RESEARCH ACTIVITIES

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

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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, and C₂- or pseudo C₂ symmetry 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 conformationally flexible components 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.

Selected Publications

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.

Intermolecular H-Bonding: \( \text{D(1)} - \text{O(4)} = 2.563 \text{ Å} \)
Intramolecular H-Bonding: \( \text{D(3)} - \text{O(2)} = 2.410 \text{ Å} \)

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.
1. Brønsted Acid Catalyzed Asymmetric 1,3-Alkyl Migration of 1,2,2-Substituted Butenyl Amines: Asymmetric Synthesis of Linear Homoprenylic 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 homoprenylic amines, we discovered chirality transferred 1,3-alkyl migration in the presence of trifluoromethyl acetic acid, and developed it as synthetic method for variety of enantioenriched linear homoprenylic amines.1) In sharp contrast, Ollis et al. previously reported that chirality was significantly dropped in 1,3-alkyl migration of N,N-dimethyl-1-substituted-3-buten-1-amine.2) To the best our knowledge, our discovery is the first example of chirality transferred 1,3-alkyl migration 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 C1-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 distinct potential of perfluorinated aryls has not been fully exploited as design tools in the development of chiral Brønsted acid catalysts. We developed the perfluoroaryl-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 FmocNH2.3)

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)

3. Halogen Bond Donor Catalyzed Reaction of N-Heteroaromatics with Allylsilatrane

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 LB. 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 halogen bond donor catalyzed allylation reaction.

We found that iodopentafluorobenzene was able to catalyze the reaction of isoquinolines, quinolines, and pyridines with allylsilatrane, crotysilatrane, and prenyl silatrane to give the corresponding products in good yields.8)

References
1) N. Momiyama et al., Manuscript in preparation.
8) N. Momiyama et al., Manuscript in preparation.