（課程博士用）
(for Degree earned by Completing Doctoral Program)

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千葉大学審査学位論文（要約）（Summary）

先進理化学 専攻 化学 コース
Division Department

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Name

ハロゲン結合供与体触媒による 2-アルケニルインドールの[4+2]環化付加反応と ICN を用いた電子豊富オレフィンのヨードシアノ化反応

[4+2] Cycloaddition of 2-alkenylindoles catalyzed by halogen-bond donor and iodocyanation of electron-rich olefins using ICN

[Introduction]

Iodine is the heaviest halogen atom among the four commonly used halogens, namely, fluorine, chlorine, bromine, and iodine. Due to its large atomic radius, iodine atom has significant polarizability and hence considered as a soft atom. In this thesis, taking advantage of the soft character of iodine, halogen-bond catalysis and reaction development of iodine cyanide (ICN) were studied.

Halogen bond (XB) is a noncovalent interaction between electrophilic region of a halogen atom, which is called σ-hole, and a nucleophilic region of a molecule (Figure 1).[1] Halogen compounds which have ability to offer σ-holes to nucleophilic sites are called XB donor. Since σ-hole is existing on the backside of R-X bond, XB shows linear property. Among four halogen atoms, iodine can make strongest XB due to its large polarizability and resulting large σ-hole, whereas fluorine atom rarely provides a σ-hole to make XB.

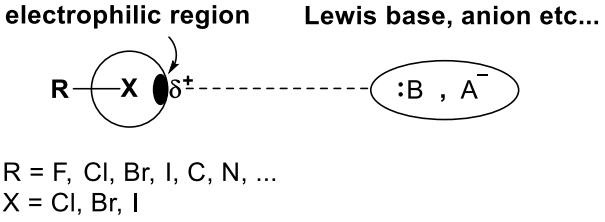


Figure 1. Schematic representation of halogen bond

Halogen bond is studied in wide variety of fields, for example, crystal engineering,[2] molecular recognition,[3] supramolecular chemistry,[4] and organic synthesis and catalysis.[5,6,7] Regarding organocatalysis, the first example of XB catalysis was reported by Bolm et al. in 2008, where perfluoroiodoalkane promoted reduction of quinoline by Hantzsch ester.[7] Since the pioneering work by Bolm et al., variety of XB catalyzed reactions have been reported, including activation of imine derivatives, carbonyl compounds, thioamides, and alkyl halides (Figure 2). These substrates all have lone pair electron which contributes to XB interaction with XB donors. To make effective use of the soft character of iodine, activation of softer molecules like π-electron system by XB is worth exploring, which would lead to expansion of substrate scope of XB catalysis.

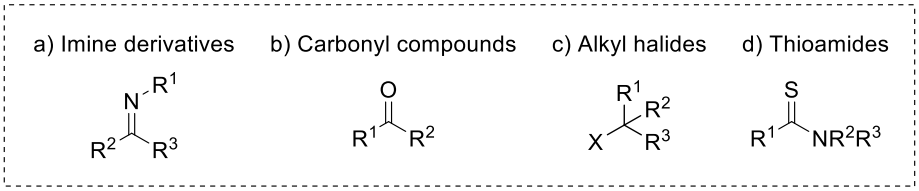


Figure 2. Activated substrates through XB

The extreme of XB formation is electrophilic halogenation reaction, resulting in the generation of a new nucleophile-halogen σ bond and leaving group. The leaving group is recognized as waste when it is not incorporated in the product (Figure 3a). If the leaving group can also be installed into the final product as the functionalization unit, multifunctionalization reaction will be possible in an atom-economical manner (Figure 3b).

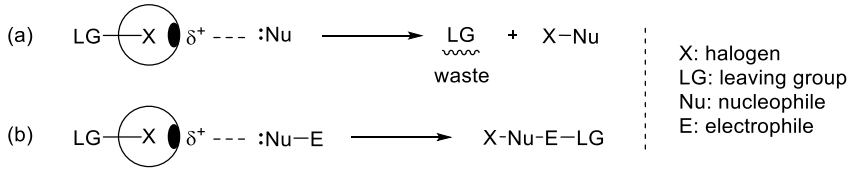


Figure 3. Electrophilic halogenation reaction

Candidates of halogen reagents for such reactions are halogen cyanides (XCN), because they have potential to react as both X^+ electrophile and ^-CN nucleophile.[8] Reactivities of halogen cyanides depend on the halogen atoms, where, in the case of reaction with Grignard reagents, iodine cyanide (ICN) reacts exclusively as I^+ and ^-CN, bromine cyanide (BrCN) reacts mainly as Br^+ and ^-CN, chlorine cyanide (ClCN) reacts mainly as Cl^- and ^+CN. [8b] A possible explanation for the difference of reactivities is drawn from comparison of LUMO shapes.[9] The LUMO of ICN is localized on the iodine atom,

whereas the LUMO of BrCN localized both on the bromine atom and on the carbon atom, and localization of the LUMO on the carbon atom is the most obvious in case the of ClCN (Figure 4). Commonly used halogen cyanides in laboratories are ICN and BrCN. ClCN and fluorine cyanide (FCN) are toxic gases. Considering that ICN is expected to be more reactive than BrCN for electrophilic halogenation reaction due to the softness of iodine atom, ICN would be more suitable for the target halocyanation.

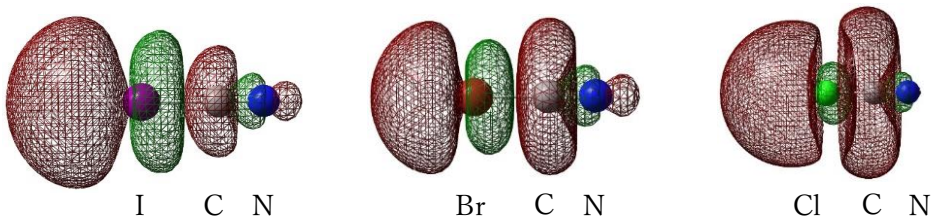
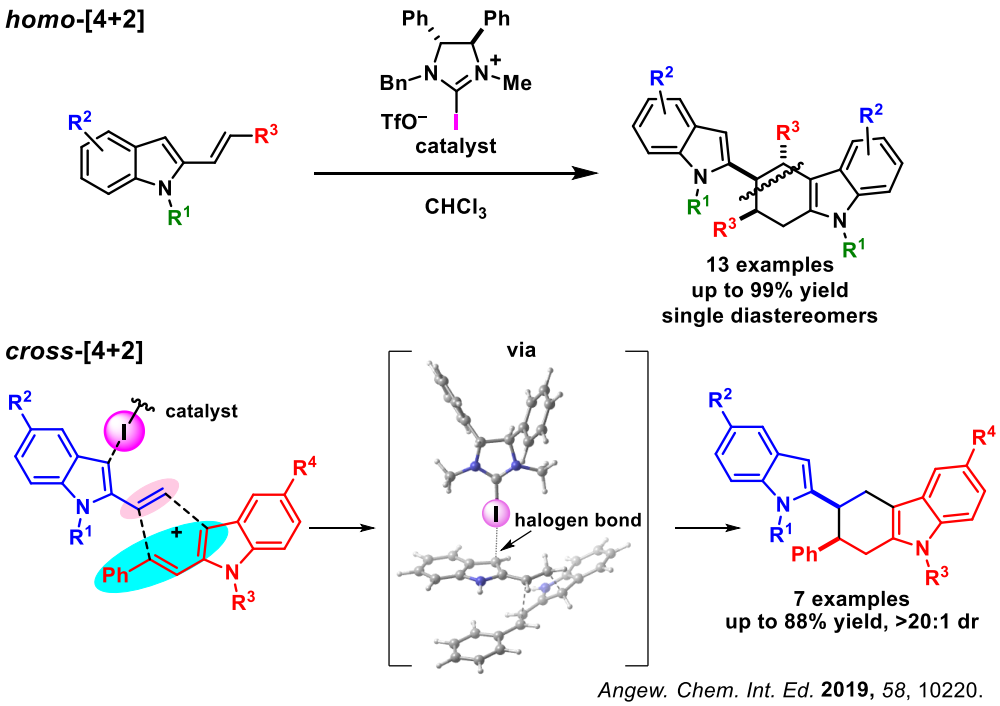


Figure 4. Comparison of LUMO shape of ICN, BrCN and ClCN

[Topic 1]

In the first topic, it was found that the 2-iodoimidazolinium salt efficiently catalyzed homo- and cross-[4+2] cycloaddition of 2-alkenylindoles. Mechanistic investigations including several control experiments, ^{1}H-NMR study, and DFT calculation study suggested that this reaction was promoted by electrophilic activation of π-electron of indo-



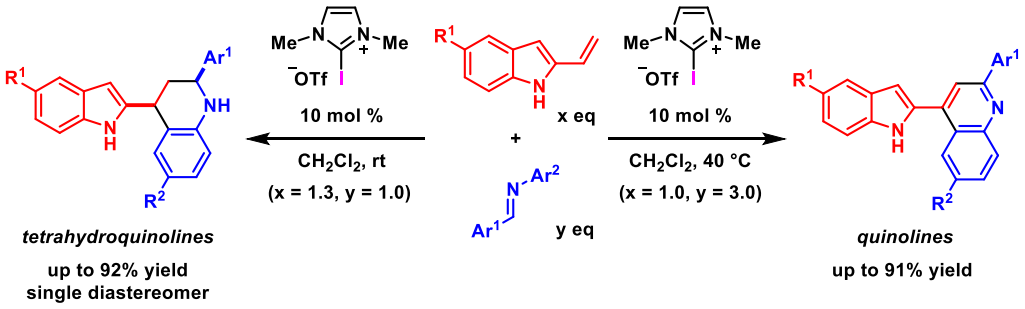
Angew. Chem. Int. Ed. **2019,** *58*, 10220.

Figure 5. [4+2] cycloaddition of 2-alkenylindoles catalyzed by XB donor

le moiety through noble C-I···π halogen bond. This is the first example of application of C-I···π halogen bond for organocatalysis (Figure 5).

[Topic 2]

In the second topic, by adding imine to the reaction system of halogen bond-catalyzed homo-[4+2] cycloaddition of 2-vinylindoles, the reaction path switched to the Povarov reaction to furnish indolyl-tetrahydroquinolines, which indicated that as with in the gas and in the solid phases, C-I···N halogen bond prevailed over C-I···π halogen bond interaction in the solution phase. In addition, the reaction system could be modified to synthesize indolyl-quinolines by using the 3 equivalents of imine. (Figure 6)



Adv. Synth. Catal. **2020,** *362*, 3208.

Figure 6. [4+2] cycloaddition of 2-alkenylindoles with imines catalyzed by XB donor

[Topic 3]

In the third topic, intermolecular iodocyanation of electron-rich olefins using iodine cyanide was developed. The use of acetonitrile as the solvent or the use of $B(C_6F_5)_3$ as the catalyst in dichloromethane were effective for the reaction promotion.

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