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	Project Information	Project Number : 23H05467 Keywords : halogen, organocatalysis, oxidation, element strategy, low environmental load	Project Period (FY) : 2023-2027

Purpose and Background of the Research

● Outline of the Research

Catalysis is a key technology in the development and production of pharmaceuticals, agrochemicals and functional organic materials, and the development of high-performance catalysts is important from the viewpoint of low environmental load and energy saving. From the viewpoint of safety and element strategy, if the active center of the catalyst can be replaced from the transition metal element to the halogen (X) element, it will have great significance and ripple effects. Japan's iodine reserves are number one in the world, accounting for 78% of total reserves. The valence of X can be changed from -1 to +7, and the redox potential can be adjusted by its substituents and ligands. In addition, it is expected to function as a soft Lewis acid catalyst that utilizes not only the redox properties of X but also the halogen bond (XB). With the goal of realizing a fine organic synthesis, which is one of the SDGs, "the foundation of industry and technological innovation," research is aimed at creating highly functional green catalysts with X as the active center (Figure 1).

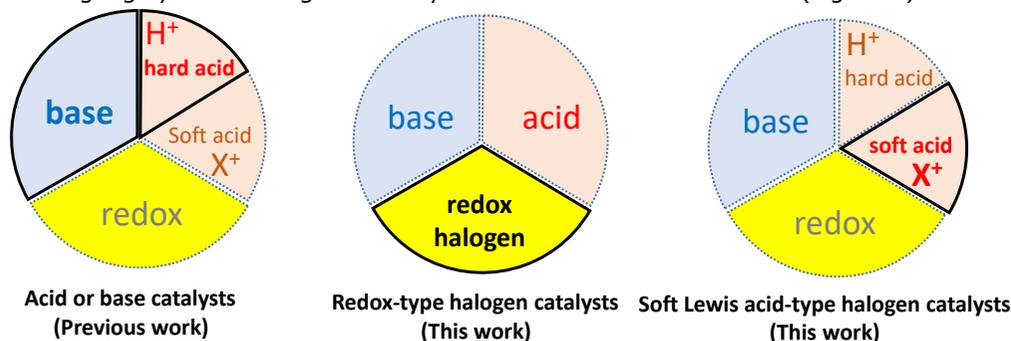


Figure 1. Conventional organocatalysts and new organocatalysts (this work)

● Redox-type halogen catalysts

From the viewpoint of elemental strategy, typical metal Lewis acid catalysts are being replaced by Brønsted acids, and metal base catalysts are being replaced by amines. However, redox-type organocatalysts are almost unexplored. We have paid attention to halogen (X), especially I, as a non-metallic element exhibiting redox activity, since 2009. In this research project, we develop redox-type X catalysts that use not only I, but also Br and Cl, which have stronger oxidizing power, as the catalytically active center (Figure 2).

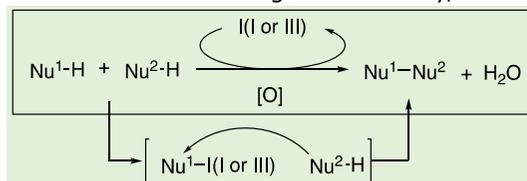


Figure 2. Redox-type iodine catalysts for coupling reactions

● Soft Lewis acid-type halogen catalysts

A non-covalent interaction between the σ -hole of a halogen atom and a Lewis base is called a halogen bond (XB) (Figure 3). XB is directional as well as hydrogen bonding, and there is a strong interest in halo-Lewis acid catalysis (soft acid) via XB versus Brønsted acid catalysis (hard acid) via hydrogen bonding. Since 2014, we have developed asymmetric iodocyclization reactions using halo-Lewis acid catalysts. In 2021, we clarified that the halogen bond is the reason why the chlorination and bromination reactions are significantly suppressed compared to the fluorination reactions in the presence of amines. In this project, we would like to develop enantioselective halogenation reactions using halo Lewis acid catalysts instead of transition metal soft Lewis acid catalysts.

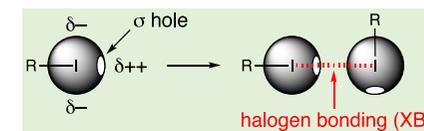


Figure 3. Halogen bonding (XB) of RI

Expected Research Achievements

● Redox-type halogen catalysts

C-C couplings have not been achieved compared to the relatively reactive C-O and C-N couplings (Table 1).

Table 2. Redox potential of halogen X (E^0/V)

	I	Br	Cl
in acid	0.99	1.33	1.48
in base	0.49	0.76	0.81
in acid:	$XOH + H^+ + 2e^- = X^- + H_2O$		
in base:	$XO^- + H_2O + 2e^- = X^- + 2HO^-$		

CRC Handbook of Chemistry and Physics, 97th Edition, CRC Press, 2016.

Table 1. Previous results using catalysts as I(I or III) catalysts

coupling	intra- · asym.	inter- · asym.
C-C	$\Delta \cdot \times$	$\times \cdot \times$
C-N	$\circ \cdot \Delta$	$\Delta \cdot \times$
C-O	$\circ \cdot \circ$	$\Delta \cdot \times$

\times No example. Δ Examples are limited.

\circ Many examples have been reported.

In addition, the intermolecular reactivity is significantly lower than the intramolecular one, and not only the reactivity but also the homo/cross-coupling selectivity is an issue that remains unsolved. Based on our previous results using I-catalysts, we expand the scope of research to include Br and Cl, which have different redox powers (Table 2).

● Soft Lewis acid-type halogen catalysts

Halogen bonding (XB) increases in the order of $F < Cl < Br < I$ in proportion to the size of X (Table 3). XB is also greatly affected by the valence of X. The σ -holes of hypervalent X have not yet been fully elucidated, and basic research including the influence of ligands (L) is required (Figure 4). We would like to do fundamental research on the chemistry of hypervalent X, the chemistry of XB donors (halo-Lewis acids) in relation to the HSAB rule, and the design of XB catalysts.

Table 3. Properties of halogen elements

Halogen (X)	F	Cl	Br	I
van der Waals radius (Å)	1.4	1.8	2.0	2.2
Electronegativity	4.0	3.0	2.8	2.5
Standard electrode potential (V)	2.85	1.36	1.07	0.54
Polarizability of X^- (a.u.)	16	37	46	66
Binding energy C-X ΔH^\ddagger (kcal/mol)	105.4	78.5	65.9	57.4
Halogen bonding	weak \longrightarrow strong			

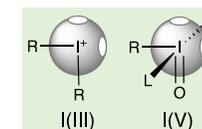


Figure 4. σ -hole of hypervalent iodines

