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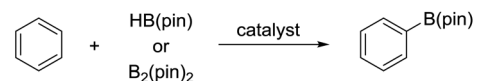
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Nickel-catalyzed borylation of arenes and indoles via C–H bond cleavage†

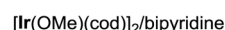
Takayuki Furukawa,^a Mamoru Tobisu^{*abc} and Naoto Chatani^{*a}

The first nickel-catalyzed method for the borylation of carbon–hydrogen bonds in arenes and indoles is described. The use of an N-heterocyclic carbene ligand is essential for an efficient reaction, with an N-cyclohexyl-substituted derivative being optimal. This method is readily applied to the gram scale synthesis of 2-borylindole.

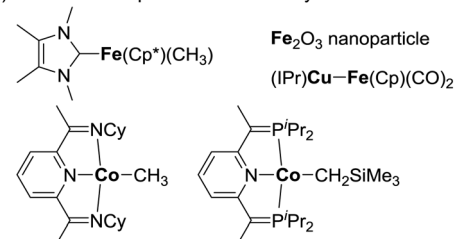
Over the past few decades, substantial progress has been made in the development of catalytic methods for C–H bond functionalization.¹ Catalytic borylation of arenes is arguably the method of paramount importance, since it allows the introduction of a synthetically useful boron functionality directly at the C–H bond of an arene without using any directing groups.² The regioselectivity of this method is predictable based on steric factors, enabling the widespread use of this borylation method in the late-stage elaboration of a range of complex aromatic molecules. Iridium complexes ligated with a bipyridine-based ligand are presently the catalyst of choice for the efficient, regioselective borylation of arenes (Scheme 1a).³ One remaining challenge in the catalytic C–H borylation methodology is the development of base metal catalysts, driven by recent concerns regarding the limited availability of precious metals. Although a seminal work by Hartwig demonstrated the potential activity of base metal complexes such as Fe and Mn in the C–H bond borylation reaction in 1995,⁴ catalytic variants were achieved only recently (Scheme 1b). Ohki and Tatsumi reported an iron-catalyzed borylation of furans and thiophenes in the presence of a hydrogen acceptor,⁵ while Kuang and Wang demonstrated that Fe₂O₃ nanoparticles can also catalyze the borylation of arenes in the presence of a more than stoichiometric amount of *tert*-butyl peroxide.⁶ A mechanistically unique C–H borylation using a Cu/Fe bimetallic catalyst under



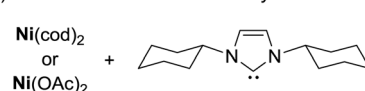
(a) State-of-the-art



(b) Alternative nonprecious metal catalysts



(c) This work: the first nickel catalyst



Scheme 1 Catalysts for the borylation of C–H bonds of (hetero)arenes.

photochemical conditions was developed by Mankad.⁷ Chirik reported a cobalt-catalyzed C–H borylation applicable to a broad range of arenes and heteroarenes.⁸ Despite these advances, the full potential of base metals to promote C–H borylation in a broader sense, to promote C–H activation, has not been explored, especially in the case of metals other than iron⁹ and cobalt.¹⁰ Herein, we report the first nickel-catalyzed borylation of C–H bonds in arenes and indoles.

During the course of our mechanistic studies of the Ni(cod)₂/PCy₃-catalyzed reductive cleavage of anilides using HBpin, we found that the hydrogens of the aromatic ring of the toluene solvent were interchanged with those of the HBpin.¹¹ This observation clearly indicated that the C–H bonds in simple arenes can be activated under nickel catalysis. We were intrigued by this finding because, to the best of our knowledge, the nickel-catalyzed C–H functionalization of simple arenes (*i.e.*, arenes bearing no directing group)

^a Department of Applied Chemistry, Faculty of Engineering, Osaka University, Suita, Osaka 565-0871, Japan. E-mail: tobisu@chem.eng.osakau.ac.jp, chatani@chem.eng.osakau.ac.jp

^b Center for Atomic and Molecular Technologies, Graduate School of Engineering, Osaka University, Suita, Osaka 565-0871, Japan

^c ESICB, Kyoto University, Katsura, Kyoto 615-8510, Japan

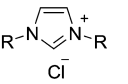
† Electronic supplementary information (ESI) available: Detailed experimental procedures and characterization of new products. See DOI: 10.1039/c5cc01378j



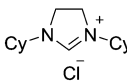
Table 1 Nickel-catalyzed borylation of benzene: ligand screening^a

$\text{HBpin} + \text{C}_6\text{H}_6 \xrightarrow[\text{solvent}]{\text{Ni(cod)}_2 (3 \text{ mol } \%), \text{Ligand} (3 \text{ mol } \%), \text{NaO}^t\text{Bu} (6 \text{ mol } \%), 80^\circ\text{C}, 20 \text{ h}}$ $\text{C}_6\text{H}_5\text{Bpin} \quad \mathbf{1}$		
Entry	Ligand	Yield ^b (%)
1	None	5
2 ^c	PCy ₃	0
3	IMes·HCl (R = 2,4,6-Me ₃ C ₆ H ₂)	51
4	IPr·HCl (2,6- ⁱ Pr ₂ C ₆ H ₃)	16
5	IMe·HCl (R = Me)	22
6	I ^t Pr·HBF ₄ (R = ^t Pr)	33
7	I ^t Bu·HCl (R = ^t Bu)	50
8	ICy·HCl (R = cyclohexyl)	75 (71) ^d
9	I(1-Ad)·HCl (R = 1-adamantyl)	36
10	I(2-Ad)·HCl (R = 2-adamantyl)	Trace
11	SICy·HCl	2
12	BICy·HCl	69

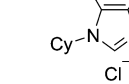
Ligand:



R-NHCy⁺Cl⁻



SICy·HCl



BICy·HCl

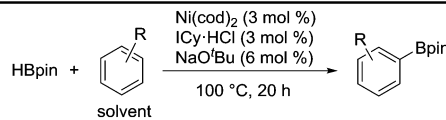

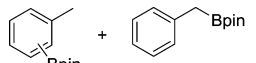



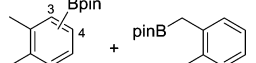

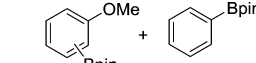





^a Reaction conditions: HBpin (1.2 mmol), Ni(cod)₂ (0.036 mmol), ligand (0.036 mmol), NaO^tBu (0.072 mmol) and benzene (1.0 mL) in a screw-capped vial under N₂ at 80 °C for 20 h. ^b GC yield based on HBpin. ^c NaO^tBu was not added. ^d Isolated yield.

has not yet been reported, with the exception of the reactions using highly fluorinated benzenes.^{12,13} We therefore envisaged that the C–H borylation of simple arenes by nickel should be possible if an appropriate catalyst system can be identified.

We initially examined the nickel-catalyzed reaction of HBpin with benzene in the presence of a variety of ligands (Table 1). Although we previously determined that the Ni(cod)₂/PCy₃ system can mediate the H/D exchange reaction *via* C–H activation of arenes,¹¹ this catalyst system did not lead to the formation of the desired borylated product **1** (entry 2). In contrast, the use of IMes, an N-heterocyclic carbene (NHC) bearing a mesityl group, was found to generate **1** in 51% yield (entry 3). Replacing the mesityl group with either the larger 2,6-ⁱPr₂C₆H₂ group (*i.e.*, IPr) or the smaller methyl group (*i.e.*, IMe) decreased the yield of **1** (entries 4 and 5). Further experimentation with the substituent on the nitrogen of the NHC ligand revealed that the cyclohexyl-substituted derivative (*i.e.*, ICy) was the most effective ligand among those tested, with **1** being formed in 71% isolated yield (entry 8). Whereas the use of a saturated analog of ICy (*i.e.*, SICy) led to a complete loss of catalytic activity (entry 11), the benzohomolog of ICy (*i.e.*, BICy) promoted the borylation of benzene with comparable efficiency (entry 12).

B₂pin₂ was also found to be a suitable boron source for this nickel-catalyzed borylation, forming **1** in a 125% yield based on B₂pin₂ (eqn (1)).

Table 2 Nickel-catalyzed borylation of various arenes^a

$\text{HBpin} + \text{Ar} \xrightarrow[\text{solvent}]{\text{Ni(cod)}_2 (3 \text{ mol } \%), \text{ICy} \cdot \text{HCl} (3 \text{ mol } \%), \text{NaO}^t\text{Bu} (6 \text{ mol } \%), 100^\circ\text{C}, 20 \text{ h}}$ ArBpin		
Entry	Arene	Product ^b
1		 +  65% (o:m:p:benzyl = 5:40:18:37)
2		 +  50% (o:m:p:benzyl = 2:44:24:30)
3		 +  43% (3:4:benzyl = 5:51:44)
4		 +  33% (o:m:p = 49:42:9) 7%
5 ^c		 68% (60%) ^d

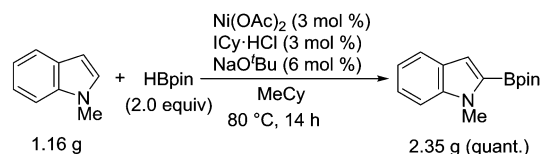
^a Reaction conditions: HBpin (1.2 mmol), Ni(cod)₂ (0.035 mmol), ICy·HCl (0.035 mmol), NaO^tBu (0.070 mmol) and arene (1.0 mL) in a screw-capped vial under N₂ at 100 °C for 20 h. ^b Isolated yield based on HBpin. ^c At 80 °C. ^d N-Methylpyrrole (2.0 mmol) in methylcyclohexane (1.0 mL).

The Ni(cod)₂/ICy-catalyzed borylation of substituted benzene derivatives was also investigated (Table 2). When toluene was used as the substrate, the borylation proceeded efficiently just as in the case of the benzene substrate (entry 1). The regioselectivity of the borylation was found to be primarily controlled by steric effects, forming the meta and para isomers as the major products, a result similar to those obtained using Ir,³ Fe⁶ or Co⁸ catalysts. The difference between the present work and these previously reported catalysts is that the borylation in the current study also occurred at the benzylic position. The observed product distribution was similar to that obtained using a rhodium-based catalyst,^{14,15} although the rhodium system allows the benzylic isomer to be formed as the major product. The borylation of ethylbenzene under these nickel-catalyzed conditions also proceeded to deliver four isomers (entry 2). Disubstituted benzenes were generally much less reactive than mono-substituted benzenes under the current reaction conditions (entry 3). The use of anisole as the substrate resulted in borylation products, with the *ortho*-borylated isomer as the major product (entry 4). This regioselectivity was in sharp contrast to that observed in homogeneous Ir,³ Fe⁷ and Co⁸ systems, wherein the major products were the meta and para isomers. This result indicated that a methoxy group can serve as an *ortho*-directing group in the current nickel-catalyzed borylation reaction. It is noteworthy that borylative cleavage of the C(aryl)–OMe bond¹⁶ in anisole was also observed, albeit in low yield (7%). Unlike the Hartwig's hydroarylation



system,¹² 1,3-bis(trifluoromethyl)benzene was not a good substrate in the present reaction (<10% yield). Halogen (Cl, Br and F) and carbonyl-containing (ketone and ester) benzenes were found to be inapplicable since these functionalities can react with the nickel species under these conditions. Heteroarenes were also examined as potential substrates for the nickel-catalyzed borylation reactions. Whereas furan, thiophene, pyridine and their benzo-fused derivatives could not be borylated under these conditions, pyrrole was found to be exceptionally reactive during this borylation, forming the 2-borylated product in a regioselective manner (entry 5). Notably, the product was obtained in good yield even when the amount of pyrrole was reduced to 1.7 equivalents relative to HBpin.

The evident high reactivity of pyrrole prompted us to examine indole derivatives in this nickel-catalyzed borylation reaction (Table 3). As expected, the borylation occurred efficiently using indole as the limiting agent and also took place regioselectively at the 2-position. In addition to *N*-methylindole (entry 1), a bulkier *N*-butyl-substituted indole successfully underwent borylation without any decrease in the regioselectivity of the reaction (entry 2). An *N,O*-acetal moiety remained intact, serving as a suitable protecting group in this reaction (entry 3). In addition, *N*-benzyl groups were also tolerated, leaving the aryl group free from borylation (entries 4 and 5). Installation of a boryl group at the sterically hindered 2-position of 3-substituted indoles



Scheme 2 Gram scale synthesis of 2-borylindole using Ni(OAc)₂.

was also possible (entry 6). The reactivity and selectivity of this borylation was unaffected by the introduction of a methoxy group to the indole framework (entry 7). Although a C(aryl)–F bond can be activated by a low valent nickel catalyst,¹⁷ fluoroindole underwent borylation with its fluoride moiety remaining intact (entry 8). Azaindole also served as a good substrate for this borylation, generating the corresponding 2-borylated product (entry 9).

Although Ni(cod)₂ was routinely used as the catalyst for this borylation during our exploratory studies, Ni(OAc)₂ was found to serve as a more useful catalyst precursor. A protocol using Ni(OAc)₂ allowed the successful implementation of this borylation on the gram-scale, highlighting the practical utility of the nickel-catalyzed system (Scheme 2).

To obtain further insights into the mechanistic aspects of the nickel-catalyzed borylation, some preliminary mechanistic experiments were performed. Comparison of the initial rates of the nickel-catalyzed borylation reactions of benzene and benzene-*d*₆ determined that *k*_H/*k*_D was 2.1, which was slightly smaller than the values reported for iridium² and iron⁷ systems. The nickel-catalyzed borylation of benzene or indole was also found to be completely inhibited when the reaction was attempted in the presence of an excess of mercury. In addition, filtration tests indicated that the liquid phase of the catalytic mixture did not contain catalytically active species (see ESI† for details). The currently available data indicate that the borylation is likely mediated by heterogeneous nickel species, although more detailed studies are required for a definitive understanding of the nature of the catalysis.¹⁸ Finally, a recent report on the KO^tBu-catalyzed silylation of heteroarenes^{19,20} motivated us to examine the borylation of indole in the presence of only NaO^tBu. The borylation product was not observed under such conditions, indicating that the nickel species play an essential role in this borylation reaction.

In summary, we have shown for the first time that the direct borylation of arenes can be mediated by a nickel-based catalyst. Indoles are particularly reactive with this catalyst system, affording the corresponding 2-borylated products. The successful use of nickel is noteworthy because nickel is rarely employed as a catalyst for the C–H bond activation process in the absence of a directing group.¹² The heterogeneous nature of the active species generated under the current conditions could be important in explaining the unprecedented reactivity of nickel,²¹ although further investigations are required for a complete understanding of the mechanism of this borylation. The application of these nickel species to other transformations as well as catalytic borylations using other base metals are currently being investigated in our laboratories.

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Table 3 Nickel-catalyzed borylation of indoles^a

Entry	Indole	Product	Isolated yield (%)
1	R = Me		78
2	R = <i>n</i> -butyl		68
3	R = CH ₂ OMe		68
4	R = H		82
5	R = OMe		76
6			87
7			76
8 ^b			82
9 ^b			56

^a Reaction conditions: indole (0.80 mmol), HBpin (1.2 mmol), Ni(cod)₂ (0.040 mmol), ICy·HCl (0.040 mmol), NaO^tBu (0.080 mmol), and methylcyclohexane (1.0 mL) in a screw-capped vial under N₂ at 80 °C for 16 h.

^b HBpin (1.2 equiv.) was used.



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