学 位 論 文 内 容 の 要 旨

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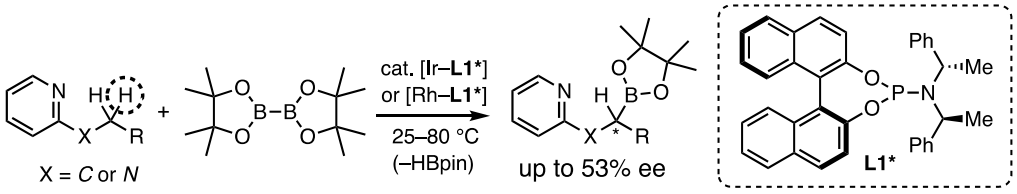
学 位 論 文 題 名

Development of Catalytic Enantioselective C(sp^3)–H Bond Borylation Reactions

（触媒的エナンチオ選択的 C(sp^3)–H 結合ホウ素化反応の開発）

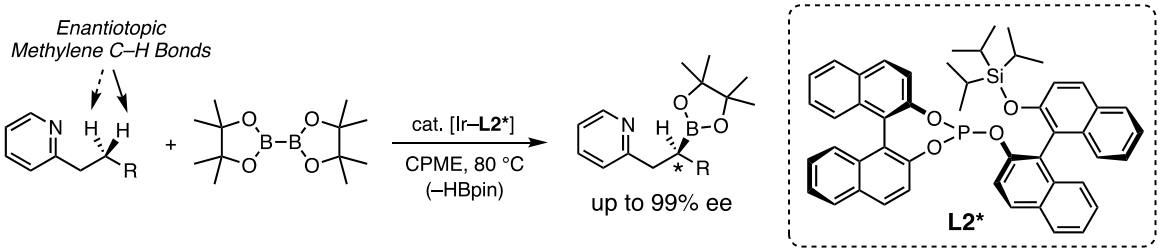
Despite the significant progress on transformative C–H bond functionalization strategies, the utilization of C(sp^3)–H bonds remains challenging. In particular, the selective functionalization of unactivated C(sp^3)–H bonds has been a long-standing challenge in organic synthesis. The heteroatom-directed borylation reactions of C(sp^3)–H bonds with Rh- or Ir-catalyst systems based on heterogeneous, silica-supported monophosphines such as Silica-SMAP and Silica-TRIP were previously reported. Along these lines, several soluble monophosphine ligands also promoted these transformations.

In Chapter 1, the preliminary investigation for the feasibility of developing an asymmetric borylation of both activated and unactivated methylene C–H bonds is described. Enantioselective heteroatom-directed C(sp^3)–H borylation reactions of 2-aminopyridines and 2-alkylpyridines with Rh- and Ir catalytic systems using readily available chiral phosphoramidite ligand (**L1***) were developed respectively (**Scheme 1**) providing an innovative example of a homogeneous catalytic system for C(sp^3)–H borylation that allows the direct synthesis of optically active alkylboronates with moderate level of enantioselectivity.



Scheme 1. Rh- or Ir-catalyzed C(sp^3)–H Borylation using Chiral Phosphoramidite Ligand

Chapter 2 outlines the development of an innovative chiral catalyst system enabling the asymmetric differentiation of enantiotopic methylene C(sp^3)–H bonds. Accordingly, the iridium-catalyzed asymmetric borylation of internal methylene C–H bonds in 2-alkylpyridine and 2-alkylbenzimidazole derivatives proceeded with excellent enantioselectivity (**Scheme 2**) using a novel BINOL-based biaryl phosphite ligand system (**L2***). This work features the realization of a homogeneous catalytic system that enables the competent enantioselective differentiation between unactivated enantiotopic methylene C–H bonds – a highly challenging synthetic transformation.



Scheme 2. Ir-catalyzed Asymmetric Borylation of Enantiotopic Methylene C(sp^3)–H Bonds

Quantum chemical calculations using the artificial force induced reaction (AFIR) method suggested the importance of the overall conformational effect featuring a trisboryliridium(III) species that allows the creation of a chiral reaction pocket for substrate accommodation along with crucial secondary attractive interactions arising from π-stacking, CH/π, and C–H···O noncovalent bonding between the substrate and the catalyst (**Figure 1**). This catalytic system presents a mechanistically rare case of a direct concerted C(sp^3)–H oxidative addition to the metal center.

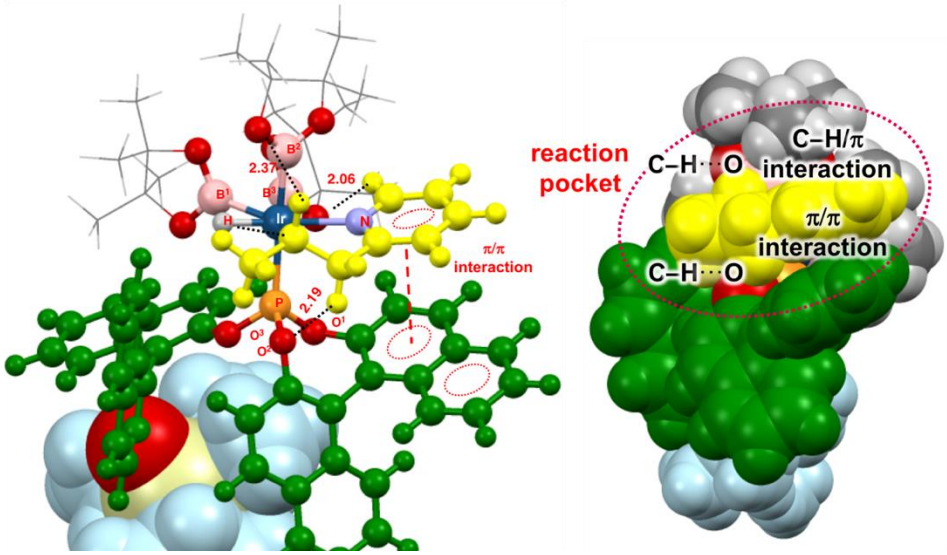
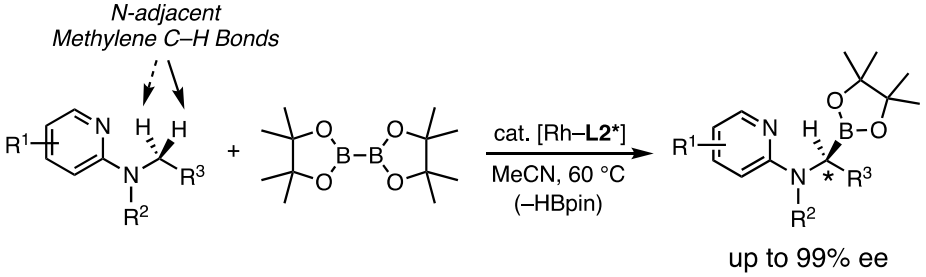


Figure 1. Geometrical and Structural Features of the Transition State formed by the [Ir–**L2***] Catalytic System following Substrate Binding within the generated Reaction Pocket [MN15/SDD&6-311G(2d,p) + SDD(Et_2O)//M06L/SDD&6-31G*(2d,p)]

In Chapter 3, the highly enantioselective borylation of methylene C–H bonds is further extended to the borylation of N-adjacent C(sp^3)–H bonds (**Scheme 3**). The competent discrimination between enantiotopic methylene C–H bonds α to the N atom in 2-aminopyridine substrates gives access to enantioenriched α-aminoboronates, an important class of boronic acid derivatives.



Scheme 3. Rh-catalyzed Asymmetric Borylation of N-adjacent Enantiotopic Methylene C–H Bonds

Overall, the highly challenging activation and subsequent borylation of enantiotopic methylene C–H bonds were achieved using a novel BINOL-based biaryl phosphite ligand system. This catalytic system competently discriminates not just activated C(sp^3)–H bonds but also proven effective towards the asymmetric borylation of unactivated methylene C(sp^3)–H bonds. Kinetic and quantum chemical calculations revealed the importance of the overall conformation of the catalyst system generating a chiral reaction pocket where the substrate is accommodated along with an assembly of weak attractive interactions including π-stacking, CH/π, and C–H···O non-covalent bonding between the substrate and the catalyst reminiscent of the active site of enzymes.