博士論文の要約

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論文題目：
三中心四電子ハロゲン結合を基盤とする非金属錯体触媒の設計と Mannich 型反応への応用

Molecular catalysts have been continually designed to supply the essential chemical products rapidly and efficiently. The design of molecular catalysts has advanced remarkably over the past two decades, and these catalysts are now valuable tools for facilitating a variety of chemical reactions. In particular, organocatalysts composed of non-metal elements have been a breakthrough in the field of catalysis in the 21st century. A variety of organocatalysts utilizing non-covalent interactions, such as hydrogen bond (H-bond) and halogen bond (X-bond), have been extensively reported to date. Halogen(I), generally X^+ (X = I, Br), acts as a strong X-bond donor site, in which one halogen concurrently interacts with two Lewis bases to form three-center-four-electron halogen bond (3c4e X-bond). Cationic 3c4e X-bond complexes have frequently been utilized in organic syntheses, particularly in the development of halogenation reagents. Despite the utility of 3c4e X-bond in synthetic chemistry, very little attention has been given to the 3c4e X-bond complexes as molecular catalysts. Therefore, this study for doctoral thesis is aimed to open a fundamental design concept for a non-metallic complex catalyst based on the 3c4e X-bond.

In Chapter 1, a comprehensive overview is provided, encompassing metal complex catalysis and organocatalysis, and the scope of this thesis are summarized as a general introduction. Initially, the advancement of catalysis in chemical reactions, the utilization of non-covalent interactions in organocatalysis, and the progress of 3c4e X-bond are exemplified based on literature reviews. Subsequently, the design concept of non-metallic complex catalyst utilizing 3c4e X-bond complex is described in detail.

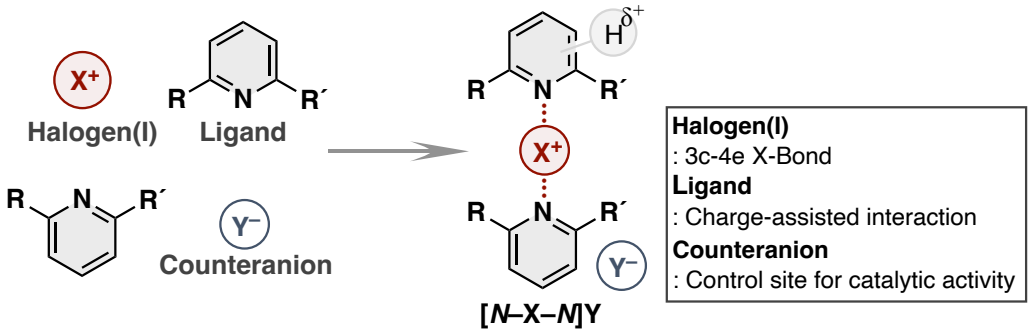
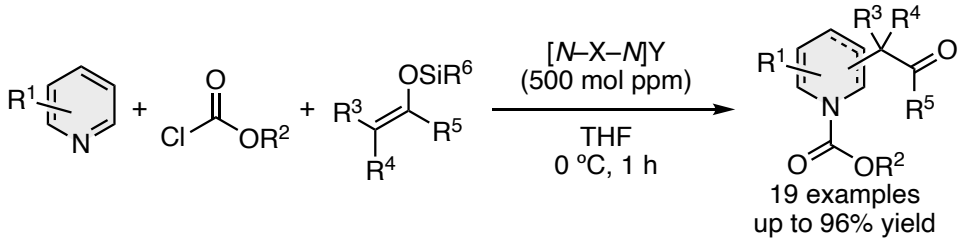


Figure 1. Design concept of halogen(I) complexes as non-metallic complex catalysts

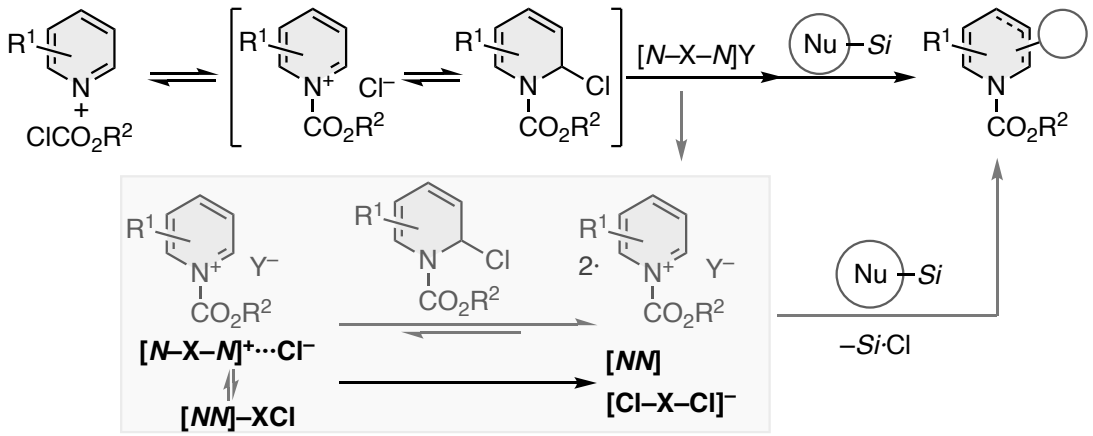
In Chapter 2, the development of halogen(I) complexes as non-metallic complex catalysts is summarized. By integrating halogen(I) (X^+: I^+, Br^+), pyridyl ligand [*N*], and non-nucleophilic counteranion Y, halogen(I) complexes [*N*–X–*N*]Ys are developed. To evaluate the catalytic activity,

Mukaiyama Mannich-type reaction of *N*-heteroaromatics via chloride-binding was selected because the reaction provides a variety of useful nitrogen-containing intermediates for the synthesis of pharmaceuticals. In the designed non-metallic complex catalyst, it would be envisaged that the halogen(I) atom would strongly uptake chloride through the 3c4e X-bond. [*N*–X–*N*]Ys exhibited outstanding catalytic activity and facilitated the Mukaiyama Mannich-type reaction of *N*-heteroaromatics with mol ppm level catalyst loading (Scheme 1). Additionally, through the modification of the halogen(I) atom, pyridyl ligands, and counteranions, catalytic activity was successfully enhanced even further. Details on the synthesis of catalysts, reaction optimization, and substrate scope are described in Chapter 2.



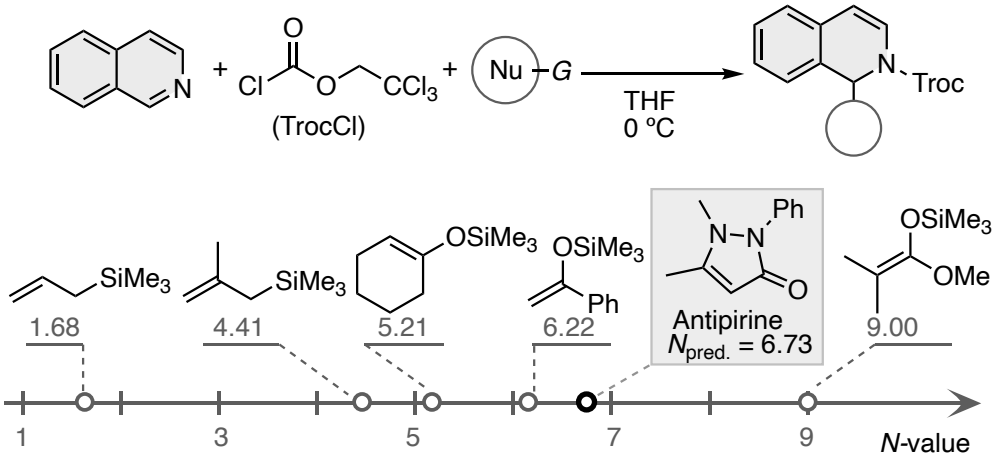
Scheme 1. Mukaiyama Mannich-type reaction of pyridines with [*N*–X–*N*]Ys

In Chapter 3, experimental results for the mechanistic studies are summarized. A catalytic cycle is proposed based on previous literature. Experimental and computational studies were conducted to clarify the reaction mechanism. Single crystals of pyridyl ligand and ICl complexes were successfully obtained. X-ray diffraction analysis revealed the possibility of dissociation from [*N*–X–*N*]Y to [*NN*]–XCl and further transformation to [Cl–X–Cl]$^-$ in the presence of chloride. ^{1}H NMR titration experiments and CSI-MS measurements were also conducted to gain insights into the chloride-binding mode in solution, and the proposed catalytic cycle was strongly supported. UV-vis spectroscopic studies of the crude reaction mixture indicated the reformation of [*N*–X–*N*]Ys from [Cl–X–Cl]$^-$ after completion of the reaction. DFT calculations and NCI-plot showed good agreement with the experimental results for the proposed chloride-binding mode of catalyst. These studies suggest that the origin of robust catalytic activity of [*N*–X–*N*]Ys lies in the unique feature of 3c4e X-bond for binding chloride through the transformation of anionic [Cl–X–Cl]$^-$ bond (Scheme 2). Further discussions of the mechanistic studies are summarized in Chapter 3.



Scheme 2. Proposed chloride-binding mode of [*N*–X–*N*]Ys

In chapter 4, exploring novel reactions using Mayr's reactivity parameters is summarized. Highly accurate prediction model of reactivity parameters was developed through machine learning. Silyl nucleophiles reported *N* values were used in the model reactions, and nucleophiles with *N* values ranging from 4.41 to 9.00 were found to be applicable in the reactions of isoquinoline (Scheme 3). Furthermore, by applying the developed model to commercially available chemicals, antipyrine was found as a nucleophile for the reaction of isoquinoline. Detailed studies on the development of prediction model, validating the reactivity scales in reactions of isoquinoline, and exploration of nucleophile candidates are described in chapter 4.



Scheme 3. Screening of nucleophile based on reactivity parameters and discovery of new nucleophile for the model reaction

In Chapter 5, the quantitative investigation of the developed non-metallic complex catalyst in Mannich-type reaction is summarized. Halogen(I) complexes with different ligands and counteranions were employed to systematically investigate the reaction yields in the reactions of isoquinoline (Figure 2). Focusing on steric- and electronic tuning of catalyst structures, insight into the future enhancements of catalytic activity was obtained. Detailed studies on catalyst preparation and comparison of catalytic activity are described in Chapter 5.

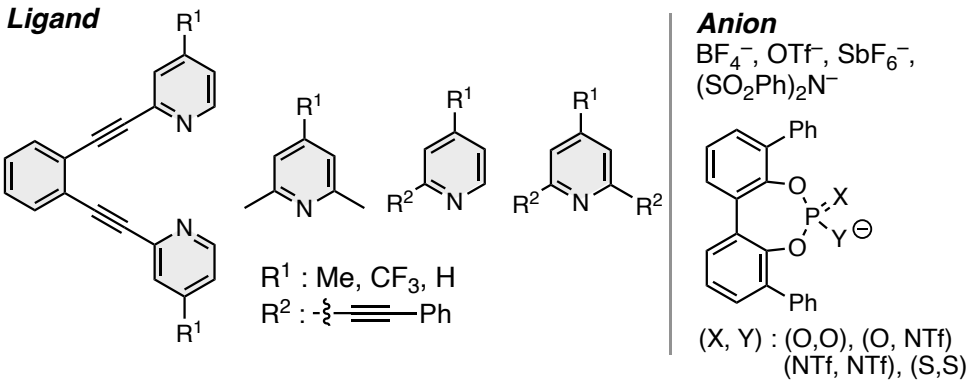


Figure 2. Components of halogen(I) complex catalyst : Ligand and Counteranion

In chapter 6, studies for this thesis are summarized, and perspective of non-metallic complex catalysis is described.