

# Design and Synthesis of Chiral Organic Molecules for Asymmetric Synthesis

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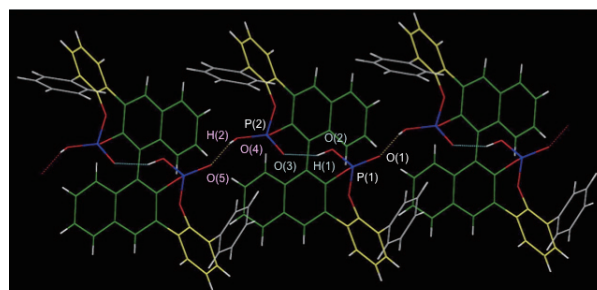
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#### Keywords

Synthetic Chemistry, Molecular Catalyst, Non-Covalent Interaction

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.



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

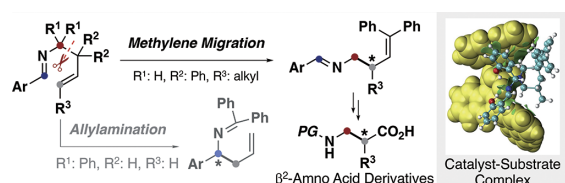
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- N. Momiyama and H. Yamamoto, “Brønsted Acid Catalysis of Achiral Enamine for Regio- and Enantioselective Nitroso Aldol Synthesis,” *J. Am. Chem. Soc.* **127**, 1080–1081 (2005).
- N. Momiyama, T. Konno, Y. Furiya, T. Iwamoto and M. Terada, “Design of Chiral Bis-Phosphoric Acid Catalyst Derived from (*R*)-3,3'-Di(2-hydroxy-3-arylphenyl)binaphthol: Catalytic Enantioselective Diels–Alder Reaction of  $\alpha,\beta$ -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 Azopyridine-carboxylate 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 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.<sup>1)</sup> Furthermore, we studied details of reaction mechanism and succeeded catalytic asymmetric version of this rearrangement.<sup>2)</sup> On the basis of our discovery, catalytic asymmetric version of this reaction was developed.<sup>3)</sup> 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 $\cdots$  $\pi$ ,  $\pi\cdots\pi$  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 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 FmocNH<sub>2</sub>.<sup>4)</sup>

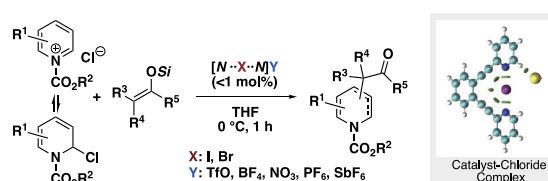
We have developed (*R*)-3,3'-di(2-hydroxy-3-arylphenyl)binaphthol derived chiral bis-phosphoric acid which efficiently catalyzed enantioselective Diels–Alder reaction of acroleins with amidodienes.<sup>5,6)</sup> We demonstrated that two phosphoric acid groups with individually different acidities can 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.<sup>7)</sup> 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.<sup>8)</sup>

## 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.<sup>9,10,11)</sup>

We found that the three-center-four-electron halogen bond become a new driving force for catalysis.<sup>9)</sup> By integrating halogen(I) (X<sup>+</sup>: I<sup>+</sup> or Br<sup>+</sup>), the bis-pyridyl ligand *NN*, and a non-nucleophilic counter anion Y, we developed non-metallic complex catalysts, [N $\cdots$ X $\cdots$ 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 $\cdots$ X $\cdots$ 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]<sup>+</sup> complexation to sp<sup>2</sup> CH as a hydrogen-bonding donor site, and ii) the noncovalent property allows for the dissociation of [N $\cdots$ X $\cdots$ N]<sup>+</sup> for the formation of [Cl $\cdots$ X $\cdots$ Cl]<sup>−</sup>. This study introduces the application of 3c4e X-bonds in catalysis *via* halogen(I) complexes.



**Figure 3.** Three-center-four-electron halogen bond enables non-metallic complex catalysis for Mukaiyama–Mannich-type reaction.

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