Design and Synthesis of Chiral Organic Molecules for Asymmetric Synthesis

Department of Life and Coordination-Complex Molecular Science
Division of Complex Catalysis

MOMIYAMA, Norie
Associate Professor
[momiyama@ims.ac.jp]

Education
2000 B.S. Nagoya University
2005 Ph.D. The University of Chicago

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
2014 The 17th Morita Science Research Award
Central Glass Co., Ltd. Award in Organic Chemistry, Japan

Member
Assistant Professor
OHTSUKA, Naoya
Post-Doctoral Fellow
FUJINAMI, Takeshi
Graduate Student
HORI, Tatsuaki
OISHI, Shunya
OTA, Hino
KATO, Masayuki
KOTANI, Shunsuke
Secretary
USHIDA, Hinano

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.

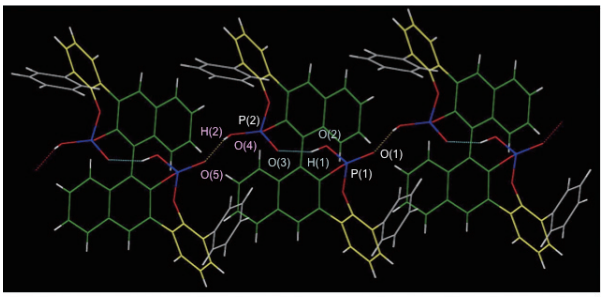

Figure 1. Hydrogen bonding network in chiral bis-phosphoric acid catalyst derived from (*R*)-3,3'-di(2-hydroxy-3 -arylphenyl)binaphthol. Hydrogen bond acts as activation unit for the substrate in asymmetric reaction space and controls atropisomeric behavior in naphthyl–phenyl axis.

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, 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 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).

1. Brønsted Acid Catalyzed Asymmetric Rearrangement: Asymmetric Synthesis of Linear Homoallylic Amines

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)] To the best our knowledge, our discovery is the first example of asymmetric formal [1,3]-rearrangement and the new entry of the synthetic methodology for the linear enantioenriched homoallylic amines.

2. Design of Chiral Brønsted Acid Catalyst

Chiral Brønsted acid catalysis has been recognized as one of the useful tools in asymmetric synthesis. We have contributed to this area by focusing on the use of perfluoroaryls and C_1-symmetric design.

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. However, unfortunately, the distinctive potential of perfluorinated aryls has not been fully exploited as design tools in the development of chiral Brønsted acid catalysts. We developed the perfluoaryls-incorporated chiral mono-phosphoric acids as chiral Brønsted acid catalysts that can deriver 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 $FmocNH_2$.[3)]

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.[4,5)] We demonstrated that two phosphoric acid groups with individually different acidities can play distinct roles in catalyst behavior through hydrogen bonding interactions. Hence, we were interested to explore whether a combination of *different acidic functional groups*, in particular an aryl phosphinic acid-phosphoric acid, would function as an efficient Brønsted acid catalyst. We developed a Brønsted acid with two different acidic sites, aryl phosphinic acid-phosphoric acid, and its catalytic performance was assessed in the hetero-Diels–Alder reaction of aldehyde hydrates with Danishefsky's diene, achieving high reaction efficiency.[6)] 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.[7)]

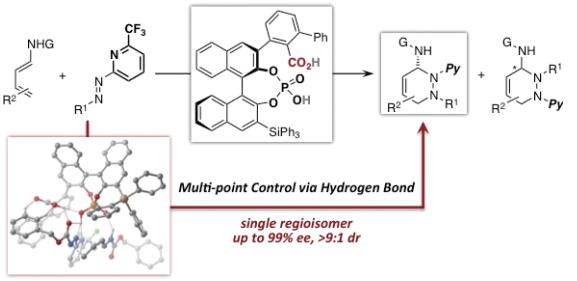

Figure 2. Chiral carboxylic acid–phosphoric acid-catalyzed azo-hetero-Diels–Alder reaction.

3. Design of Catalysis with Halogen Bond for Carbon–Carbon Bond Forming Reactions

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. We recently developed synthetic methodology for perfluorinated aryl compounds, and applied it for the development of chiral Brønsted acid catalysts. On the basis of our achievements, we have examined it to develop catalysis with halogen bond for carbon–carbon bond forming reactions.

We found that perfluorinated iodoaryls are able to catalyze the Mukaiyama Mannich-type reaction and allylation reaction.[8)]

References

1) C. Jongwohan, Y. Honda, T. Suzuki, T. Fujinami, K. Adachi and N. Momiyama, *Org. Lett.* **21**, 4991–4995 (2019).
2) N. Momiyama *et al.*, submitted.
3) N. Momiyama, H. Okamoto, J. Kikuchi, T. Korenaga and M. Terada, *ACS Catal.* **6**, 1198–1204 (2016).
4) N. Momiyama, T. Konno, Y. Furiya, T. Iwamoto and M. Terada, *J. Am. Chem. Soc.* **133**, 19294–19297 (2011).
5) N. Momiyama, K. Funayama, H. Noda, M. Yamanaka, N. Akasaka, S. Ishida, T. Iwamoto and M. Terada, *ACS Catal.* **6**, 949–956 (2016).
6) N. Momiyama, T. Narumi and M. Terada, *Chem. Commun.* **51**, 16976–16979 (2015).
7) 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, *J. Am. Chem. Soc.* **138**, 11353–11359 (2016).
8) N. Momiyama *et al.*, Two manuscripts: Submitted; four manuscripts under preparation for submission.