

Nickel-catalyzed (hetero)aryl borylations: an update

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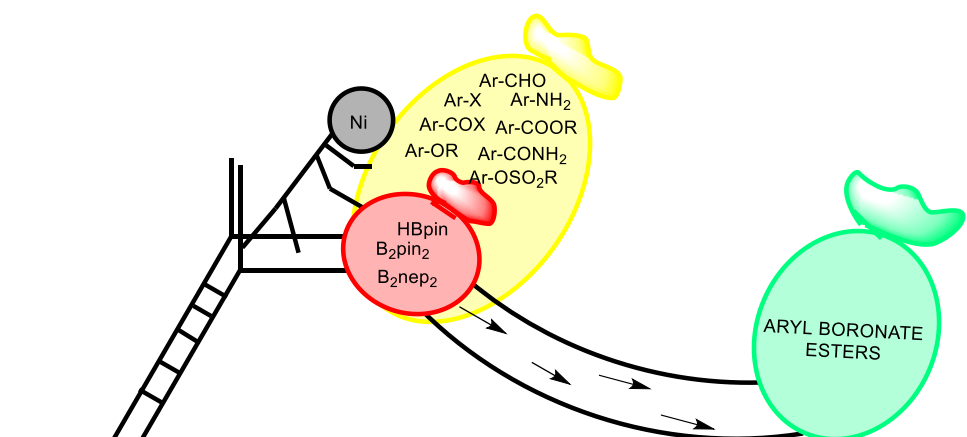
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Abstract

Aromatic organoboron compounds serve as important intermediates in synthetic organic chemistry. While the traditional electrophilic borylations using aromatic lithium or magnesium reagents had several limitations, transition metal catalyzed borylations emerged as a promising method. In recent years, borylation reactions catalyzed by Ni have gained great attention due to its enormous importance as a cheaper and less toxic alternative to Pd catalysts. The present review focuses on the recent developments in the arena of Ni catalyzed (hetero)aryl borylations after 2013.



Keywords: Organoboron compounds, borylation, Ni catalysts, aryl borylation, Hetero aryl borylation

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1. Introduction

Organoboron reagents are indispensable tools in the organic chemistry toolbox of synthetic chemists.¹ Organoboron compounds, being the essential synthetic components for carbon-heteroatom and carbon-carbon bond making reactions^{2,3} provide access to a wide array of valuable and diverse transformations. Their non-toxic nature, excellent functional-group tolerance and diverse reactivity profile are some of the characteristics, which make them unique among the members of the organometallic family, such as organomagnesium or organozinc reagents.⁴ The utility of aromatic boron derivatives such as aryl boronic acids and aryl boronate esters as critical intermediates in organic synthesis, elements of functional materials and therapeutic drugs has always attracted the attention of synthetic organic chemists.⁵

The preparation of sensitive functional group-containing arenes could be achieved by this alternative strategy of catalytic aromatic carbon–boron bond formation.⁶ The traditional method of electrophilic² borylation reaction of aromatic lithium or magnesium reagents derived from aromatic halides with trialkylborates for their synthesis⁷⁻¹⁰ had the major drawback of low functional group compatibility.² In contrast, the use of transition-metal catalysts in nucleophilic borylation led to the production of organoboronic esters under mild reaction conditions with higher selectivity and reactivity.^{Error! Bookmark not defined.} Thus, the direct C–H borylation of arenes using Re¹¹, Rh,^{12,13} and Ir¹⁴⁻¹⁶ catalysts using tetraalkoxydiboron and dialkoxyborane emerged as a powerful strategy, but poor regioselectivity was observed.⁵ Ishiyama *et al.* disclosed the first Pd-catalyzed borylation of aryl halides with bis(pinacolato)diboron (B₂pin₂), which unveiled an efficient route towards the synthesis of aryl-BPin units in 1995.¹⁷ The regiospecific conversion of aryl triflates, iodides and bromides to the corresponding arylboronate esters was accomplished by such Pd-catalyzed borylations.¹⁸⁻²³

Later, a range of inexpensive, abundant, and less toxic transition metals including Cu, Ni, Zn, and Fe were introduced as alternatives to Pd catalysts.¹ Nickel, the “spirited horse” of transition metal catalysis²⁴ can exhibit new reactivity patterns beyond the traditional framework of metal catalysts. Nickel is more electropositive than many other transition metals and can thus easily undergo oxidative addition.²⁵ This oxidative addition property of nickel enables the facile cleavage of inert carbon–carbon and carbon–heteroatom bonds, hence electrophiles that are less reactive towards palladium catalysts can be borylated through the action of Ni catalysts.²⁶

The first report on Ni-catalyzed pinacolborylation using the catalytic system, Ni(dppp)Cl₂ was published by Tour and co-workers in 2000.²⁷ Since then, there was much focus on the use of Ni catalysts for aryl borylations. The remarkable progress of nickel catalysts in this area was attributed to their diverse reactivity

pattern and cost-efficiency.¹⁵ The first nickel complex bearing a boryl moiety that could act as a recyclable reagent for the borylation of bromobenzene was reported by Mindiola and co-workers in 2007.^{28,29} Later, numerous Ni based catalytic systems were developed for aryl borylation reactions. The boron sources, used in general, for the reactions were pinacolborane(HBpin), Bis(neopentylglycolato)diboron(B₂nep₂) and bis(pinacolato)diboron(B₂pin₂).

The first catalytic system for neopentylglycolborylation, NiCl₂(dppp)/dppp [dppp = 1,3-bis(diphenylphosphanyl)propane] was effective for aryl iodide and bromide substrates.^{30,31} The borylation of even more challenging substrates such as aryl chlorides³², and the less reactive aryl sulfonates⁵ was attained by the use of mixed-ligand systems, in particular NiCl₂(dppp)/dppf [dppf = bis(diphenylphosphanyl)ferrocene].¹² Interestingly, though some aryl mesylates and tosylates were successfully neopentylglycolborylated in high yields with NiCl₂(dppp)/dppf, without any additives, the inclusion of zerovalent Zn metal as additive was found to further enhance the rate of thereaction, presumably by activating the Ni catalyst. The role of Zn was assumed to be as a reducing agent, which arguably compensated for the slower reduction of the precatalyst or oxidative addition adduct in such systems. Such reactions exhibited broad substrate compatibility and higher reaction rates and the neopentylglycolborylation of iodides, bromides, and chlorides proceeded faster achieving complete conversions and high yields.³³ Using bis(pinacolato)diboron as the borylating agent, borylation of aryl chlorides was catalyzed by NiCl₂(PMe₃)₂.³⁴ In addition to the general borylating agents mentioned earlier, 4,4,6-trimethyl-1,3,2-dioxaborinane was presented as an alternative, cheaper boron source for the borylation of aryl halides catalyzed by NiCl₂(dppp).³⁵

Though a detailed discussion on the Ni-catalyzed borylation of aryl halides and sulfonates up to late 2012 is included in the review paper by Kwong *et al*⁶ of 2013, attempts to summarize (hetero)aryl and benzyl borylation reactions catalyzed by Ni specifically are rather scarce. Considering the ever-increasing demand for Ni catalysts owing to their low cost compared to Pd catalysts, wide applicability, and the potential of aryl substrates with boron functionality for synthetic transformations, we have consolidated the works on Ni-catalyzed aryl and (hetero)aryl borylation reactions reported from 2013 to late 2021. In this review, for the sake of convenience, we have categorized the (hetero)aryl borylation reactions into different sections based on the substrates used.

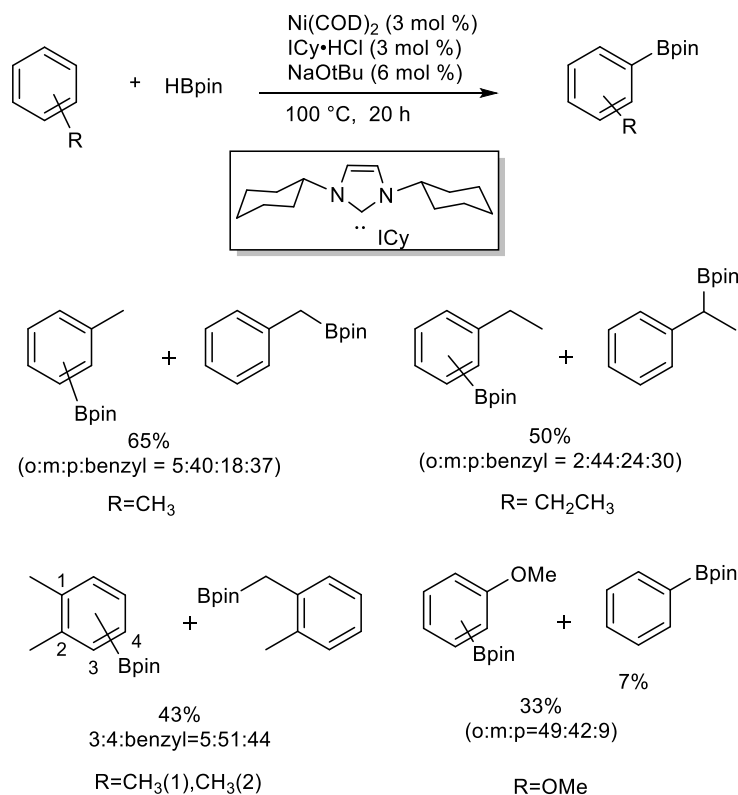
2. Borylation of Simple (Hetero)Arenes

The following section illustrates the use of Ni catalysts for the borylation of simple arenes and heteroarenes like benzene, naphthalene, indole, pyridine and their derivatives. Such reactions, in general, proceed *via* C–H activation, and Ni(COD)₂ based catalytic systems are used in all cases, except for the directed C3–H borylation of indoles, where a [Ni(IMes)₂] based system is employed.

In 2015, Tobisu *et al.* carried out the first nickel-catalyzed borylation of C–H bonds in arenes and indoles.³⁶ Their study focused on the development of an appropriate Ni based catalytic system for the direct introduction of useful boron functionality at the C–H bond of an arene without the aid of a directing group. A cyclohexyl-substituted N-heterocyclic carbene, ICy (1,3-dicyclohexylimidazolin-2-ylidene) was proven to be the most efficient ligand with Ni(COD)₂ for the reaction (Scheme 1). On the borylation of benzene and its derivatives with HBpin as boron source and 3 mol% of Ni(COD)₂/ICy system in the presence of 6 mol% of NaOtBu at 80 °C, good to excellent yields was obtained. In the case of mono and disubstituted alkyl benzenes, the proportion of *ortho*, *meta*, *para* and benzylic products varied greatly depending on the steric factors of the substrate, however, *meta* and *para* products predominated and the mono substituted compounds were more

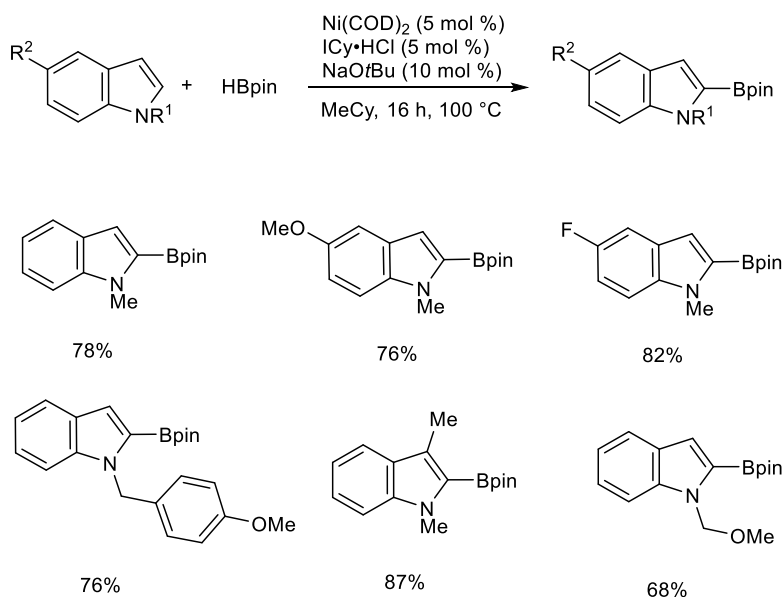
reactive than the disubstituted ones. Surprisingly with anisole, *ortho*-borylated isomer was the major product and the C(aryl)-OMe bond in anisole was also cleaved to give the corresponding borylated product.

On analyzing heteroarenes as potential substrates, pyrrole was found to be exceptionally reactive while other heteroarenes like furan, thiophene, pyridine and their benzo-fused derivatives were unreactive. Regioselective borylation at position-2 was observed for indole derivatives in relatively high yields (Scheme 2). The practical utility of the nickel-catalyzed system was established by the gram scale synthesis of 2-borylindole using $\text{Ni}(\text{OAc})_2$ as the precatalyst. Further investigation into the mechanistic aspects suggested the involvement of heterogeneous Ni species, though the authors emphasized the need for further studies to provide a detailed explanation.

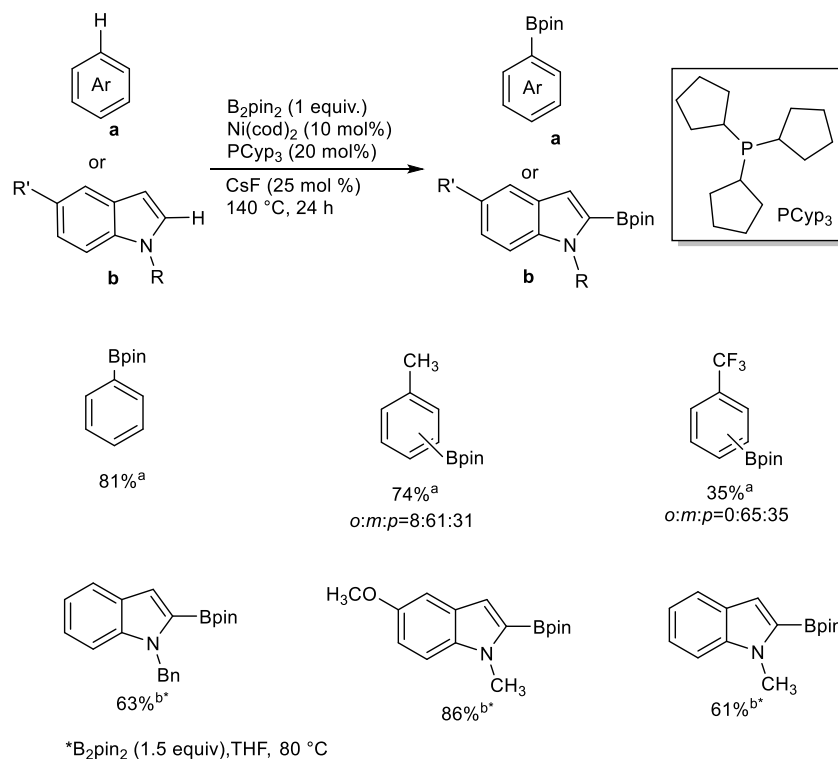


Scheme 1. Borylation of benzene and its derivatives using $\text{Ni}(\text{COD})_2/\text{ICy}$ catalytic system.

At the same time, Itami and coworkers documented the C–H borylation of aromatic compounds using a Ni based catalyst.³⁷ The aromatic C–H borylation of benzene and its derivatives was achieved using $[\text{Ni}(\text{COD})_2]/\text{PCyp}_3$ catalytic system, with B_2pin_2 as boron source and CsF as additive at $140\text{ }^\circ\text{C}$ and rendered the products in reasonable yields (Scheme 3). The carbene ligand, IPr was found to be more efficient than PCyp_3 for electron-deficient benzene derivatives. Though $[\text{Ni}(\text{COD})_2]/\text{PCyp}_3/\text{CsF}$ catalysis was not compatible with electron-deficient heteroarenes, electron-rich indole derivatives proceeded with C–H borylation exclusively at C-2 position. The work demanded further studies to expand the substrate scope of the reaction under study.



Scheme 2. Borylation of indole derivatives by the $\text{Ni(COD)}_2/\text{ICy}$ catalytic system.

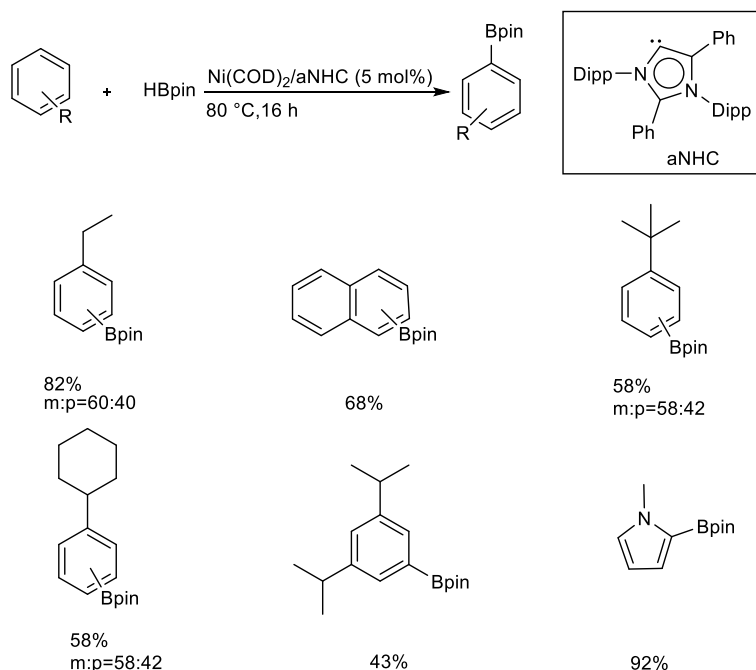


Scheme 3. Nickel-catalyzed borylation of aromatic compounds using the $[\text{Ni(COD)}_2]/\text{PCyp}_3$ system.

More recently, Mandal *et al.* came up with a novel strategy for $\text{C(sp}^2\text{)}\text{-H}$ borylation of arenes mediated by an abnormal NHC based nickel catalyst to compensate for the limited substrate scope encountered in the former works.³⁸ The abnormal N-heterocyclic carbene 1,3-bis(2,6-diisopropylphenyl)-2,4-diphenylimidazol-5-ylidene in association with the Ni precursor Ni(COD)_2 was found to be more catalytically active and nucleophilic than its normal NHC counterpart (Scheme 4).³⁹ The reaction proceeded under the conditions of 5

mol% of catalyst, HBPin as boron source and arene at 80 °C for 16 h to give C(sp²)-H borylated compounds. In addition to the direct C(sp²)-H borylation of simple arenes like benzene, different alkyl and alkoxy arenes like *n*-hexylbenzene, *n*-butylbenzene, *n*-propylbenzene, phenylcyclohexane, naphthalene, biphenyl, 1,3-diisopropylbenzene, and 1,3-dimethoxybenzene were borylated at C(sp²)-H position for the first time using this catalytic system.

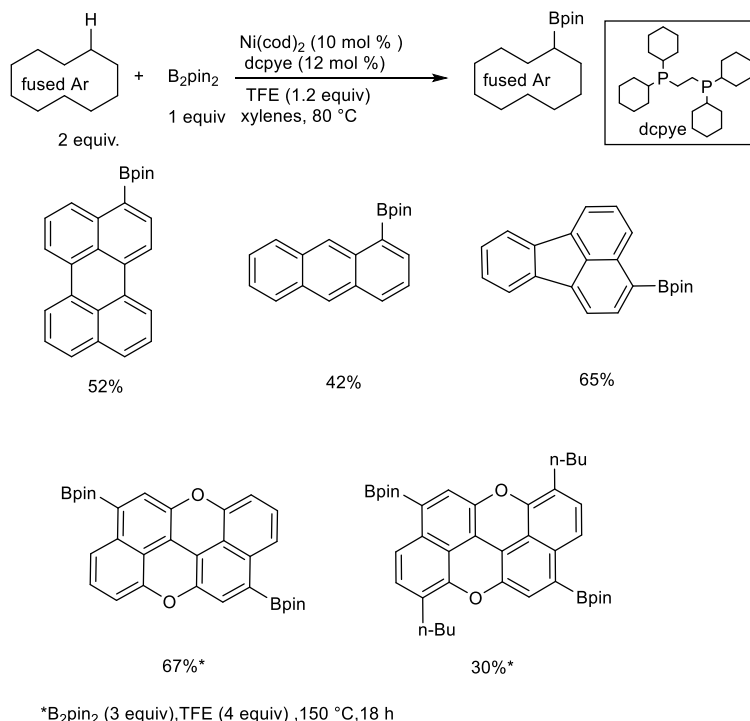
Mechanistic studies revealed the existence of a heterogeneous pathway. They identified the black particles formed during the reaction on the walls of the reaction vessel as nickel nanoparticles through several control experiments and characterization techniques, which along with a boron(III) compound constituted the catalytically active species.



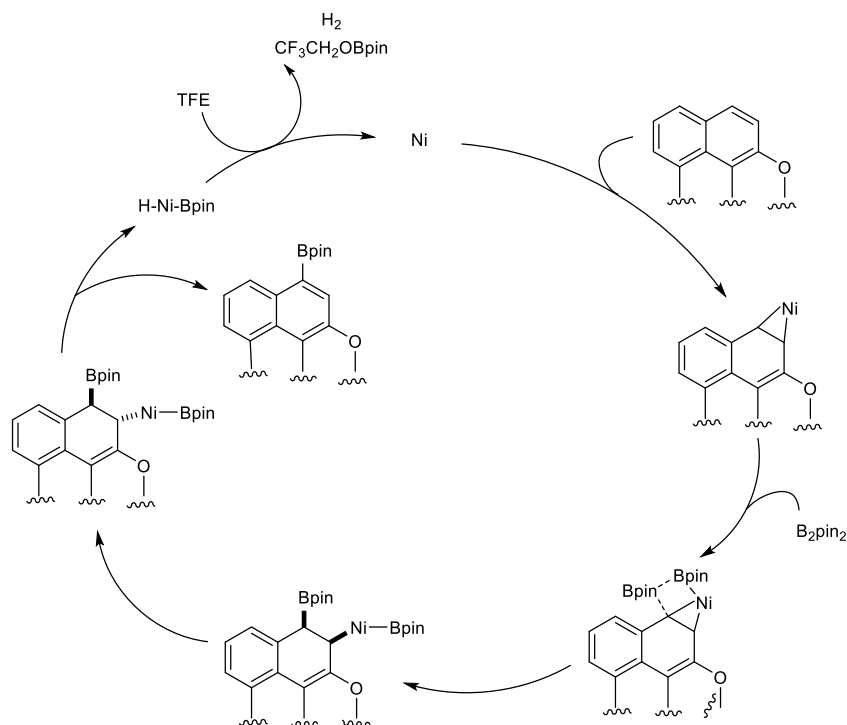
Scheme 4. C(sp²)-H borylation of arenes by Ni/aNHC system.

A method for nondirected α -C-H borylations of naphthalene-based aromatic compounds catalyzed by Ni was demonstrated by Kamei *et al.*⁴⁰ Regioselective C-H diborylations of *peri*-xanthenoxanthene derivatives were accomplished by their reaction with B₂pin₂ in the presence of Ni(COD)₂ and 1,2-bis(dicyclohexylphosphino)ethane (dcype) as the catalyst in the presence of an additive, trifluoroethanol in xylene at 150 °C in 18 h (Scheme 5). Monoborylation of fused aromatic compounds including *peri*-xanthenoxanthene(PXX), perylene, fluoranthene, and anthracene at their sterically congested α -positions was achieved under the similar reaction conditions, but the amounts of B₂pin₂ and trifluoroethanol were reduced to 1 equivalent and 1.2 equivalent respectively, and a lower temperature of 80 °C was employed for the completion of the reaction in 36 h. On the contrary, the reaction did not work with naphthalene, *N*-methylindole and anisole.

The mechanism put forward by the group was different from that of the previous reports, where a σ -bond metathesis mechanism has been proposed and the first step is considered to be the formation of a nickel(0)-anthracene η^2 -complex by the η^2 -coordination of the C4-C5 double bond of PXX to the Ni species (Scheme 6).



Scheme 5. α -C–H borylations of polycyclic aromatic compounds.

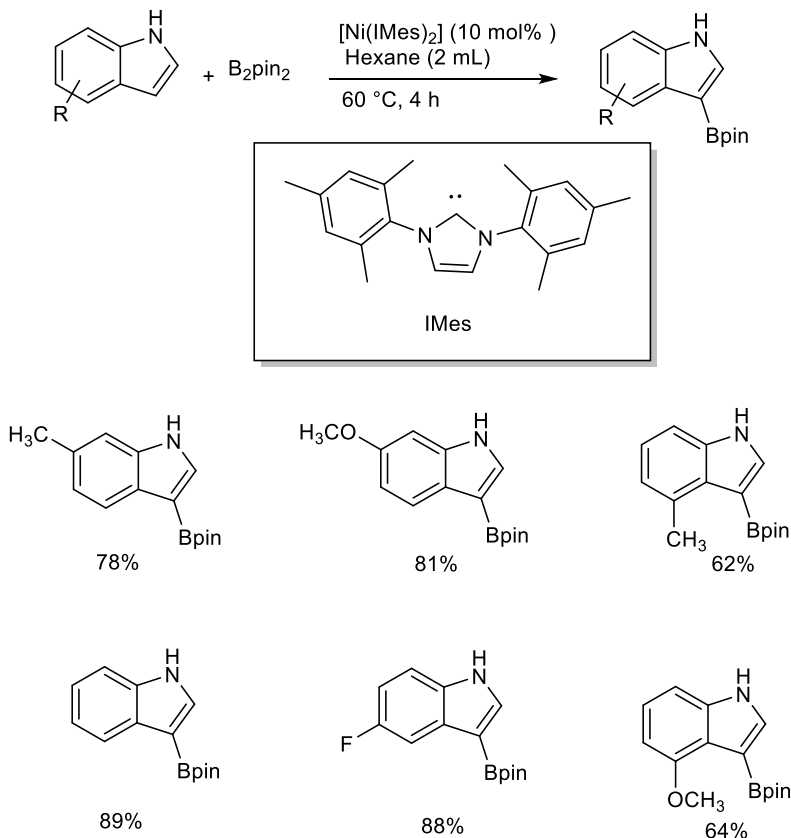


Scheme 6. Mechanism proposed by Kamei *et al.* for the borylation of naphthalene-based aromatic compounds.

A highly selective, traceless, directed C3–H borylation of indoles using a Ni catalyst was documented by Radius *et al.* in 2020.⁴¹ The catalyst, $[\text{Ni}(\text{IMes})_2]$ (10 mol%) borylated indole derivatives selectively at C3–H position using B_2pin_2 as the boron source in hexane at 60 °C within 4 h (Scheme 7). Irrespective of the nature

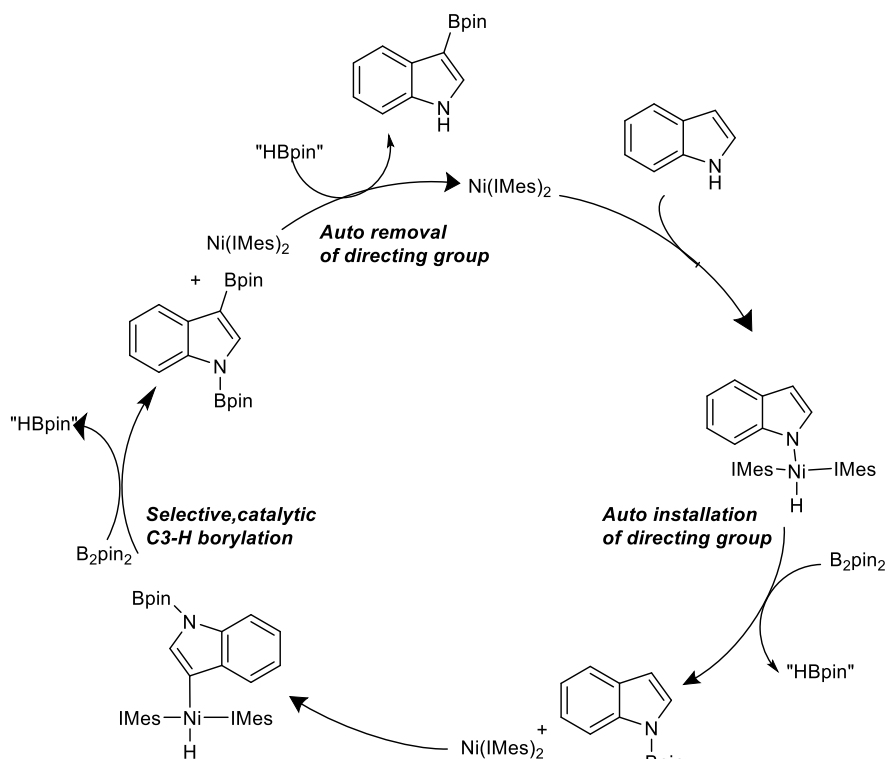
of the substituent present, C3-borylated indoles were obtained in good to excellent yields which revealed the functional group tolerance of the protocol. Of note, the reactions proceeded under mild conditions in the absence of a base.

The direct synthesis of a C3-arylated indole by a one-pot C3-H borylation/Suzuki-Miyaura cross-coupling sequence was accomplished by the group to prove the synthetic utility of the proposed reaction.



Scheme 7. C3-H borylation of indoles using $[\text{Ni}(\text{IMes})_2]$.

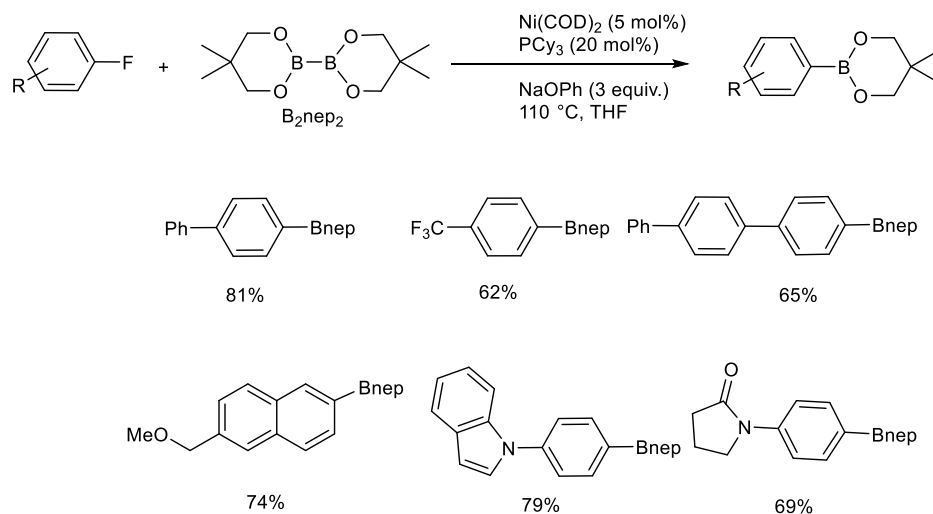
Mechanistic studies suggested the activation of the N-H bond by $[\text{Ni}(\text{IMes})_2]$ leading to the installation of Bpin, as a traceless directing group at the N-position with the subsequent release of the catalyst as the initial steps (Scheme 8). In the next steps, the regenerated $[\text{Ni}(\text{IMes})_2]$ catalyses the C3-selective C-H borylation of the N-borylated indole forming bis-N/C3-borylated indole. In the final step, the N-Bpin moiety is converted into N-H by $[\text{Ni}(\text{IMes})_2]$ and in situ-generated HBpin affording the C3-borylated indole product.



Scheme 8. Mechanism proposed by Radius *et al.* for the C3-H borylation of indoles using $[\text{Ni(IMes)}_2]$.

3. Borylation of Aryl and Aroyl Halides or Pseudo Halides

Earlier, the reports on Ni-catalyzed borylations of aryl halides were less frequent than that of Pd catalyzed aryl halide borylations.⁴² More works on the borylation of aryl halides were published in the subsequent years. The present section discusses the borylation of aryl fluorides, chlorides and bromides catalyzed by Ni. Two reports on Ni-catalyzed borylations of aroyl fluorides are also included.

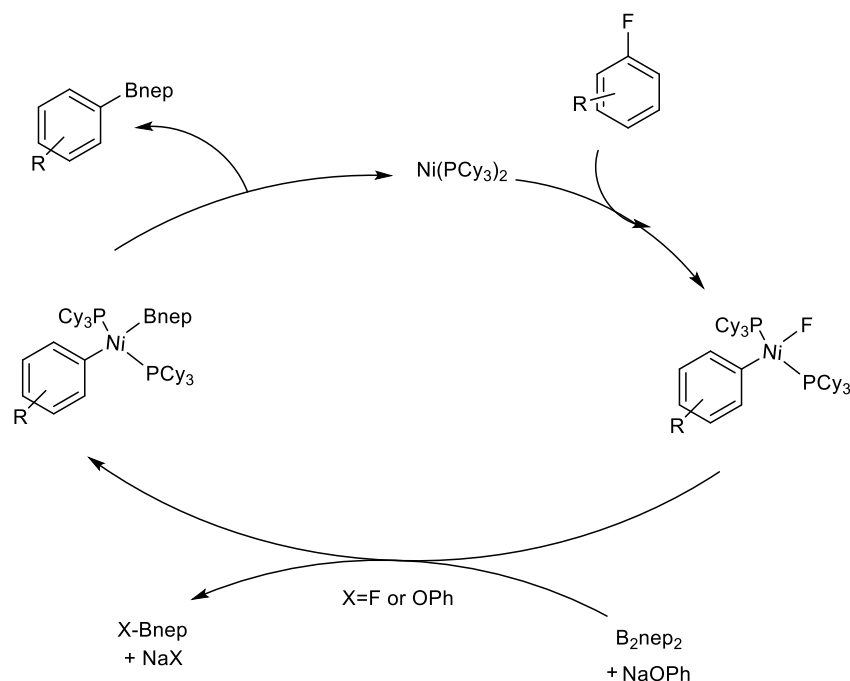


Scheme 9. Ni-catalyzed borylation of monofluoroarenes by $\text{Ni(COD)}_2/\text{PCy}_3$ system.

The first Ni-catalyzed borylation of monofluoroarenes was demonstrated by Martin *et al.* employing $\text{Ni}(\text{COD})_2/\text{PCy}_3$ in 1:4 ratio with $\text{B}_2(\text{nep})_2$ as boron source, THF as solvent and NaOPh as an additive that rendered borylated aryl fluorides in good to high yields (Scheme 9).⁴³ The reaction was found to be highly chemoselective and unaffected by the presence of other functional groups.

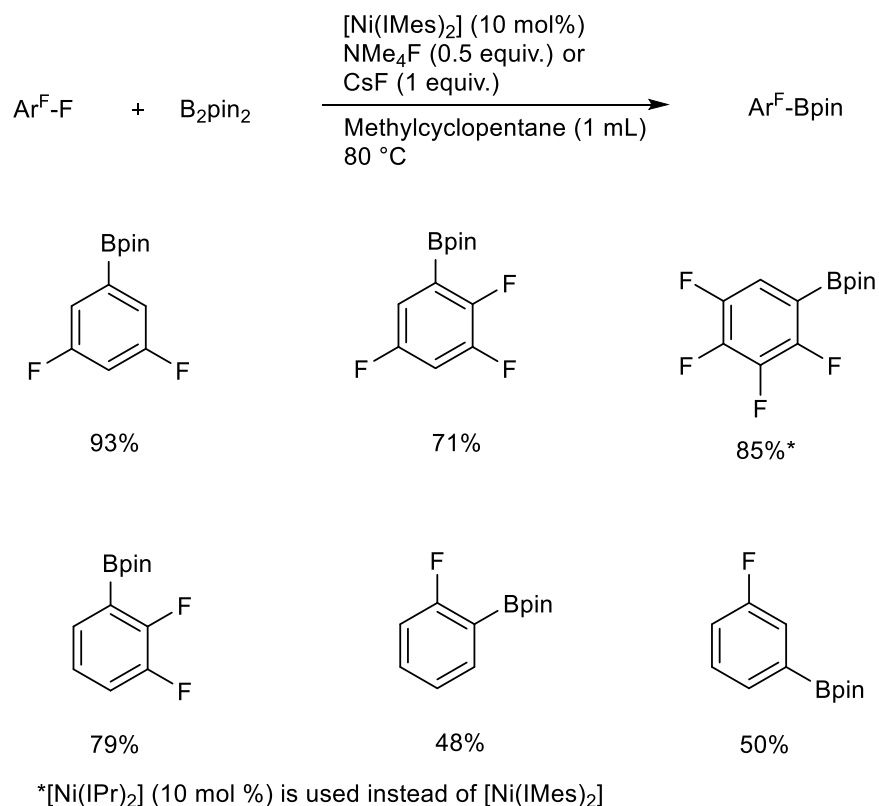
Mechanistic studies revealed the existence of an oxidative addition complex *via* $\text{C}(\text{sp}^2)\text{--F}$ activation which is then subjected to a boryl transfer from the boron source assisted by NaOPh (Scheme 10). The final borylated arene is released by C–B bond-reductive elimination and the active species $\text{Ni}(\text{PCy}_3)_2$ is regenerated.

This unconventional strategy for C–C–B bond-formation *via* catalytic C–F cleavage of unactivated fluoroarenes marked the synthetic utility of such compounds for the development of novel molecules of interest.

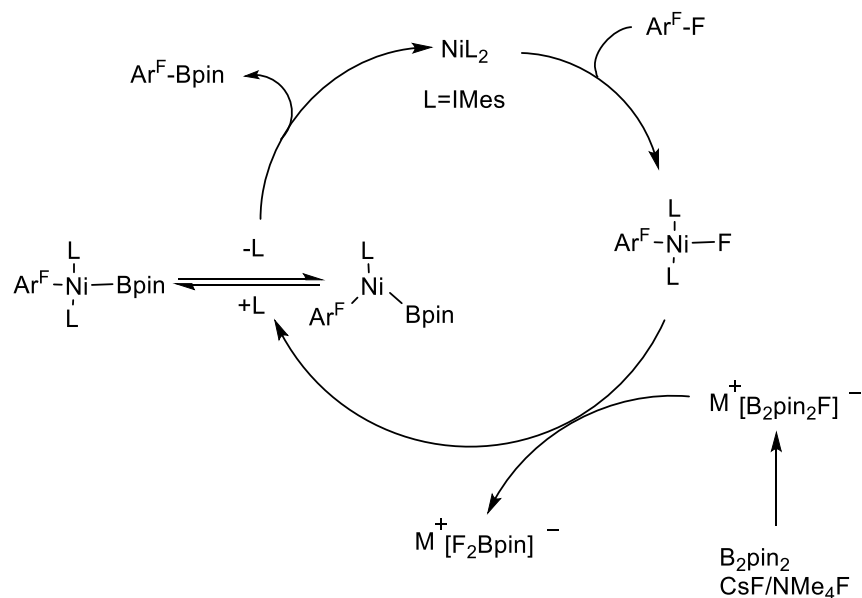


Scheme 10. Mechanism proposed by Martin *et al.* for the Ni-catalyzed borylation of monofluoroarenes using $\text{Ni}(\text{COD})_2/\text{PCy}_3$.

Inspired by the pioneering works of Martin *et al.*⁴³ and Niwa and Hosoya⁴⁴ *et al.* in the field of Ni-catalyzed borylation of monofluoroarenes, the research group of Marder and Radius studied the scope of NHC nickel-catalyzed borylation of polyfluorinated aromatic systems.⁴⁵ They assessed the C–F bond cleavage and subsequent borylation in several polyfluoroarenes using the catalyst $[\text{Ni}(\text{IMes})_2]$ (10 mol%), B_2pin_2 (0.2 mmol) as the source of boron, NMe_4F or CsF (0.5 equiv.) as fluoride source and methylcyclopentane (1 mL) as solvent at 80 °C affording moderate to good yields of the product (Scheme 11). Interestingly, the catalytic system $[\text{Ni}(\text{IMes})_2]$ was found to be less effective for pentafluorobenzene, whereas $[\text{Ni}(\text{IPr})_2]$ improved the reaction yield considerably. They also proposed a mechanism for the reaction (Scheme 12). The work is significant due to the high utility of borylated fluoroaromatics as precursors in organic synthesis.



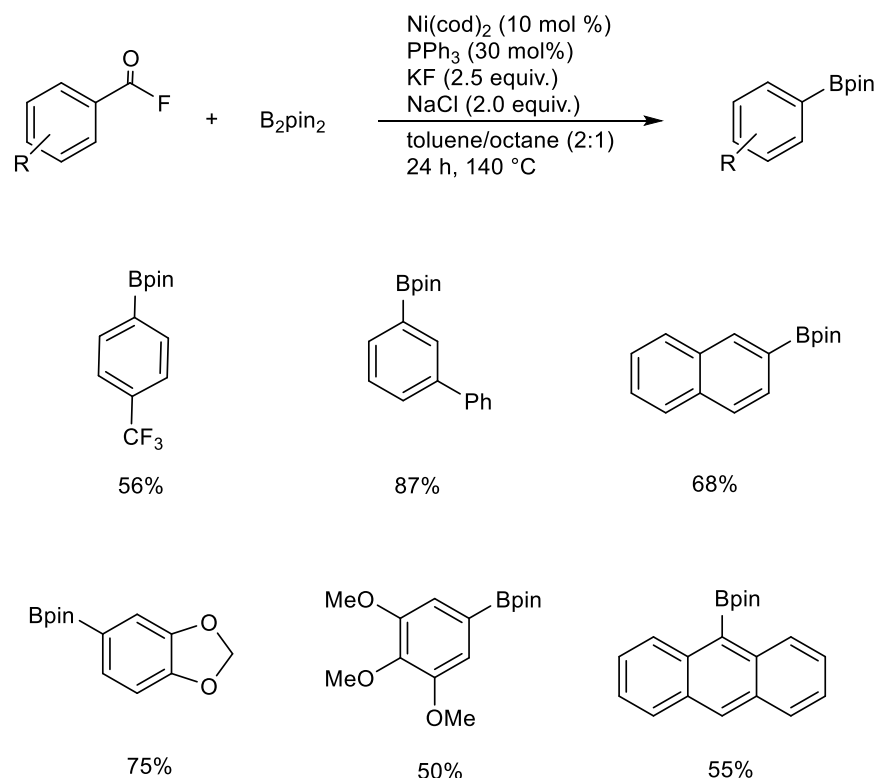
Scheme 11. Borylation of fluorinated aromatic systems with $[\text{Ni}(\text{IMes})_2]$.



Scheme 12. Mechanism proposed by Radius *et al.* for the borylation of fluorinated aromatic systems with $[\text{Ni}(\text{IMes})_2]$.

Nishihara *et al.* disclosed an efficient method for the decarbonylative borylation of aroyl fluorides aided by Ni/PPh_3 catalytic system.⁴⁶ The reaction of aroyl fluorides with bis(pinacolato)diboron in the presence of 10 mol% of $\text{Ni}(\text{COD})_2$, 30 mol% of PPh_3 , 2.5 equiv. of KF , and 2.0 equiv. of NaCl at 140°C for 24 h in a mixed

solvent system of toluene and octane(v/v = 2/1) proceeded to give the corresponding arylboronates in good to high yields (Scheme 13). The scope for large scale synthesis was also established.



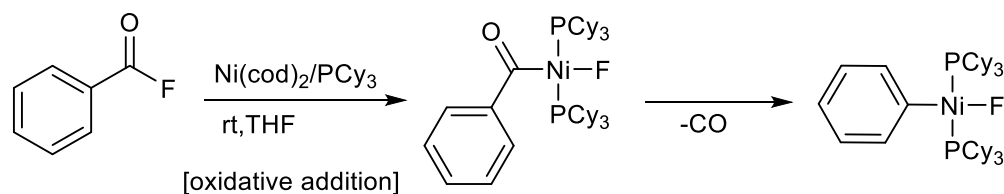
Scheme 13. Decarbonylative borylation of aryl fluorides aided by Ni/ PPh_3 catalytic system.

A general and selective base-free decarbonylative borylation of carboxylic acid fluorides catalyzed by Ni was described by Sanford and coworkers in 2019.⁴⁷ The study aimed at solving the riddle of competing transmetalation reactions of the Ar-Ni-F intermediate with the organoboron product and the diboron reagent which resulted in the formation of undesired biaryl products by undesirable cross-coupling reactions instead of selective borylation.

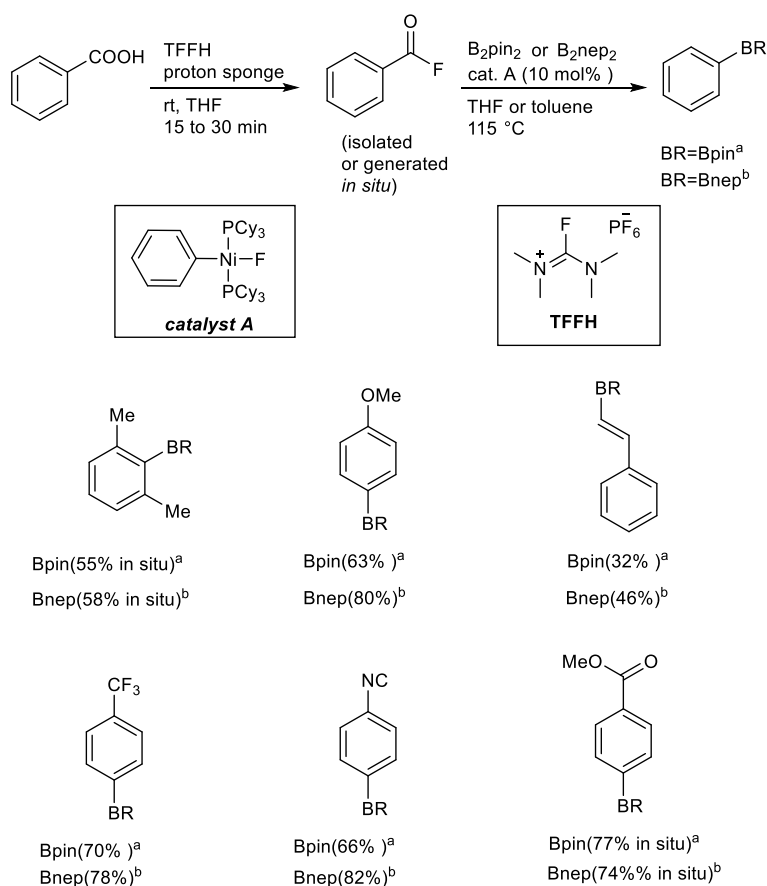
The group investigated the scope of decarbonylative borylation in the absence of a base because it had already been established from the previous works that Ar-Ni-F intermediate, formed by the oxidative addition and carbonyl deinsertion of aryl fluorides to the nickel catalyst was able to take part in direct, base-free transmetalation with the boron source (Scheme 14). They isolated the Aryl-Ni-F intermediate and investigated its transmetalation reactivity with aryl boronate esters and alkoxy diboron reagents separately in toluene at room temperature under base free conditions. The results revealed that the relative rates of transmetalation of the intermediate with diboron reagents were significantly faster than that of their aryl boronate ester congeners so that the conditions can be tailored to favour the selective formation of Ar-B(OR)_2 products over unwanted biaryls. Interestingly, in both cases, the transmetalation activities were found to be directly proportional to the Lewis acidity at the boron center.

Furthermore, they investigated the potential of the transmetalation active intermediate, $(\text{PCy}_3)_2\text{Ni-Ph(F)}$ (10 mol%) to act as an air-stable Ni precatalyst for the conversion of aryl fluorides to aryl boronates and the catalyst was found to be effective for the reaction (Scheme 15). Using the precatalyst, they also

carried out the direct conversion of aryl carboxylic acids to aryl boronic acid esters *via in situ* generation of acid fluorides by activation followed by nickel-catalyzed decarbonylative borylation.



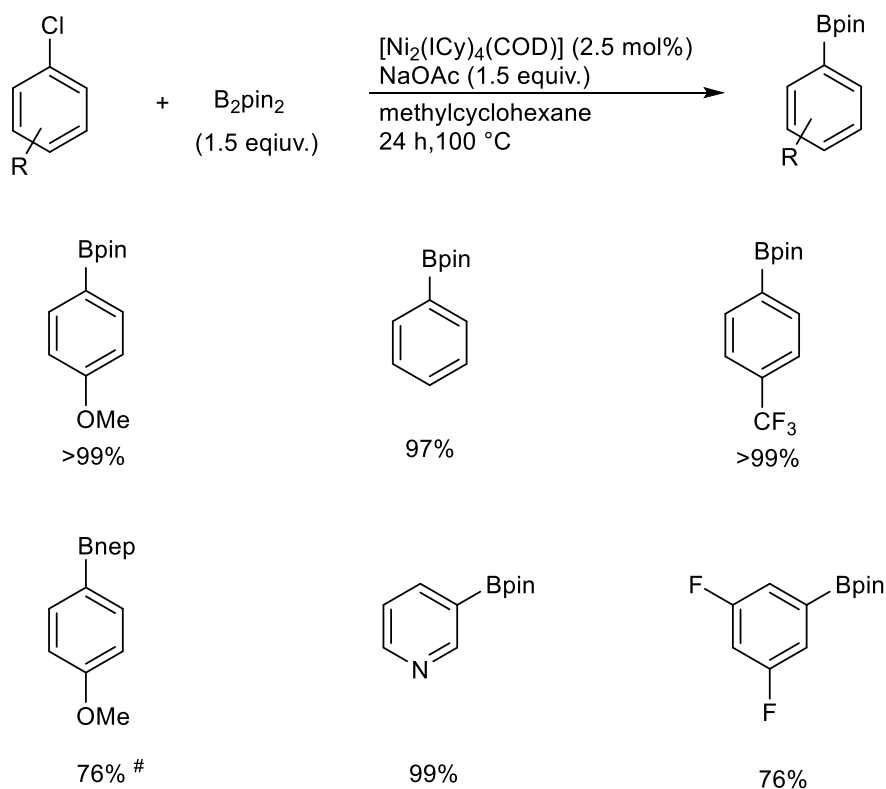
Scheme 14. Generation of Ar–Ni–F intermediate.



Scheme 15. Decarbonylative borylation of carboxylic acid fluorides catalyzed by transmetalation active intermediate, $(\text{PCy}_3)_2\text{Ni}(\text{Ph})(\text{F})$ as air-stable Ni precatalyst.

Marder and Radius *et al.* described the catalytic role of NHC-stabilized nickel(0) complex $[\text{Ni}_2(\text{ICy})_4(\mu-(\eta^2:\eta^2)\text{-COD})]$ in the borylation of aryl chlorides (Scheme 16).⁴⁸ The uniqueness of the catalytic system was marked by its ability to work efficiently even in the absence of other coligands or additives except for the mild base NaOAc as additive. Chloroarenes with electron-donating or electron-withdrawing groups on reaction with B_2pin_2 as boron source using 2.5 mol% of $[\text{Ni}_2(\text{ICy})_4(\mu-(\eta^2:\eta^2)\text{-COD})]$ as the catalyst, 1.5 equiv. of NaOAc as an additive in methylcyclohexane at 100 °C gave the expected borylated products in good to excellent yields. The boron source, Bis(neopentylglycolato)diboron (B_2nep_2) was also found to be effective with the catalyst. The

formation of C–Cl oxidative addition products of the type *trans*-[Ni(ICy)₂(Cl)(Ar)] was also investigated by the stoichiometric reactions of the proposed catalyst with different aryl chlorides.

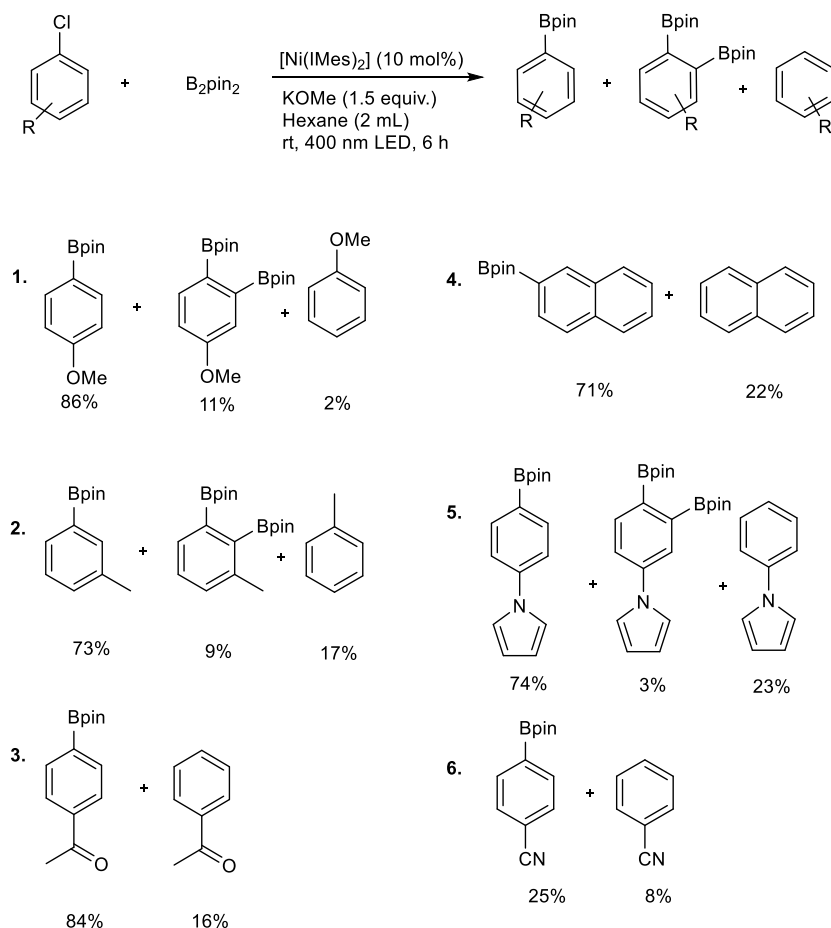
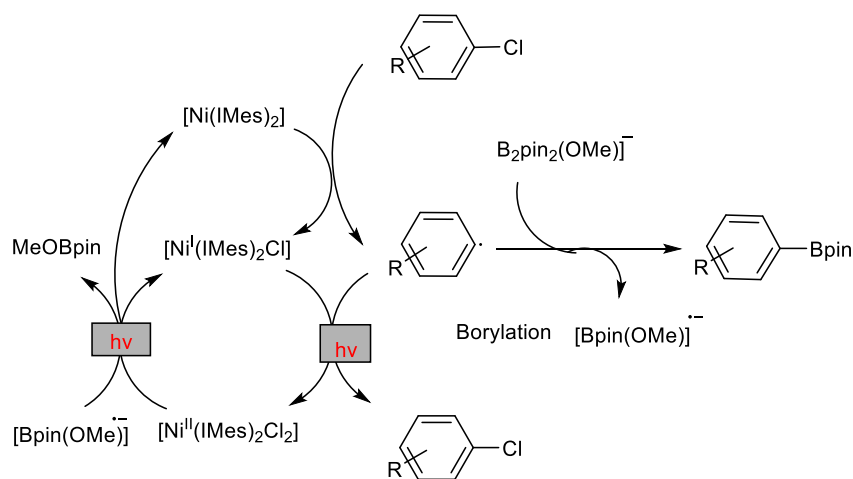


B_2nep_2 is used as the boron source

Scheme 16. Borylation of aryl chlorides by $[\text{Ni}_2(\text{ICy})_4(\mu-(\eta^2:\eta^2)\text{-COD})]$.

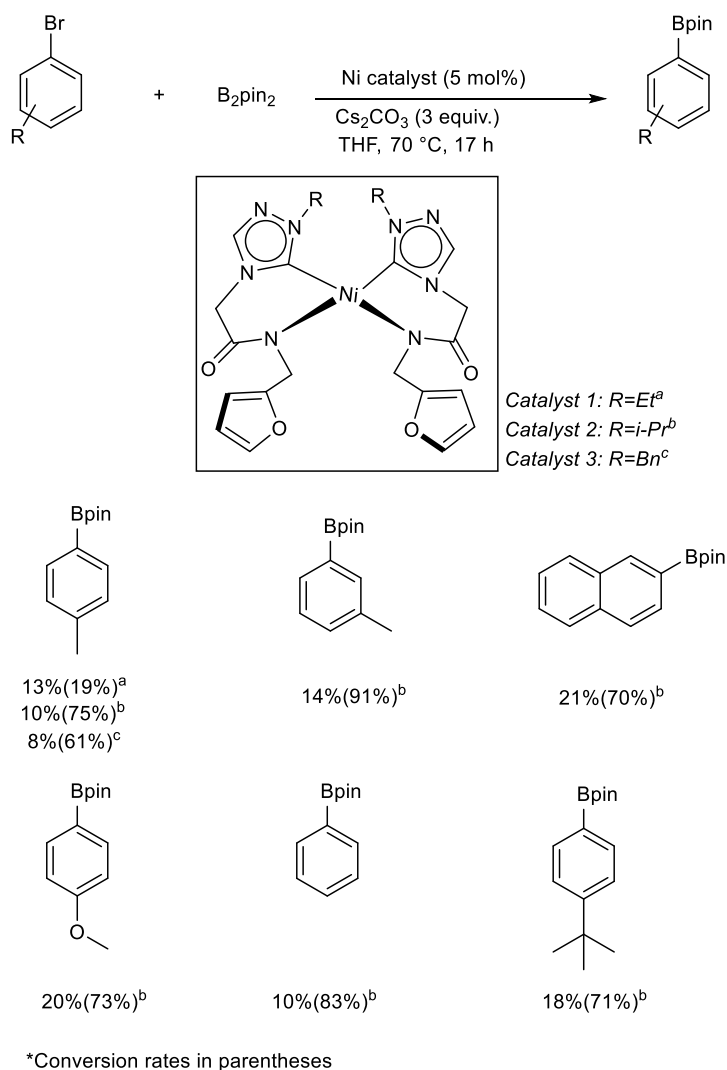
In 2020, Marder *et al.* presented a novel work on photoinduced borylation of chloroarenes catalyzed by $[\text{Ni}(\text{IMes})_2]$.⁴⁹ Differently substituted chloroarenes, on treatment with B_2pin_2 as the boron source in the presence of KOMe as the base in hexane, formed the respective arylboronic esters at room temperature upon irradiation with a 400 nm-LED for 6 h using the $[\text{Ni}(\text{IMes})_2]$ catalyst (Scheme 17). Bis(neopentylglycolato)diboron, (B_2nep_2) was employed as an alternative source of boron and the corresponding aryl neopentylglycolatoboronate esters were obtained in similar yields. The proposed reaction was found to be highly selective and functional group tolerant with broad utility.

Mechanistic studies indicated the involvement of a radical process where $[\text{Ni}^{\text{I}}(\text{IMes})_2\text{Cl}]$ and aryl radicals are generated by the fast chlorine atom abstraction of $[\text{Ni}(\text{IMes})_2]$ from aryl chlorides (Scheme 18). Additional aryl radicals and $[\text{Ni}^{\text{II}}(\text{IMes})_2\text{Cl}_2]$ are produced by the reaction of $[\text{Ni}^{\text{I}}(\text{IMes})_2\text{Cl}]$ with aryl chlorides triggered by light. Anionic $\text{sp}^2\text{-sp}^3$ diborane [$\text{B}_2\text{pin}_2(\text{OMe})$] formed from B_2pin_2 and KOMe reacts with the aryl radical to give the corresponding borylation products along with another radical anion, $[\text{Bpin}(\text{OMe})]^{\bullet-}$ which, in turn, reduces $[\text{Ni}^{\text{II}}(\text{IMes})_2\text{Cl}_2]$ to $[\text{Ni}^{\text{I}}(\text{IMes})_2\text{Cl}]$ and $[\text{Ni}(\text{IMes})_2]$ for the next catalytic cycle. This reaction proceeds via an unconventional pathway following a radical mechanism, where most of the borylation reactions involve an oxidative addition as a key step.

Scheme 17. Photoinduced borylation of chloroarenes catalyzed by $[\text{Ni}(\text{IMes})_2]$.Scheme 18. Mechanism proposed for the photoinduced borylation of chloroarenes catalyzed by $[\text{Ni}(\text{IMes})_2]$ by Marder *et al.*

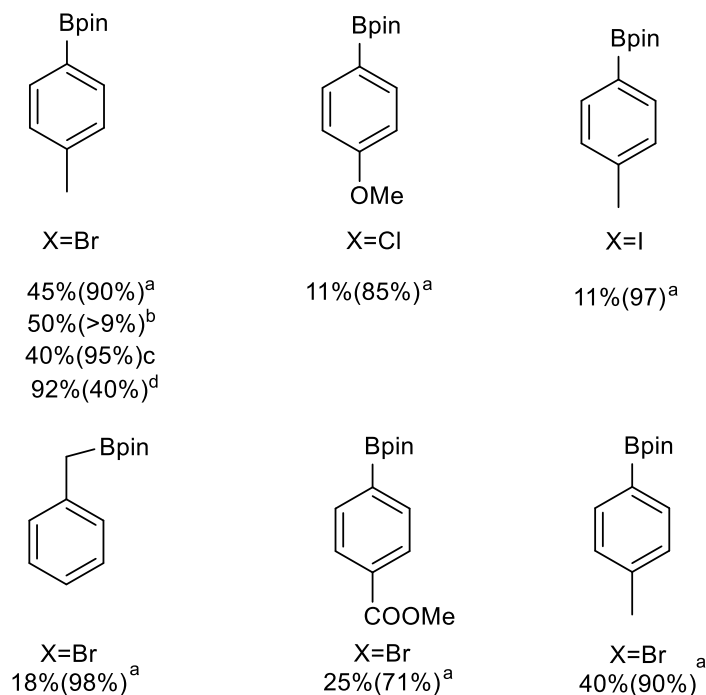
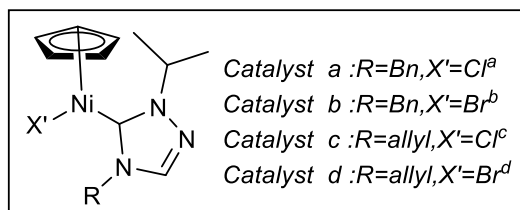
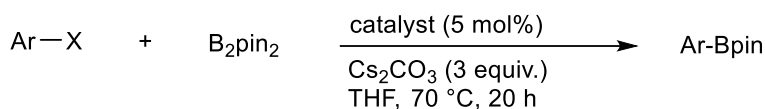
The research groups of Darcel and Ghosh synthesized a series of nickel complexes of the chelating anionic amido functionalized N-heterocyclic carbene ligands and investigated their role as potential catalysts for the borylation reactions of different aryl bromides.⁵⁰ The reaction between 1.5 equiv. of bis(pinacolato)diboron reagent (B_2pin_2) and 1 equiv. of arylbromide substrates, in the presence of 3 equiv. of

Cs_2CO_3 and 5 mol% of Ni complexes as catalysts at 70 °C exhibited moderate conversions with low yields of target products (Scheme 19).



Scheme 19. Ni/NHC catalyzed borylation reactions of aryl bromides.

In the same year, Bheeter *et al.* studied the catalytic potential of half-sandwich nickel complexes derived from N-heterocyclic carbene ligands for the borylation of aryl bromides.⁴³ They reported the synthesis and characterization of a series of novel nickel complexes with 1,2,4-triazole-based NHC backbones and a cyclopentadienyl ligand. The reaction of 1,2,4-triazolium chloride and bromide salts each bearing isopropyl and benzyl groups at 1,4-positions or isopropyl and allyl groups at 1,4-positions with nickelocene in THF under reflux for 20 h resulted in the corresponding $\text{CpNi}(\text{NHC})\text{Cl}$ and $\text{CpNi}(\text{NHC})\text{Br}$ complexes respectively. Using these NHC–nickel complexes as catalysts in the borylation of aryl bromide derivatives with bis(pinacolato)diboron in the presence of Cs_2CO_3 base in THF at 70 °C for 20 h gave the borylated compounds in moderate yields (Scheme 20).

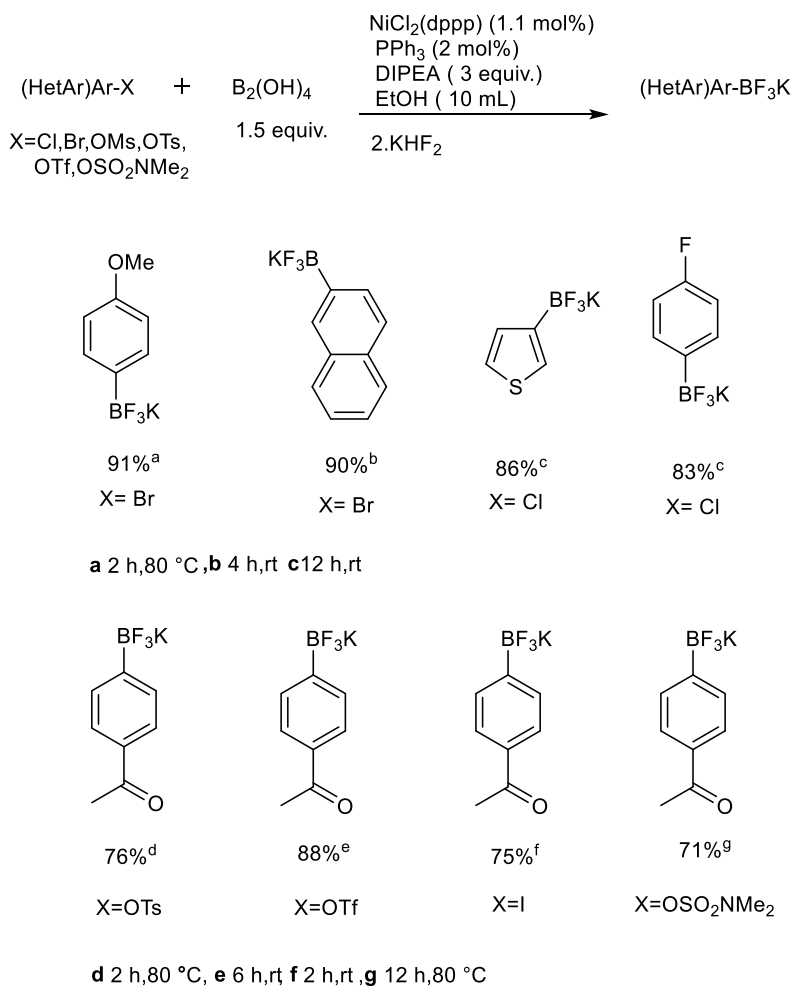


Scheme 20. Borylation of aryl bromides with 1,2,4-triazole-based NHC complexes.

The Ni-catalyzed borylations discussed below assume importance due to their widespread applications. In 2013, a facile route towards arylboronic acids by Ni-catalyzed borylation of aryl halides and pseudohalides, utilizing tetrahydroxydiboron (BBA) was documented by Molander *et al.*⁵¹ This important reaction was later employed in several other works by He *et al* and Wisniewski *et al.* The reaction of aryl and heteroaryl halides with BBA was carried out using $\text{NiCl}_2(\text{dppp})$ in the presence of PPh_3 (2 mol%) and DIPEA (3 equiv.) in 10 mL of degassed ethanol at 80 °C (Scheme 21). The unstable boronic acid intermediate was then converted into potassium trifluoroborate salt by the subsequent treatment of the reaction mixture with aqueous KHF_2 . The reaction employed stable reagents that can be stored on the benchtop, and it presented the first-ever report of an effective Ni-catalyzed Miyaura borylation conducted under such mild conditions.

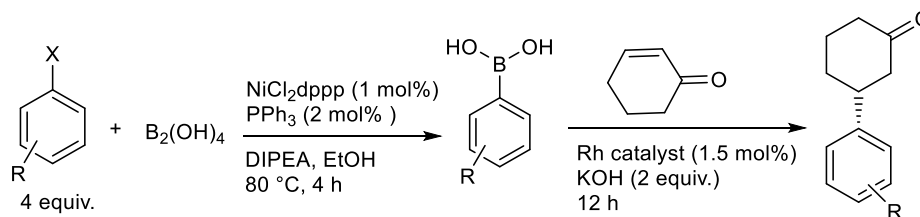
The methodology was compatible with a wide range of substrates including electron-rich, neutral, electron-deficient and heteroaryl bromides. In addition to bromides, a diverse set of compounds such as aryl and heteroaryl chlorides, mesylates, tosylates, triflates and sulfamates underwent the reaction under the same conditions. Surprisingly, while good to excellent yields were obtained for a range of heteroarenes, heteroaryls like pyrimidine, isoxazole, and thiazole failed to give the reaction. Aryl mesylates, which did not

give the desired product in Pd-catalyzed borylarions, proceeded under the given reaction conditions to yield potassium trifluoroborate salts in good yields.



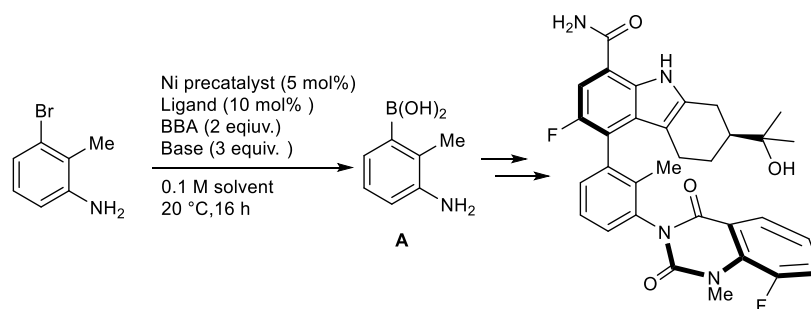
Scheme 21. Ni-catalyzed borylation using BBA and NiCl₂(dppp).

Later in 2019, He *et al.* employed the aforementioned reaction as the first catalytic cycle in a sequential nickel- and rhodium-catalyzed relay reaction incorporating Miyaura borylation and Hayashi–Miyaura conjugate addition in one pot (Scheme 22).⁵² The aryl halides or triflates were converted into the corresponding boronic acids by the Ni catalyst and enantioselective conjugate addition to the electron-deficient olefins was mediated by the chiral-diene rhodium catalyst

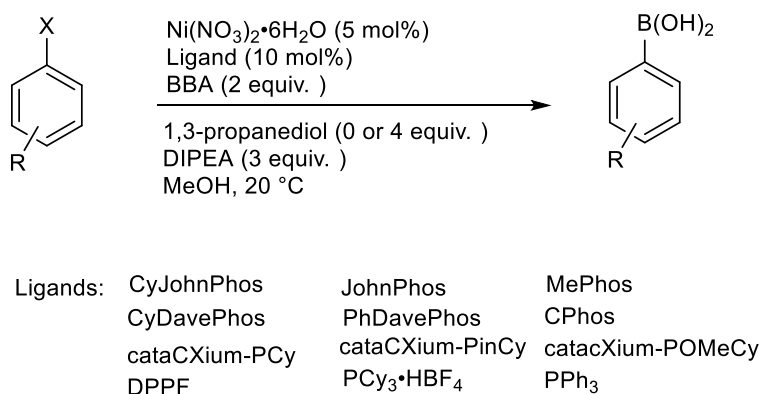


Scheme 22. General representation of the sequential nickel- and rhodium-catalyzed relay reaction.

The work of Molander also served as a reference for the development of a screening platform for nickel-catalyzed borylations of aryl(pseudo)halides with $B_2(OH)_4$ by the research group of Wisniewski in 2019.⁵³ Initially, the screening study was focused on the development of an arylboronic acid of their interest for the generation of an active pharmaceutical ingredient (API), BMS-986142 (Scheme 23). Their first attempt was to analyse the effect of class variables like ligand, solvent and base on this particular borylation reaction, but later they extended the scope of their work to develop a general screening platform that can be applied for the borylation of any aryl halide. A general set of 24 reaction conditions that can be applied to any aryl (pseudo)halide was designed to serve as an effective guide for the borylation of aryl chlorides, bromides, and iodides and pseudohalides (Scheme 24).



Scheme 23. Model reaction for the synthesis of arylboronic acid A, used in the synthesis of API, BMS-986142.



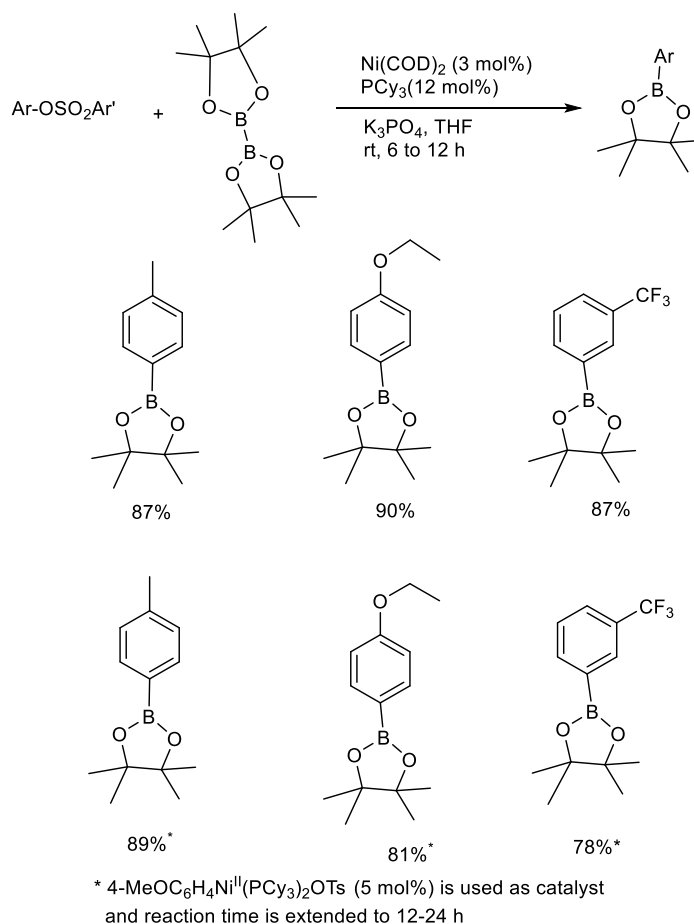
Scheme 24. General reaction for the development of the 24-reaction screening platform for Ni-catalyzed borylations.

Later, in 2020, Frantz *et al.* conducted a comparative study on the catalytic borylation of aryl (pseudo)halides with $B_2(OH)_4$ by Pd- and Ni-based systems.⁵⁴ Compared to Pd based catalysts, Ni catalysts were inexpensive, and unligated Ni(II) salts were utilized in the borylation procedure. Their attempt to make a comparison between Pd and Ni-catalyzed borylations with BBA was based on three catalytic systems developed by the Frantz team,⁵⁵ (AtaPhos)₂PdCl₂ (Pd-1), XPhos-Pd-G3 (Pd-2) and NiCl₂·6H₂O/CyJohnPhos (Ni-1). The catalysts selected for the study were efficient to progress under milder reaction conditions in terms of temperature and catalyst loadings.

Initially, borylation reactions of simple aryl electrophiles using the three catalyst systems were assessed and the resultant boronic acids or diethanolamine adducts were isolated. While all the three catalyst systems were found to be efficient, differential reactivity between Pd-1 for aryl bromides and iodides, Pd-2 for aryl

chlorides and Ni-1 catalysts for a range of aryl halides and (pseudo)halides was observed for some entries. They extended the scope of their work by conducting late-stage borylations coupled with sequential Suzuki–Miyaura cross-coupling reactions. A tandem one-pot borylation/cross-coupling reaction sequence with Pd-1 and Pd-2 catalyst systems was carried out, but a similar strategy could not be adopted for Ni-1 catalyst system and therefore, a Ni/Pd tandem sequence was designed. The work holds the potential to serve as a “user’s guide” to design feasible metal-catalyzed direct borylations with BBA to drive the synthesis of complex organic molecules.

In 2017, Hu *et al.* performed $\text{Ni}(\text{COD})_2/\text{PCy}_3$ -catalyzed borylation of aryl arene sulfonates with bis(pinacolato)diboron at room temperature.⁵⁶ With respect to the previous reports on the same reaction at higher temperatures of 80 °C, the present work at room temperature achieved better results (Scheme 25). The base, K_3PO_4 and the solvent, degassed THF were found to have a profound influence on the reaction rates. To account for the extreme air sensitivity of $\text{Ni}(\text{COD})_2$ in $\text{Ni}(\text{COD})_2/\text{PCy}_3$, air stable $4\text{-MeOC}_6\text{H}_4\text{Ni}^{\text{II}}(\text{PCy}_3)_2\text{OTs}$, the oxidative addition adduct of $4\text{-MeOC}_6\text{H}_4\text{OTs}$ with $\text{Ni}(\text{COD})_2/\text{PCy}_3$ was developed and employed in Miyaura borylation reaction. Good to high yields were obtained which proved the efficiency of $4\text{-MeOC}_6\text{H}_4\text{Ni}^{\text{II}}(\text{PCy}_3)_2\text{OTs}$ as catalyst.

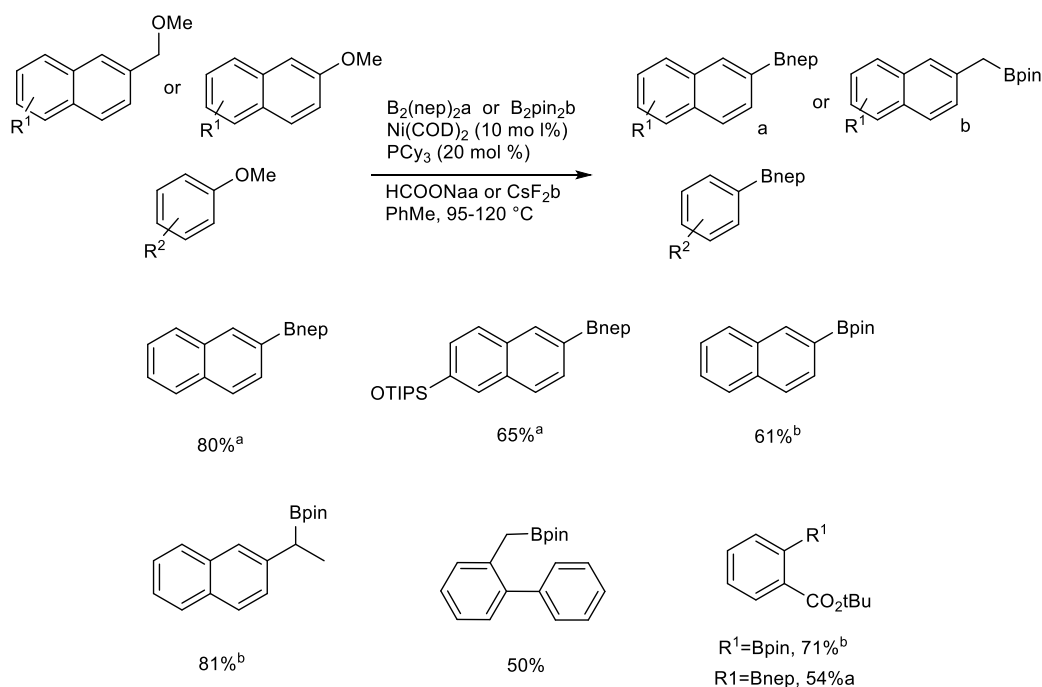


Scheme 25. $\text{Ni}(\text{COD})_2/\text{PCy}_3$ and $4\text{-MeOC}_6\text{H}_4\text{Ni}^{\text{II}}(\text{PCy}_3)_2\text{OTs}$ catalyzed borylation of aryl arene sulfonates.

4. Borylation of Aryl (Silyl)Ethers

This section includes reports on the Ni-catalyzed borylations of aryl ethers and silyl ethers. The reactions proceed *via* the activation of relatively inert C–O bonds.

The first *ipso*-borylation of aryl methyl ethers to achieve a carbon–heteroatom bond *via* an unconventional Ni-catalyzed C–OMe bond cleavage was reported by Martin and coworkers in 2015.⁵⁷ Naphthyl methyl ethers were productively *ipso*-borylated by Ni(COD)₂/PCy₃ catalytic system *via* C(sp²)–OMe bond cleavage using B₂(nep)₂ in the presence of HCO₂Na at 95 °C (Scheme 26). *Ipso* borylation was also achieved by the same catalytic system *via* C(sp³)–OMe cleavage when B₂(pin)₂ was used in the presence of CsF at 120 °C. Thus, orthogonal site-selective C–B bond formation was achieved using specific boron reagents. When C(sp³)–OMe cleavage was observed with B₂(pin)₂, B₂(nep)₂ resulted in C(sp²)–OMe bond cleavage of naphthyl methyl ethers. On the other hand, C(sp²)–OMe bond cleavage with B₂(pin)₂ was achieved in regular arenes. This novel approach was extended towards the *ipso*-halogenation of aryl methyl ethers in good yields employing a one-pot borylation/iodination sequence.

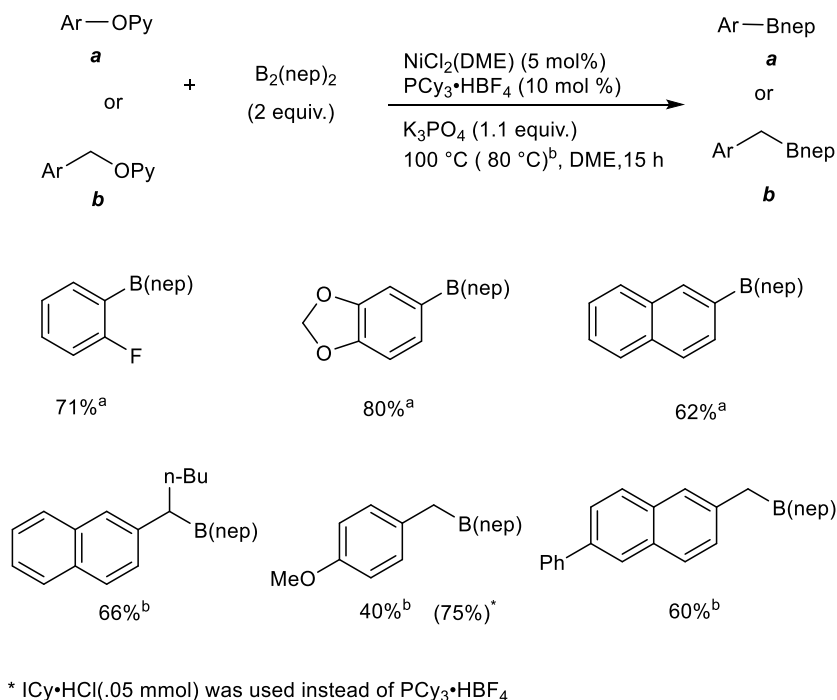


Scheme 26. Ni-catalyzed *ipso* borylation of naphthyl and aryl methyl ethers.

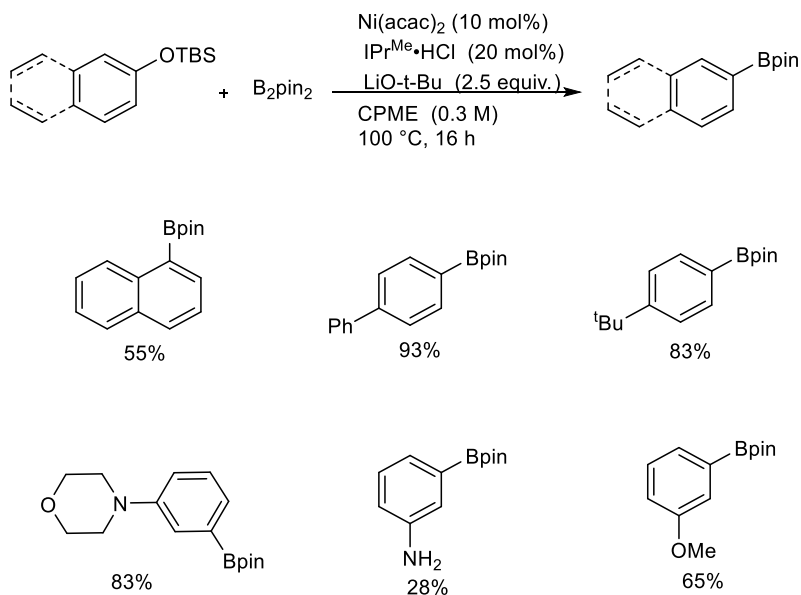
In 2016, Chatani *et al.* developed an efficient method for the catalytic borylation of aryl and arylmethyl 2-pyridyl ethers *via* the cleavage of C(aryl)–O bonds.⁵⁸ The borylation of C(aryl)–O bond in diverse aryl 2-pyridyl ethers activated by the presence of a 2-pyridyl moiety, was performed in good to high yields using NiCl₂(DME) catalytic system with PCy₃·HBF₄ as ligand and K₃PO₄ as the base in DME at 100 °C for 15 h (Scheme 27). The reaction was found to be chemoselective and functional group tolerant, which worked well with amines, ethers, fluorides, esters, acetals and even heteroaromatic systems.

The same catalytic system was applied to arylmethyl 2-pyridyl ethers and the reaction proceeded under similar reaction conditions to give borylated products in notable yields. However, there was a need for a stronger ligand, ICy to achieve the C(benzyl)–O borylation of benzyl ethers, which were found to be less reactive than naphthyl ethers. Further, the study was extended to secondary benzylic substrates to determine

the stereospecificity of the reaction. Retention of configuration was observed following the initial C(benzyl)-O bond cleavage, contrary to the previously reported overall inversion of the benzylic stereocenter in common substrates. The transformation of a useful directing group like OPy to a boryl group enhances the scope of its synthetic utility.



Scheme 27. Ni-catalyzed borylation of aryl and arylmethyl 2-pyridyl ethers.



Scheme 28. *Ipso*-borylation of silyloxyarenes by Ni(acac)₂/IPr^{Me}·HCl catalytic system.

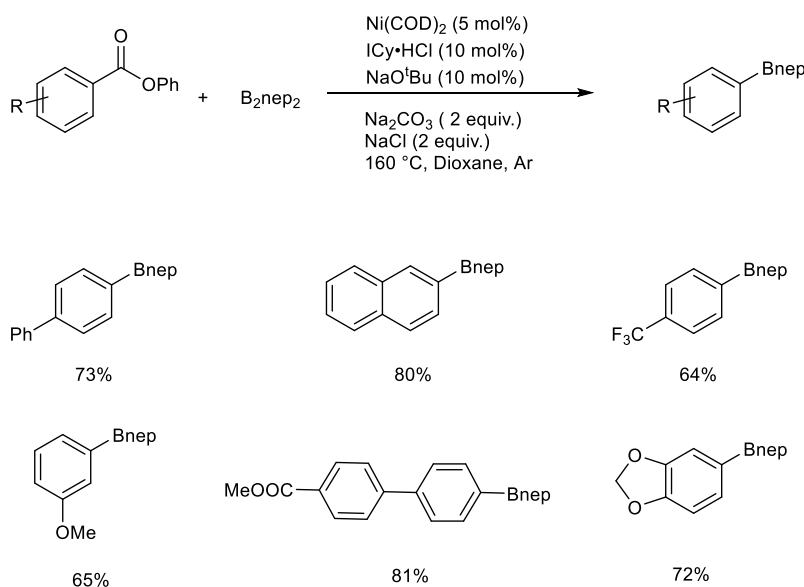
Montgomery *et al.* proposed a novel strategy for the *ipso*-borylation of silyloxyarenes aided by a Ni catalyst (Scheme 28).⁵⁹ The method succeeded in the activation of relatively inert C–O bond in the absence of

any directing group in isolated aromatic systems, and thus stands out from the previous works where the focus was on polyaromatic systems bearing *ortho*-directing groups. A range of silyoxyarenes were *ipso*-borylated in good to excellent yields by Ni(acac)₂/IPr^{Me}·HCl catalytic system with B₂pin₂ as the boron source, and LiO^tBu as the base in cyclopentyl methyl ether solvent. Aryl fluorides and isolated aromatic species bearing ester and amide groups failed to give the reaction. However, the direct borylation of silyl ethers by the functionalization of relatively less reactive C(sp²)-O and C(sp³)-O bonds was achieved, and the synthetic utility of the method was also demonstrated.

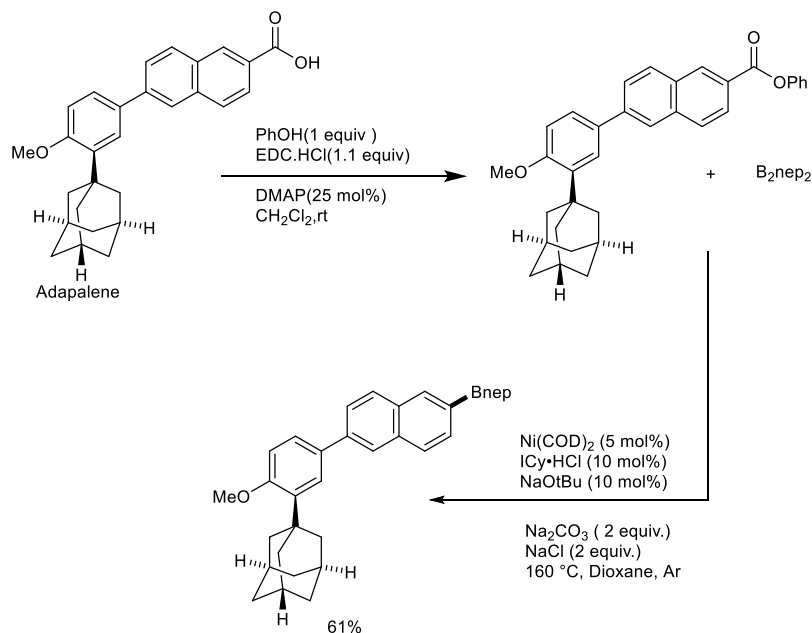
5. Borylation of Esters and Aldehydes

This part describes the Ni-catalyzed decarbonylative borylation of phenolic esters and aldehydes, which proceed *via* C(acyl)-O and C(acyl)-H activation respectively.

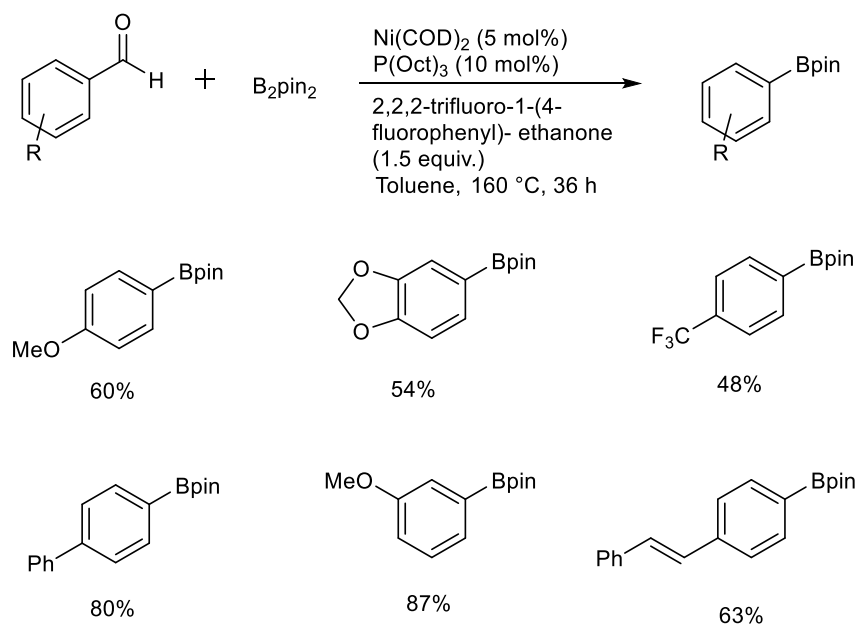
Shi *et al.* carried out a nickel-catalyzed direct borylation of phenolic esters by acyl C-O bond activation in 2016.⁶⁰ The conversion of a ester functionality into a readily convertible C-B bond in phenolic esters was achieved in moderate to excellent yields by their reaction with B₂(nep)₂, in the presence of 5 mol% of Ni(COD)₂ as the catalyst, ICy·HCl (10 mol%) as ligand, 2.0 equiv. Na₂CO₃ and NaCl (1:1) as the additive and NaO^tBu (10 mol%) as the base in dioxane at 160 °C (Scheme 29). The novel strategy was successfully applied in the late-stage decarbonylative borylation of a second-generation topical retinoid, adapalene, and the targeted arylboronate was obtained in 61% yield (Scheme 30).



Scheme 29. Acyl C-O bond activation and borylation of phenolic esters with Ni(COD)₂/ICy·HCl.



Scheme 30. Application of the reaction strategy in the late stage decarbonylation of adapalene.



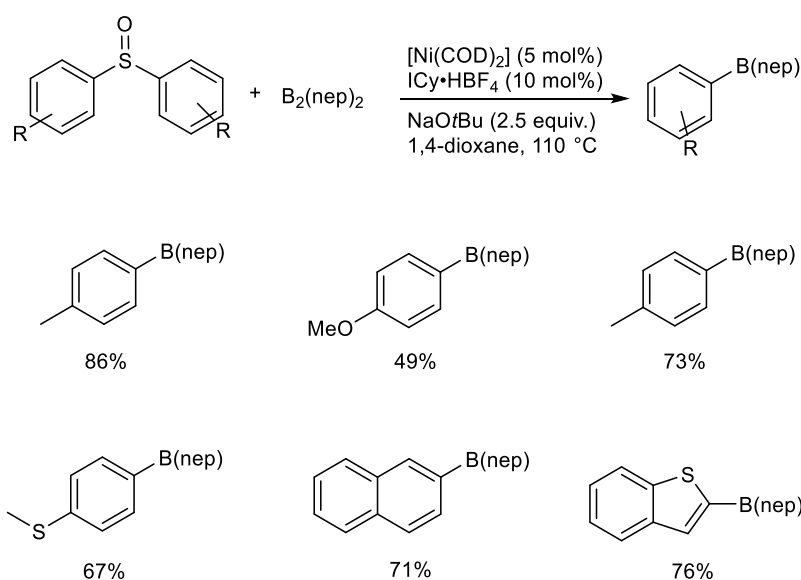
Scheme 31. *Ipso*-borylation of aldehydes by Ni(COD)₂/P(Oct)₃ system.

A novel strategy for the Nickel-catalyzed *ipso*-borylation of aldehydes was reported by the research group of Rueping in 2020.⁶¹ The decarbonylative borylation of aldehydes was carried out using Ni(COD)₂ (5 mol%)/P(Oct)₃ (10 mol%) catalytic system, 2,2,2-trifluoro-1-(4-fluorophenyl)-ethanone (1.5 equiv.) as H-acceptor in toluene at 160 °C for 36 h resulting in good to high yields (Scheme 31). The role of the H-acceptor was found to be crucial in the reaction as it prevented the conversion of the acyl nickel hydride species formed in the first step into the corresponding arenes *via* CO migration and subsequent reductive elimination by a key hydride transfer step to the pi-coordinated H-acceptor. The base-free decarbonylative *ipso* borylation of aldehydes was successfully applied to a wide variety of substrates including the derivatives of complex natural products. The reaction exhibited functional group tolerance and a chemoselective bond cleavage in the case of

esters, leaving the ester groups intact. Furthermore, the scalability of the proposed reaction was also established.

6. Borylation of Aryl Sulfoxides

The transformation of aryl sulfoxides into the corresponding aryl boronic esters by a nickel/NHC catalytic system was performed by Marder *et al.* in 2021.⁶² The Ni-NHC catalyzed borylation of aryl sulfoxides with $B_2(nep)_2$ in the presence of 5 mol% of $[Ni(COD)_2]$, 10 mol% of $ICy\cdot HBF_4$, and 2.5 equivalents of $NaOtBu$ in 1,4 dioxane at 110 °C afforded arylboronates in good yields (Scheme 32). The reaction exhibited a wide substrate scope wherein both electron-rich and electron-poor diaryl sulfoxides underwent borylation to give the desired products in good yields. On the contrary, cyano-, amino-, ester- and indole based substrates failed to give the reaction. The group also reported regioselective borylation with sterically biased unsymmetrical diaryl sulfoxides. In addition, the effect of the electronic properties of aryl sulfoxides was studied through competition reactions. Intramolecular and intermolecular competitive borylations of unsymmetrical diaryl sulfoxides revealed the selective preference for electron-deficient moieties.



Scheme 32. NHC Ni-catalyzed borylation of aryl sulfoxides.

7. Borylation of Aryl amines, Amides and Carbamates

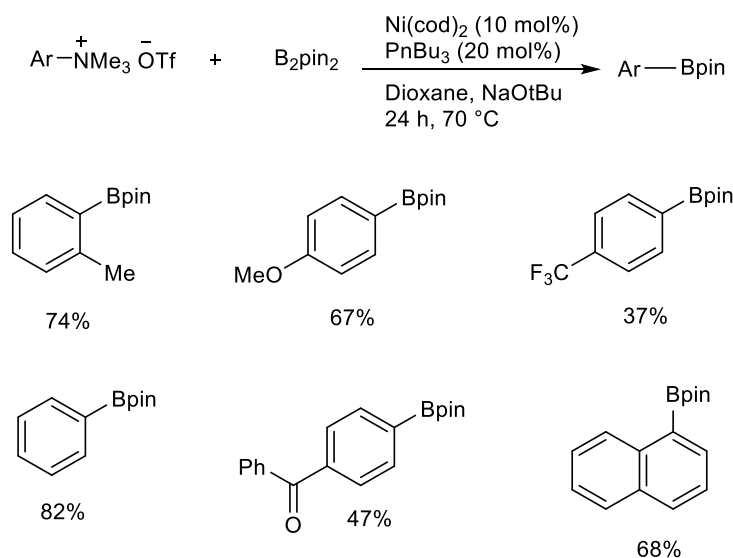
The Ni-catalyzed borylations of amines, amides and carbamates that proceed *via* C–N bond cleavage are included in this section.

A promising method for aromatic and benzylic C–N borylation catalyzed by nickel–phosphine complexes was proposed by Itami and his group in 2015.⁶³ The borylation of aryl ammonium salts (0.2 mmol) was carried out by employing bis(pinacolato)diboron (B_2pin_2 , 0.4 mmol) as the boron source in the presence of $[Ni(COD)_2]$ (10 mol%; cod = 1,5-cyclooctadiene), *trin*-butylphosphine ($PnBu_3$, 20 mol%), and $NaOtBu$ (2 equiv.) in 1,4-dioxane at 70 °C for 24 h resulting in good yields (Scheme 33). Under standard conditions, substrates

with electron-donating substituents achieved higher yields compared to those bearing electron-withdrawing groups. Interestingly, on studying the C–N borylation of benzylic amine derivatives, the precatalyst $\text{Ni}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ was found to be more efficient than the previously used $\text{Ni}(\text{COD})_2$ catalyst for C–N borylation of phenyl amines (Scheme 34). Another notable difference between aromatic and benzylic C–N borylation was in the choice of the solvent, where 1,4-dioxane was found to be the best solvent for aromatic C–N borylation, higher yields were observed when DME was used as the solvent in the latter case.

An investigation into the mechanism based on the experimental observations suggested three main steps, namely oxidative addition, σ -bond metathesis and reductive elimination. The first step involves the oxidative addition of aryl or benzylic ammonium salt to the $\text{Ni}^0\text{-PnBu}_3$ species with the elimination of NMe_3 . In the next step, (boryl)organonickel(II) species is obtained by the σ -bond metathesis of the organonickel(II) triflate formed in the first step with B_2pin_2 . This σ -bond metathesis is considered to be promoted by the *tert*-butoxide base. In the final step, the borylated product is released by the reductive elimination of the C–B bond and the active Ni^0 species is regenerated.

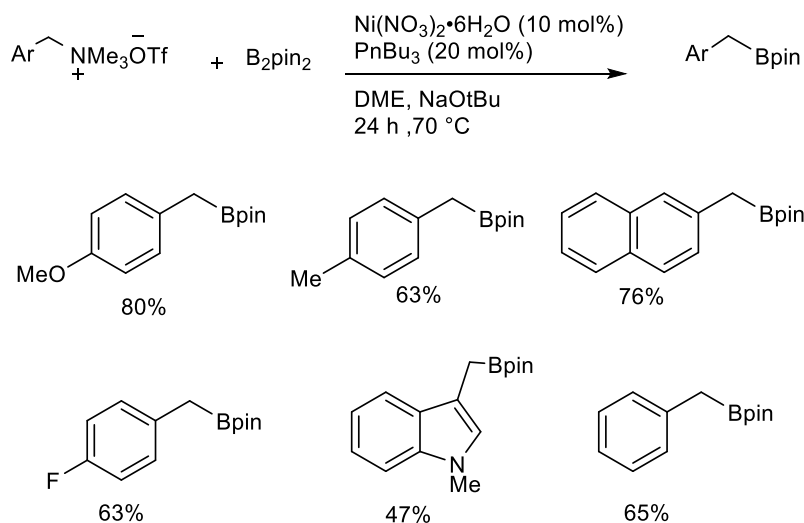
The group explored the synthetic utility of the reaction by coupling C–N borylation with a class of Me_2N -directed aromatic functionalization reactions and C–B transformations which made possible the synthesis of a wide variety of aromatics in good to high yields. The work highlighted the scope of using Me_2N group as a potential transformable directing group to drive diverse organic transformations.



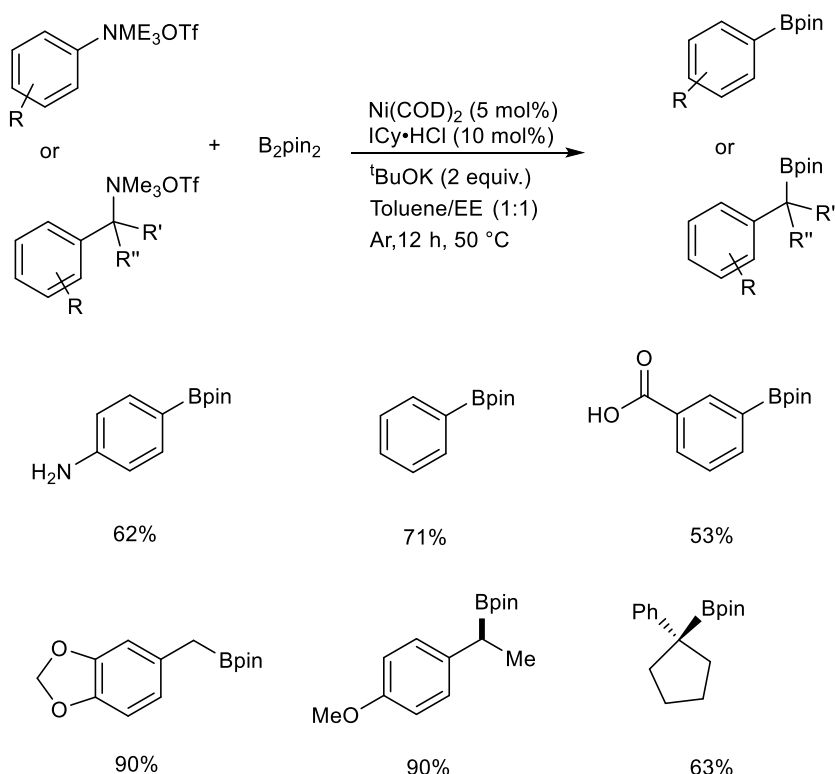
Scheme 33. C–N borylation of phenyl amines with $\text{Ni}(\text{COD})_2/\text{PnBu}_3$ catalytic system.

Shi *et al.* proposed a highly chemo- and regioselective C–N bond borylation method for aryl and benzyl trimethylammonium salts catalyzed by nickel under mild conditions.⁶⁴ The reaction of various arylammonium triflates with bis(pinacolato)diboron aided by $\text{Ni}(\text{COD})_2$ (5 mol%)/ $\text{ICy}\cdot\text{HCl}$ (10 mol%) catalytic system in 1:1 Toluene/EE (2-ethoxyethanol) solvent mixture in the presence of $t\text{BuOK}$ as the base at 50 °C, provided the corresponding aryl boronic esters in moderate to good yields (Scheme 35). Benzylamines were also found to be borylated by this protocol. Selective C–N borylation was observed even in the presence of functional groups except for halide substituents (other than aryl fluorides) where borylation proceeded at both C–N and C–X sites. Importantly, the group also reported the tertiary C–N bond activation of benzylamines for the first time. The potential of the method for gram-scale synthesis and late-stage borylative C–N bond cleavage of

complex molecules was also demonstrated. Ring-opening *via* borylative cleavage of C–N bonds in aza heterocyclic compounds was also accomplished in moderate to good yields using this strategy.



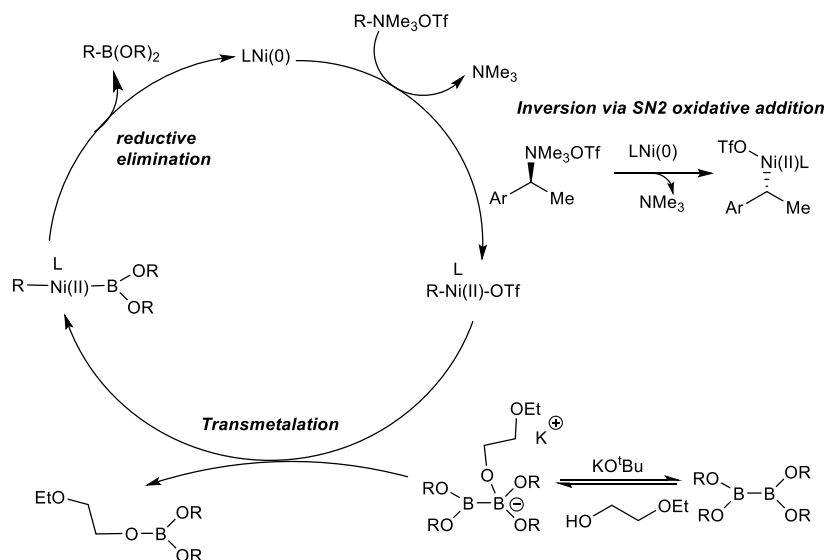
Scheme 34. C–N borylation of benzylic amine derivatives with the $\text{Ni}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ / PnBu_3 catalytic system.



Scheme 35. Ni-catalyzed C–N bond borylation of aryl and benzyl trimethylammonium salts.

The mechanistic studies suggested three important steps, namely oxidative addition, transmetalation and reductive elimination (Scheme 36). An $\text{S}_{\text{N}}2$ mechanism is likely to get involved in the oxidative addition of the nickel catalyst into the benzylic C–N bond, resulting in an inversion of configuration at the benzylic stereo

center. The co-solvent EE generates an anionic adduct of the borylating agent in the presence of KO^tBu , which facilitates the transmetalation. The significance of the work is highlighted by the incorporation of this functional group tolerant, highly efficient and chemoselective strategy into various synthetic routes for the preparation of versatile biologically active compounds and other relevant transformations.



Scheme 36. Mechanism of Ni-catalyzed C–N bond borylation of aryl and benzyl trimethylammonium salts proposed by Shi *et al.*

In 2014, Tobisu *et al.* developed a novel strategy for C(aryl)–N bond cleavage of N-aryl amides and carbamates *via* Ni-catalyzed reduction and borylation reactions (Scheme 37).⁶⁵ While the previous reports on C–N bond cleavage catalyzed by ruthenium were restricted only to aniline derivatives bearing an *ortho* group, Tobisu's group derived an efficient route towards the catalytic conversion of C–N bonds in aryl amides and carbamates having no *ortho* substituents into C–H and C–B bonds for the first time. The borylation reaction catalyzed by the $\text{Ni(COD)}_2/\text{IMes}$ system using the diborane reagent $\text{B}_2(\text{nep})_2$, worked well with both cyclic and acyclic amides. Polyaromatic compounds like naphthalenes, quinolines, anthracenes and phenanthrenes exhibited high reactivity, but the steric environment of the substrate had a profound effect on the reaction yield. Similarly, they also conducted the reductive C–N cleavage reaction using the hydroborane reagent HB(pin) . The present work demonstrated a valuable approach towards a new bond disconnection strategy that can be utilized in synthetic applications.

Rueping *et al.* developed a useful procedure for the Ni-catalyzed decarbonylative borylation of amides *via* the cleavage of C–N bond.⁶⁶ Aryl amides, on reaction with bispinacolato diboron in the presence of Ni(COD)_2 (10 mol%) / P^nBu_3 (40 mol%) catalyst and Li_2CO_3 (1.5 equiv.) base in dioxane at 160 °C for 36 h produced the corresponding arylboronates in acceptable yields (Scheme 38). The group also studied nickel-catalyzed decarbonylative silylations and aminations of amides under similar reaction conditions.

Conclusions

In this review, we have attempted to summarize the available works on (hetero)aryl borylations catalyzed by nickel, reported since 2013. While nickel was initially introduced as a cost-effective substitute for other transition metal catalysts, the later works demonstrated its ability to display a unique reactivity profile, and even substrates that were previously inaccessible to other transition metals were successfully borylated. A wide spectrum of substrates including, but not limited to, aryl halides, N-aryl amides, carbamates, aryl methyl ethers, amides, phenolic esters, arenes, indoles, aryl sulfoxides, and aldehydes were successfully borylated by Ni catalysts.

Most of the Ni-based catalysts, with a few exceptions, demanded the presence of suitable coligand for their activity, whereas the reason behind the preferential choice of specific coligands in a reaction could not be mechanistically explained in all instances. A detailed investigation into this aspect may contribute towards the development of more efficient reactions in near future. Recently, there has been a tendency to incorporate innovative routes encompassing the realms of photochemistry and sonochemistry into the genre of transition metal catalysis to enhance catalytic efficiency. Though the advent of such methodologies into Ni-catalyzed hetero(aryl) and benzylic borylation reactions are still in their infancy, attempts to move out of the conventional catalytic systems and to embrace newer pathways can be regarded as a positive change capable of bringing in promising results. The progress made in the field of (hetero)aryl borylation by Ni catalysts within the discussed short period is indicative of the multitude of reactions to be born in the brains of researchers in the following years

Acknowledgements

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