research in Chemistry, University of Chicago
2004	Abbott Laboratories Graduate Fellowship
2005	Damon Runyon Cancer Research Foundation Post Doctoral Research Fellowship
2008	Thieme Chemistry Journals Award
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Our research aims to establish new principles for molecular catalysis and functional molecule discovery by integrating halogen-driven molecular design with digitalized synthesis frameworks. We have focused on two unique classes of halogen-based molecular systems. The first is *perfluorohalogenated arenes*, which exhibit unprecedented cooperative σ-hole and π-hole bonding interactions and provide new insights into organic materials. The second is *halenium complexes* featuring three-center-four-electron (3c4e) halogen bonds, which serve as strong and tunable non-metallic driving forces in catalysis. These studies highlight the potential of non-covalent halogen interactions to expand the chemical space of molecular catalysts and functional small molecules.

Furthermore, we are advancing the digitalization of organic synthesis through collaborations that combine *augmented intelligence* and *automated synthesis systems*. This approach allows accurate prediction of reaction outcomes under untested conditions, thereby accelerating the exploration of novel functional molecules. At the same time, our batch-type automated organic synthesis platform integrates reaction execution, purification, and analysis into a unified process, enabling Human-in-the-Loop collaboration between chemists and AI systems. Together, these approaches pave the way toward a new paradigm of "AI- and data-driven molecular discovery."

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. Suzuki, 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).
- N. Ohtsuka, H. Ota, S. Sugiura, S. Kakinuma, H. Sugiyama, T. Suzuki and N. Momiyama, "Perfluorohalogenated Naphthalenes: Synthesis, Crystal Structure, and Intermolecular Interaction," *CrystEngComm* **26**, 767–772 (2024).

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 perfluorohalogenated arenes, aimed at creating functional molecules.[1,2]

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. 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.[2)]

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 been thoroughly investigated until our report.[3,4]

We discovered that the 3c4e halogen bond can serve as a new driving force for catalysis. 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 to bind 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.[4]

3. Digitalization of Organic Synthesis

Recent advances in our group have been directed toward the digitalization of organic synthesis. In collaboration with Professor Kazuhiro Takeda (Shizuoka University), we explored the use of generative machine learning with virtual variables (GMLV) to predict reaction outcomes under untested conditions. In particular, a predictive framework was developed for the deuteration of polyfluoroperylene (PFDPR), a promising luminescent material, based on small experimental datasets. By introducing virtual descriptors that capture the intrinsic relationships between reactants, the model achieved accurate estimation of reaction yields and provided mechanistic insights into reaction processes. This study highlights the potential of digitalized data and AI frameworks to accelerate the discovery of functional molecules.[5]

Furthermore, we have developed a batch-type automated organic synthesis system. Unlike previously developed systems, our platform integrates reaction execution, work-up, purification, and analysis into a unified automated process. The system comprises modular equipment, including a multi-reaction station, robotic arms for liquid handling, automated purification, and mass spectrometry analysis. Importantly, it enables non-experts in organic synthesis to access a comprehensive experimental environment—"pushing a button does almost everything." This infrastructure provides a foundation for Human-in-the-Loop collaborations, where organic chemists and AI agents can work synergistically to accelerate reaction development and molecular discovery.[6]

References

1) T. Hori, S. Kakinuma, N. Ohtsuka, T. Fujinami, T. Suzuki and N. Momiyama, *Sylett* **34**, 2455–2460 (2023).
2) N. Ohtsuka, H. Ota, S. Sugiura, S. Kakinuma, H. Sugiyama, T. Suzuki and N. Momiyama, *CystEngComm* **26**, 767–772 (2024).
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).
5) K. Takeda, N. Ohtsuka, T. Suzuki and N. Momiyama, *Comput.-Aided Chem. Eng.* **53**, 2689 (2024).
6) Automated organic synthesis system: This platform was developed with support from the Institute for Molecular Science (IMS), Moonshot Goal 3 (Ushiku Project), and Transformative Research Areas (A) "Digitalization-driven Transformative Organic Synthesis (Digi-TOS)."