

Design and Synthesis of Chiral Organic Molecules for Asymmetric Synthesis

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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
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Awards

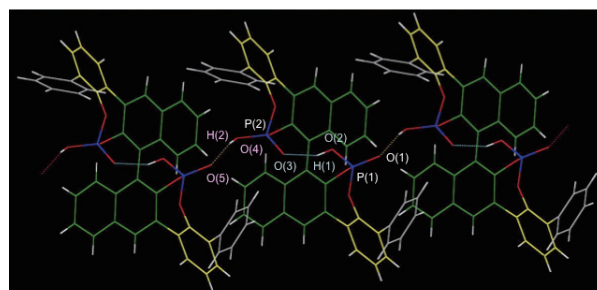
2003 The Elizabeth R. Norton Prize for Excellence in Research in Chemistry, University of Chicago
2004 Abbott Laboratories Graduate Fellowship
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2008 Thieme Chemistry Journals Award
2014 The 17th Morita Science Research Award
Central Glass Co., Ltd. Award in Organic Chemistry, Japan

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Keywords Synthetic Chemistry, Molecular Catalyst, Non-Covalent Interaction

The field of molecular catalysis has been an attractive area of research to realize efficient and new transformations in the synthesis of functional molecules. The design of ligands and 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, “metal” has been frequently used as the activation center, and conformationally rigid catalyst framework has been preferably components for the catalyst design. To develop new type of molecular catalysis, we have focused on the use of hydrogen and halogen atom as activation unit, and have utilized non-covalent interactions as organizing forces of catalyst framework in the molecular design of catalyst, which had not received much attention until recently. We hope that our approach will open the new frontier in chiral organic molecules from chiral molecular chemistry to chiral molecular science.



Intermolecular H-Bonding : O(5)⋯O(4) = 2.503 Å
Intramolecular H-Bonding : O(3)⋯O(2) = 2.490 Å

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, “Bronsted Acid Catalysis of Achiral Enamine for Regio- and Enantioselective Nitroso Aldol Synthesis,” *J. Am. Chem. Soc.* **127**, 1080–1081 (2005).
- N. Momiyama, H. Tabuse and M. Terada, “Chiral Phosphoric Acid-Governed Anti-Diastereoselective and Enantioselective Hetero-Diels–Alder Reaction of Glyoxylate,” *J. Am. Chem. Soc.* **131**, 12882–12883 (2009).
- 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 Enantio-

selective 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 Bronsted Acid with Two Different Acidic Sites: Regio-, Diastereo-, and Enantioselective Hetero-Diels–Alder Reaction of Azopyridine-carboxylate with Amidodienes Catalyzed by Chiral Carboxylic Acid–Monophosphoric Acid,” *J. Am. Chem. Soc.* **138**, 11353–11359 (2016).

1. Design of Hydrogen Bond-Based Molecular Catalysts

Allylation of imines with allylic metal reagents has been one of the most valuable tools to synthesize enantioenriched homoallylic amines. Due to the inherent nature of allylic metal reagent, however, regioselectivity has been a long-standing subject in this area. To develop the synthetic reaction for enantioenriched linear homoallylic amines, we discovered chirality transferred formal 1,3-rearrangement of ene-aldimines in the presence of Brønsted acid, and developed it as synthetic method for variety of enantioenriched linear homoallylic amines.¹⁾ Furthermore, we studied details of reaction mechanism and succeeded catalytic asymmetric version of this rearrangement.²⁾ On the basis of our discovery, catalytic asymmetric version of this reaction was developed.³⁾ To the best of our knowledge, our discovery is the first example of catalytic asymmetric methylene migration.

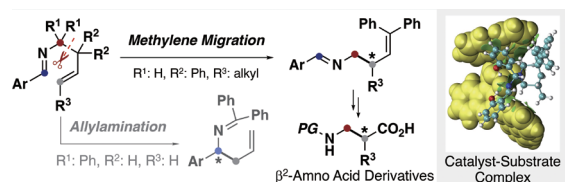


Figure 2. Asymmetric counteranion-directed catalysis via OH \cdots O, CH \cdots O, CH \cdots π , $\pi\cdots\pi$ interactions.

Perfluorinated aryls have emerged as an exquisite class of motifs in the design of molecular catalysts, and their electronic and steric alterations lead to notable changes in the chemical yields and the stereoselectivities. We developed the perfluoroaryls-incorporated chiral mono-phosphoric acids as chiral Brønsted acid catalysts that can deliver high yields and stereoselectivities in the reactions of imines with unactivated alkenes. We have described the first example of a diastereo- and enantioselective [4+2] cycloaddition reaction of *N*-benzoyl imines, as well as the enantioselective three-component imino-ene reaction using aldehydes and FmocNH₂.⁴⁾

We have developed (*R*)-3,3'-di(2-hydroxy-3-arylphenyl)binaphthol derived chiral bis-phosphoric acid which efficiently catalyzed enantioselective Diels–Alder reaction of acroleins with amidodienes.^{5,6)} We demonstrated that two phosphoric acid groups with individually different acidities can play distinct roles in catalyst behavior through hydrogen bonding interactions. Therefore, we developed a Brønsted acid with two different acidic sites, aryl phosphinic acid-phosphoric acid.⁷⁾ Furthermore, molecular design of a chiral Brønsted acid with two different acidic sites, chiral carboxylic acid-cyclic mono-phosphoric acid, was identified as a new and effective concept in asymmetric hetero-Diels–Alder reaction of 2-azopyridinoester with amidodienes.⁸⁾

2. Design of Halogen Bond-Based Molecular Catalysts

Halogen bonds are attractive non-covalent interactions between terminal halogen atoms in compounds of the type R—X (X = Cl, Br, I) and Lewis bases LBs. It has been known

that strong halogen bonds are realized when “R” is highly electronegative substituents such as perfluorinated alkyl or aryl substituents. On the basis of electrophilic feature for halogen atom, we have examined it to develop catalysis with halogen bond for carbon–carbon bond forming reactions.^{9,10)}

We found that perfluorinated iodoaryls are able to catalyze the allylation reaction to *N*-activated heteroaromatics. On the basis of this discovery, a quantitative approach was studied using 4-substituted perfluorinated iodobenzene.¹¹⁾ Examination of the electrostatic potential surfaces showed that substituent R groups significantly affected the charge density of iodine, fluorine, and carbon on the benzene ring. ¹⁹F NMR titrations were used to determine the binding constants *K* for chloride, and their catalytic activities were evaluated in the allylation reaction. We revealed that the log *K* and product yields were linearly correlated, and that they were dependent on the Hammett substituent parameter, σ_{meta} . This linear correlation provided a quantitative predictive model for both the binding constant and the reaction yield. Concomitantly, this efficiently permitted the development of a highly active anion-binding catalyst, namely 4-CNC₆F₄I. The catalytic activity of 4-CNC₆F₄I was established in the allylation and crotylation of silatrane reagents to *N*-activated isoquinolines.

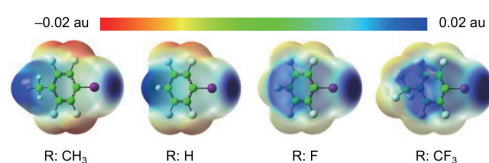


Figure 3. Molecular electrostatic potential surfaces of 4-RC₆F₄I (R: CH₃, H, F, and CF₃) at the M06-2X-D3/6-311+G(d,p)-SDD level of theory.

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