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Aromatic C–H Borylation by Nickel Catalysis

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The first nickel-catalyzed aromatic C–H borylation is described. In the presence of catalytic amounts of [Ni(cod)$_2$], tricyclopentylphosphine, and CsF, benzene and indole derivatives can be borylated with B_2pin_2. The *N*-heterocyclic carbene IPr was also found to be an effective ligand. Kinetic isotope effect experiments showed that C–H cleavage is likely involved in the rate-determining step.

In recent years, C–H functionalization has been extensively investigated and widely used as it allows the streamlined synthesis of functional molecules such as pharmaceuticals, natural products, and organic materials.[1] For example, increasing efforts have been devoted to the development of C–H borylation for aromatic compounds, due to the significant opportunity of using organoboron compounds in synthesis (Figure 1).[2] For C–H borylation, various transition-metal catalysts have been developed, among which iridium[3] and rhodium[4] complexes have proved to be the most effective. Although these precious metals exhibit high efficiency, the utilization of inexpensive catalysts in C–H borylation is attractive for good reasons. Recently, several non-noble metal catalysts such as cyclopentadienyl iron *N*-heterocyclic carbene,[5] Fe_2O_3 nanoparticles,[6] heterobimetallic copper complexes,[7] and pincer-ligated cobalt complexes[8] have been reported to catalyze C–H borylation reactions. On the other hand, nickel has not been utilized as a catalyst for C–H borylation although various nickel-catalyzed C–H functionalizations have been reported in recent years.[9] We herein report our discovery of enabling ligands and additives to achieve the first nickel-catalyzed C–H borylation (Figure 1).

We began our study by examining various nickel salts, ligands, and additives in the reaction of toluene (**1a**) and bis(pinacolato)diboron (B_2pin_2). After extensive screening, we determined that the reaction of **1a** (56 equiv, 3 mL) with B_2pin_2 (0.5 mmol, 1.0 equiv) in the presence of [Ni(cod)$_2$] (10 mol %; cod: 1,5-cyclooctadiene), tricyclopentylphosphine (PCyp$_3$, 20 mol %), and CsF (25 mol %) at 140 °C for 24 h afforded the corresponding borylated product **2a** in 88% GC yield (based on B_2pin_2) as a mixture of regioisomers ($o/m/p = 8$:61:31) (Figure 2).

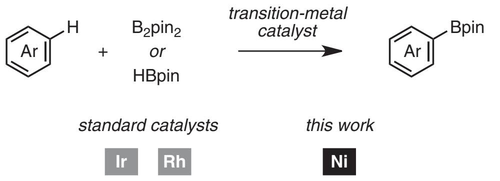


Figure 1. Transition-metal-catalyzed aromatic C–H borylation.

The list in Figure 2 contains some examples of variations from the standard conditions. In the absence of [Ni(cod)$_2$] or using nickel(II) salts, essentially no C–H borylation reaction occurred. The use of HBpin resulted in a much lower yield of **2a** (29%). The product **2a** was obtained in lower yield without PCyp$_3$. Triisopropylphosphine (P^{i}Pr$_3$) and tributylphosphine (P^{n}Bu$_3$) showed less efficiency than PCyp$_3$, and triphenylphosphine (PPh$_3$) was completely ineffective for C–H borylation. Bidentate ligands such as 1,2-bis(dicyclohexylphosphino)ethane (dcype) and 4,4′-di-*tert*-butyl-2,2′-dipyridyl (dtbpy),[3] the standard ligands for iridium-catalyzed C–H borylation, were also not effective. However, we found that the *N*-heterocyclic carbene ligand 1,3-bis(2,6-diisopropylphenyl)-1,3-dihydro-2*H*-imidazol-2-ylidene (IPr) showed efficiency similar to PCyp$_3$ under these conditions and a dramatic additive effect of CsF was notable. No products were obtained in the absence of CsF or presence of other alkali fluorides. Lowering the temperature led to decreased yield.

With the optimized conditions in hand, the substrate scope of the [Ni(cod)$_2$]/PCyp$_3$-catalyzed C–H borylation was investigated (Table 1). The borylation of toluene afforded **2a** in 74%

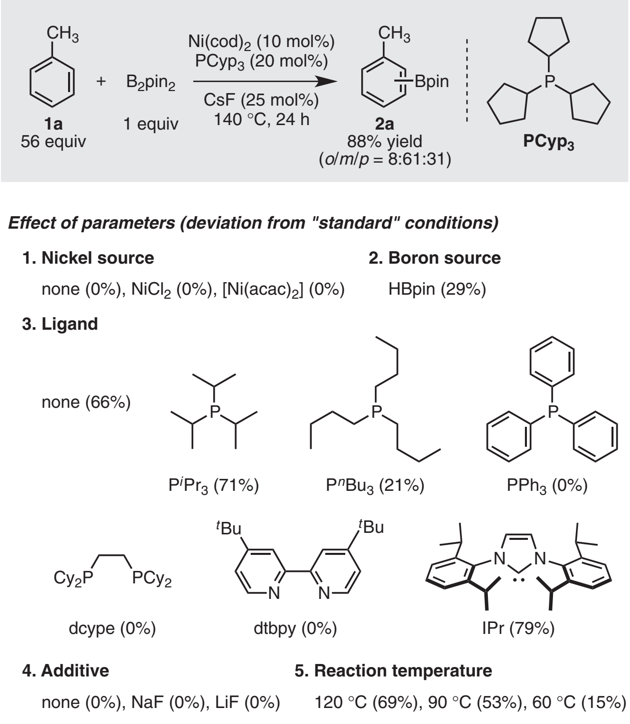
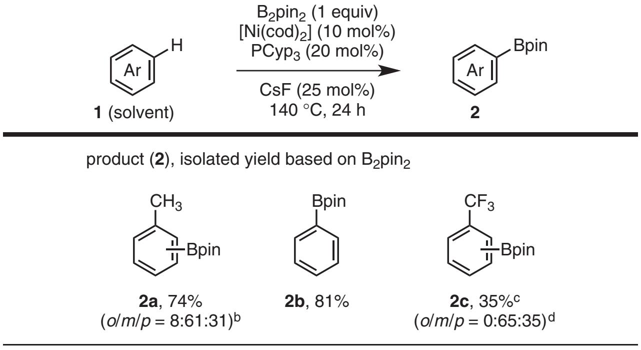


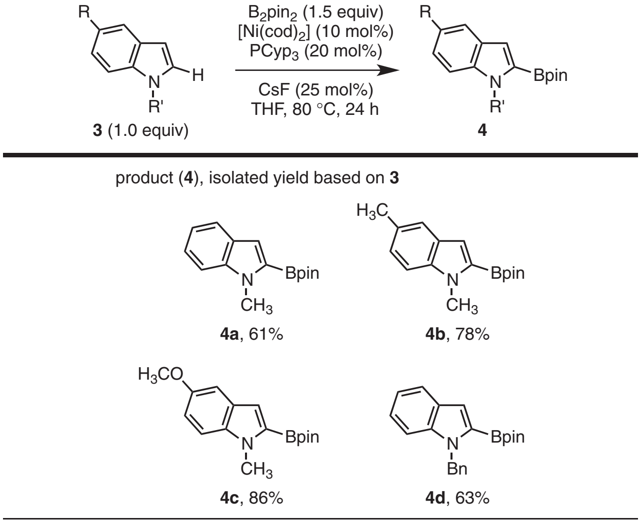
Figure 2. Discovery of nickel-catalyzed C–H borylation and effect of parameters.

Table 1. C–H borylation of benzene derivatives[a]



[a]Reaction conditions: **1** (3 mL), B_2pin_2 (0.5 mmol), $[Ni(cod)_2]$ (10 mol %), $PCyp_3$ (20 mol %), CsF (25 mol %), 140 °C, 24 h. [b]Determined by GC analysis. [c]Conditions: Trifluoromethylbenzene (**1c**: 1.5 mL), B_2pin_2 (0.2 mmol), IPr•HCl (10 mol %), NaO^{t}Bu (50 mol %). [d]Determined by ^1H NMR analysis.

Table 2. C–H borylation of indole derivatives[a]



[a]Reaction conditions: **3** (0.2 mmol), B_2pin_2 (0.3 mmol), $[Ni(cod)_2]$ (10 mol %), $PCyp_3$ (20 mol %), CsF (25 mol %), THF (1 mL), 80 °C, 24 h.

isolated yield as a mixture of *ortho*-, *meta*-, and *para*-borylated products, among which the *meta*-borylated product was predominant. This selectivity is similar to the iridium-catalyzed process, which is controlled by steric effects.[2,3] Benzene (**1b**) worked well under the standard conditions, giving C_6H_5Bpin (**2b**) in 81% isolated yield. The C–H borylation of electron-deficient benzene derivatives is sluggish with $[Ni(cod)_2]/PCyp_3$ catalyst. However, we found that the use of the carbene ligand IPr helps promote such processes. For example, trifluoromethylbenzene (**1c**) was borylated under the catalytic influence of $[Ni(cod)_2]$/IPr to furnish the corresponding borylated product **2c** in 35% isolated yield. In this reaction, the *meta*- and *para*-products were formed in a ratio of 65:35 and the *ortho*-product was not observed.

We also investigated the applicability of $[Ni(cod)_2]/PCyp_3$/CsF catalysis to heteroarene C–H borylation. Although electron-deficient heteroarenes such as pyridine were completely inactive, electron-rich heteroarenes underwent C–H arylation (Table 2). For example, *N*-methylindole (**3a**: 1.0 equiv) was borylated with B_2pin_2 (1.5 equiv) in THF at 80 °C under the influence of the $[Ni(cod)_2]/PCyp_3$/CsF catalytic system to afford 2-borylated indole **4a** in 61% isolated yield. The reaction occurred exclusively at the C2 position. It should also be mentioned that, unlike benzene derivatives, **3a** is so reactive to allow using **3a** as the limiting reagent. The C–H borylation of *N*-methylindoles substituted with methyl and methoxy groups at the C5 position produced the corresponding boronic esters **4b** and **4c** in 78% and 86% yield, respectively. In a similar manner, *N*-benzylindole (**3d**) reacted smoothly resulting in 63% yield of desired product **4d**. Similar to the case of benzene derivatives, electron-rich indoles were converted to the borylation products in higher yields. We also investigated other electron-rich heteroarenes such as pyrroles, thiophenes, and furans. However, C–H borylation was sluggish with these substrates and the yield was generally less than 10%.

Although mechanistic details such as the mode of C–H cleavage and the effect of $PCyp_3$ and CsF remain unclear at present, we conducted several experiments to determine the kinetic isotope effect (KIE) values of present nickel-catalyzed aromatic C–H borylation. For example, the competition experiments of benzene and benzene-d_6 were performed under $[Ni(cod)_2]/PCyp_3$/CsF catalysis (Figure 3a). Under the standard conditions, C_6H_5Bpin (**2b**) and C_6D_5Bpin (**2b′**) were obtained in 82% combined yield in a ratio of 1.99:1. We also independently monitored the reaction progress[10] of the C–H borylation of toluene (**1a**) and toluene-d_8 with B_2pin_2 under $[Ni(cod)_2]/PCyp_3$/CsF, from which the KIE value (k_H/k_D) of 2.71 was determined (Figure 3b). These experiments indicate that C–H cleavage is probably involved in the rate-determining step of

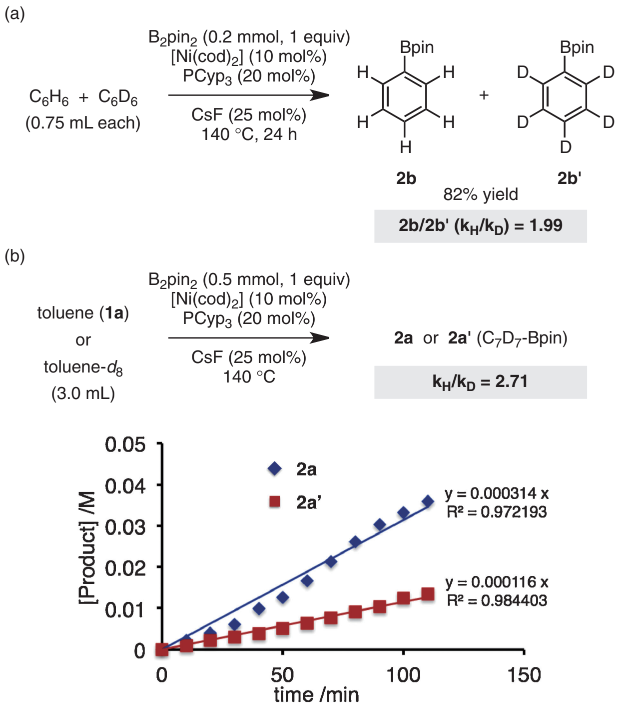


Figure 3. Determination of KIE values by (a) competition experiment and (b) independent kinetic analysis.

C–H borylation. However, we must stress that extensive studies are needed to elucidate the mechanism of current nickel catalysis.

In summary, we have developed the first nickel-catalyzed aromatic C–H borylation. The use of $PCyp_3$ or IPr as ligands and the use of CsF as an additive are crucial to render nickel functional as a catalyst. Although the substrate scope is rather limited, electron-neutral and -rich benzene derivatives and indoles can be borylated efficiently under nickel catalysis. Further studies expanding the substrate scope and elucidating the mechanism are currently underway.

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Supporting Information is available electronically on J-STAGE.

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