REVIEWS DOI: 10.1002/adsc.202001291 Advanced Synthesis & Catalysis

Very Important Publication

Fluorinated Aryl Boronates as Building Blocks in Organic Synthesis

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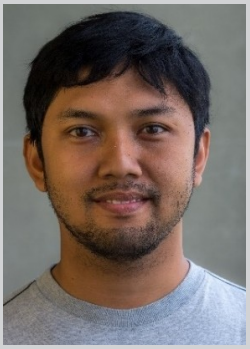
Manuscript received: October 19, 2020; Revised manuscript received: December 1, 2020;
Version of record online: January 29, 2021

Abstract: Organoboron compounds are well known building blocks for many organic reactions. However, under basic conditions, polyfluorinated aryl boronic acid derivatives suffer from instability issues that are accelerated in compounds containing an *ortho*-fluorine group, which result in the formation of the corresponding protodeboronation products. Therefore, a considerable amount of research has focused on novel methodologies to synthesize these valuable compounds while avoiding the protodeboronation issue. This review summarizes the latest developments in the synthesis of fluorinated aryl boronic acid derivatives and their applications in cross-coupling reactions and other transformations.

Keywords: homogeneous catalysis; boron reagents; boronates; fluorine; fluoroarene

1. Introduction

Interest in fluorinated organic compounds has increased in recent years as these remarkable compounds have a vast array of important applications, including but not limited to, material science, pharmaceutical and agricultural chemistry, specialty chemical industries, and catalysis. Indeed, fluorine-containing organic molecules constitute one-third of the pharmaceuticals on the market today.[1–8] To the best of our knowledge, there are no known examples of naturally occurring aryl fluorides; therefore, these molecules must be accessed through chemical synthesis. The integration of fluorine groups has several physiological advantages



Yudha P. Budiman obtained his B.Sc. degree in 2012, from Universitas Padjadjaran, Indonesia and M.Sc. degree in 2015, from King Abdulaziz University, Saudi Arabia, under supervision of Prof. Ibraheem Mkhalid, who is a former PhD student of Prof. Todd B. Marder. Afterwards, he became a Lecturer in the Department of Chemistry, Universitas Padjadjaran, Indonesia. He has recently completed hi Ph.D. studies at the University of Würzburg supported by an Indonesia Endowment Fund for Education (LPDP) scholarship under the supervision of Profs. Udo Radius and Todd B. Marder. His current research interests focus on the development of new catalytic processes in organic synthesis.

Steve Westcott was born in the sixties somewhere around Tecumseh and received his Ph.D. from the University of Waterloo under the joint supervision of Profs. Todd B. Marder (now at the University of Würzburg) and R. Tom Baker (now at the University of Ottawa) working on metal-catalyzed hydroborations. He was an NSERC PDF, spending one year at Emory University in Atlanta with Prof. Lanny Liebeskind, and more than one year working with Prof. Maurice Brookhart at the University of North Carolina at Chapel Hill, NC, as a postdoctoral fellow. He has been on the faculty at Mount Allison University since August 1995 and is currently a Canada Research Chair in Boron Chemistry. Westcott was recently elected to Fellowship of the Canadian Institute of Canada and he is also a Fellow of the Royal Society of Chemistry (UK). More importantly, he has had the great privilege and honor of training many excellent students during his time at Mount Allison University (a primarily undergraduate institution), many of whom now have high profile careers in academia, industry and the health sciences all over the world. His research interests include catalysis and the synthesis and development of biologically active boron and transition metal compounds. His research group is called the 'Wild Toads' and it is best not to ask why.

Udo Radius received his Diploma and Ph.D. from the University of Würzburg. For his Ph.D. he worked with Helmut Werner and Jörg Sundermeyer on organometallic chemistry of group 6 transition metals in high oxidation states. After postdoc research with Roald Hoffmann at Cornell University he started his independent career at the University of Karlsruhe (TH), now Karlsruhe Institute of Technology (KIT), where he obtained his habilitation in 2001 for research on early transition metal calix[n]arene complexes. After two short stays at the University of Rostock and the University of Vienna, he joined the faculty at the University of Würzburg in 2008. Udo's major research interests lie in the fields of main group element and transition metal chemistry with an emphasis on the chemistry of NHCs and related molecules in inorganic chemistry, the catalytic activation of small molecules, the manipulation of fluorinated organic molecules in the coordination sphere of transition metals and recently on borylation reactions using 3d metals as catalysts.

Todd Marder received his B.Sc. in Chemistry from M.I.T. (1976), and his Ph.D. from the UCLA (1981) where he was a University of California Regents Intern Fellow. Following postdoctoral research at the University of Bristol in England, he spent two years as a Visiting Research Scientist at DuPont Central Research in Wilmington. He joined the faculty at the University of Waterloo, Canada in 1985, and in 1995 was awarded the Rutherford Memorial Medal for Chemistry of the Royal Society of Canada. He moved to the University of Durham in England in 1997 to take the Chair in Inorganic Chemistry previously held by Ken Wade. In 2012, he accepted a Chair in Inorganic Chemistry at the University of Würzburg, Germany, a major center for boron and organometallic chemistry. Marder's diverse research interests include synthesis, structure, bonding and reactivity of organometallic and metal–boron compounds, homogeneous catalysis, small molecule triggers of stem cell differentiation, luminescence, nonlinear optics, bioimaging, liquid crystals, and crystal engineering.

such as decreased metabolism, solubility (deliverability), hydrophobicity and decreased negative side effects. For example, the fluoroarene-containing molecules Vemuravenib (Figure 1, left) and Sitagliptin (Figure 1, right) are used for the treatment of late-stage of melanoma and diabetes, respectively.[1] Some fluori-

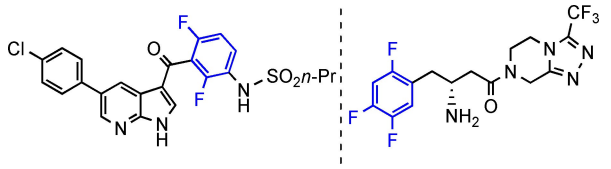


Figure 1. Fluoroarene-containing drugs: Vemuravenib (left) used for treatment of late-stage melanoma. Sitagliptin (right) is used in the treatment of diabetes.[1]

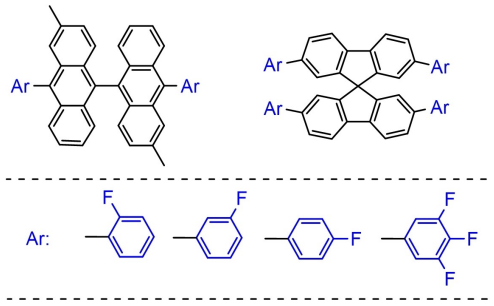


Figure 2. Fluoroarenes in materials science I: Fluorinated 3,3'-dimethyl-9,9'-bianthracene (left) and 9,9'-spirobifluorenes (right) derivatives for OLEDs.[13]

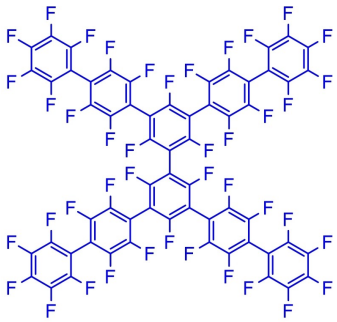


Figure 3. Fluoroarenes in materials science II: perfluorinated phenylene dendrimers for electron transport materials.[14]

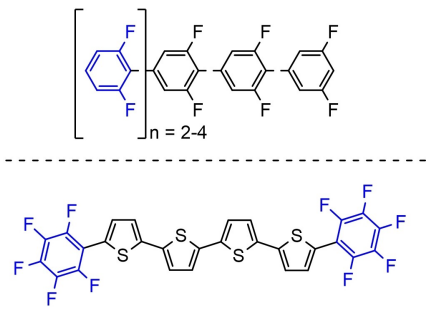


Figure 4. Fluoroarenes in materials science III: 2,6-difluorinated oligophenyls (top) and fluoroarene-thiophene oligomer (bottom) for semi-conductors.[20,21]

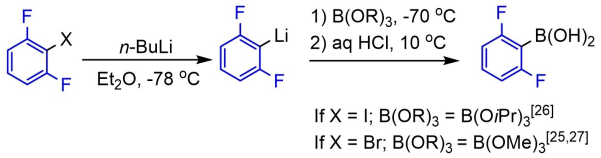
nated organic and fluorinated organometallic compounds have also shown promise as antiproliferative agents against HT29 (colon carcinoma) and MCF-7 (breast adenocarcinoma).[9] Fluorine-containing organic compounds have also shown tremendous potential in other areas of science and industry as polyfluorobiphenyls show significant promise for use in organic light emitting diodes (Figure 2),[10–13] electron-transport materials (Figure 3),[14] crystal engineering,[15–17] metal-organic frameworks (MOFs),[18] supramolecular chemistry,[21] and low-dimensional semi-conducting materials (Figure 4).[20,21] As such, there is a growing demand for the development of novel synthetic methodologies for the generation of these valuable compounds.[22,23]

One promising methodology that has emerged recently for generating functionalized fluorine-containing organic compounds incorporates borylation chemistry,[24] whereupon the resulting boron group can be transformed into a vast array of functional groups. Methods to generate fluorinated aryl boronate esters in catalytic process have been developed over the last 2 decades, including C–H, C–F, C–X (X = Cl, Br, I) borylations using iridium, rhodium, cobalt, platinum, palladium, and nickel metal catalyst systems. Unfortunately, some of the resulting boron-fluorine-containing products are prone to decomposition that limits their applicability in organic synthesis. For example, the employment of fluorinated aryl boronates in the Suzuki-Miyaura cross-coupling reaction to generate fluorinated biaryl compounds has been a significant challenge over the past 20 years. Applications of fluorinated aryl boronates in other cross-coupling reactions such as Chan-Evans-Lam aminations and etherification reactions have also been limited by decomposition pathways. In this review we summarize the latest developments regarding the synthesis of fluorinated aryl boronate derivatives, discuss the stability issue of these molecules, and highlight the latest developments in the applications of fluorinated aryl boronates in organic synthesis.

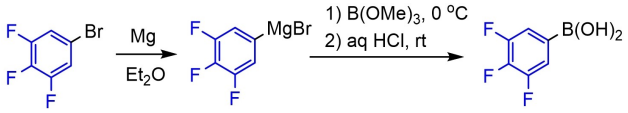
2. Synthesis of Fluorinated Aryl Boronates

2.1. Traditional Methods

Procedures to generate fluorinated aryl boronic acids traditionally involved stoichiometric processes *via* conversion of fluorinated aryl halides into aryl lithium[25–27] (Scheme 1) or aryl Grignard reagents[25,27] (Scheme 2) followed by addition of trialkoxyborates to yield fluorinated aryl trialkoxyborates. Subsequent addition of HCl resulted in the formation of the corresponding boronic acid. Unfortunately, these early methodologies suffered from harsh reaction conditions, low yields, and the formation of stoichiometric metal salts which made isolation of the desired products



Scheme 1. Synthesis of 2,6-fluorophenyl boronic acid using a lithium reagent.[25–27]



Scheme 2. Synthesis of 3,4,5-trifluorophenyl boronic acid using a Grignard reagent.[27]

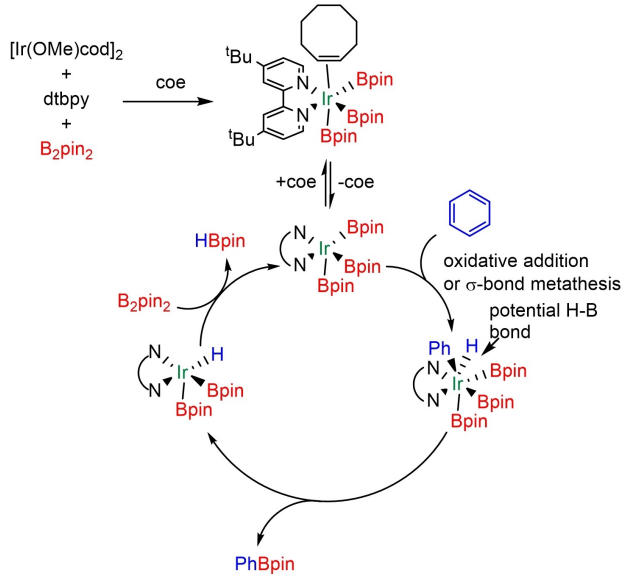
problematic. However, borylation methods for the synthesis of fluorinated aryl boronates have been developed *via* catalytic processes that can be carried out under much milder conditions and with improved yields.

2.2. Catalytic C–H Borylation

2.2.1. Iridium-Catalyzed C–H Borylation of Fluoroarenes

The first study that showed that iridium complexes had the ability to promote the C–H borylation of arenes was reported by Marder *et al.* in 1993.[28] In this report, the first trisboryl iridium complex, [(η^6-tol)Ir(Bcat)$_3$], was prepared by reaction of excess HBcat (cat = catecholato) with [(η^5-indenyl)Ir(cod)] (cod = *cis*-1,5-cyclooctadiene) in toluene (tol). The GC/MS total ion chromatogram included in the Supporting Information section showed the formation of small amounts of two isomers of tolyl-Bcat as a byproduct (< 1%) arising from borylation of the toluene solvent. However, attempts to optimize this remarkable C–H borylation reaction as a catalytic process were not conducted in this study.

Ishiyama, Hartwig, and Miyaura *et al.* reported the iridium-catalyzed C–H borylation of arenes using a combination of [Ir(cod)OMe]$_2$ as a precatalyst, 4,4'-di-*tert*-butylbipyridine (dtbpy) as a ligand, and B$_2$pin$_2$ (Bpin = 4,4,5,5-tetramethyl-1,3,2-dioxaborolanyl) as the boron source. This catalyst system is one of the most widely used methods currently employed for the C–H borylation of arenes.[29] Based on NMR data, detection of proposed intermediates, kinetic data and isotopic labelling studies Hartwig *et al.* proposed a mechanistic pathway for this iridium-catalyzed borylation reaction (Scheme 3). The trisboryl complex [Ir(dtbpy)(coe)(Bpin)$_3$] (coe = cyclooctene), was reported to be the resting state in these borylation reactions.



Scheme 3. A plausible mechanism for the iridium-catalyzed C–H borylation of arenes.[30,31]

This species could also be prepared in high yields from the independent reaction of [Ir(cod)OMe]$_2$ with dtbpy, coe, and HBpin. Interestingly, attempts to generate this trisboryl species using B$_2$pin$_2$ gave significantly lower yields. Once this trisboryl species is generated, the reaction is believed to proceed *via* dissociation of the labile coe ligand to give an unsaturated catalytically-active trisboryl iridium(III) complex. Sakaki *et al.* carried out DFT calculations which also indicated that this type of trisboryl iridium(III) complex is the active species in the catalytic process. This is followed by a rate-limiting C–H bond cleavage of the arene to give an hydridotrisboryl iridium(V) intermediate which is stabilized by the electron-rich dtbpy ligand and by strong σ-donation by the boryl ligand. Reductive elimination would proceed to give the borylated arene product along with a hydridobisboryl iridium(III) species. Oxidative addition of B$_2$pin$_2$ with loss of HBpin would then regenerate the active catalytic species.[30,31]

The selectivity of this iridium-catalyzed borylation method was found to be influenced more by the steric effects of the substituent groups on the arene ring rather than by directing or electronic effects. Thus, borylation occurred predominantly at less sterically-hindered C–H bonds (Figure 5).[31]

Hartwig's borylation method was used by Smith *et al.* employing fluorinated arene substrates such as 1,3-difluorobenzene using HBpin.[32] As shown in Scheme 4, the regioselectivity of the borylation follows the order 5 > 4 > 2, due to the steric effect of the fluorine substituents.

A subsequent study by Hartwig *et al.* expanded the scope of the iridium-catalyzed C–H borylation reaction

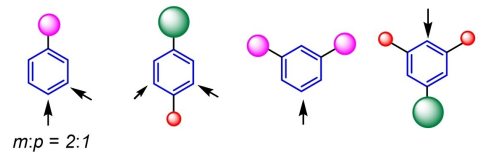
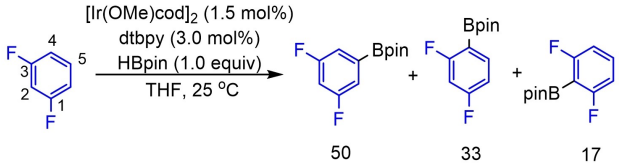
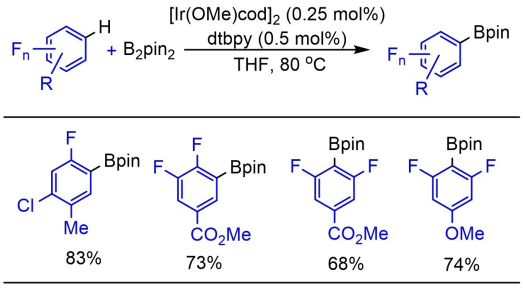


Figure 5. Regioselectivity of iridium-catalyzed C–H borylations.[31]

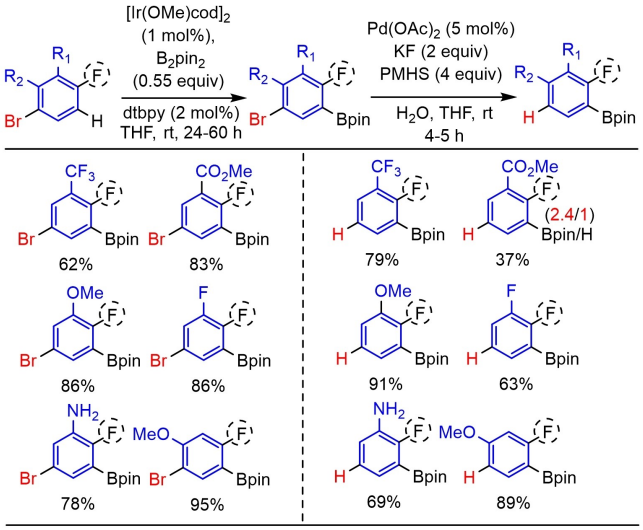


Scheme 4. The iridium-catalyzed C–H borylation of 1,3-difluorobenzene.[32]

to include disubstituted fluoroarenes bearing ancillary substituents with various steric parameters.[33] As shown in Scheme 5, this borylation method utilized



Scheme 5. Iridium-catalyzed C–H borylation of fluoroarenes.[33]

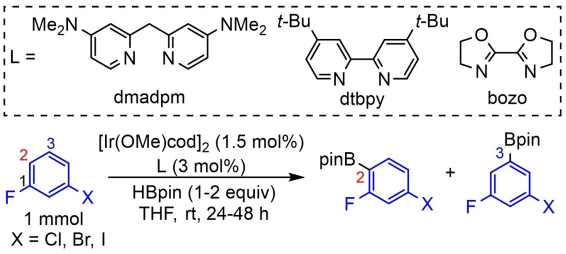


Scheme 6. A two-step iridium-catalyzed borylation/palladium-catalyzed dehalogenation.[34]

B_2pin_2 and was effective in targeting the least sterically-encumbered C–H bond. As a result, reactions with substituted 1,3-difluoroarene derivatives gave the corresponding borylated products in which the Bpin groups have been incorporated at the 2-position.

In 2014, Maleczka Jr. and Smith III *et al.*[34] introduced a two step catalytic iridium-catalyzed C–H borylation and palladium-catalyzed dehalogenation process as a way of selectively generating *ortho*-fluoro aryl boronates. The arene substrates originally contain bromide as the leaving group *para* to the fluorine substituent (Scheme 6). The key to this selectivity is blocking borylation at the position *meta* to the fluorine substituent due to steric repulsion from the bulkier bromide group. A subsequent palladium-catalyzed hydrodehalogenation of the bromide substituent in the presence of the reducing agent polymethylhydrosiloxane (PMHS), which is activated by potassium fluoride, leads to the final product. Notably, it was also observed that electron poor arenes led to dehalogenation at a greater rate than electron rich arenes. It is important to note that protodeboronation was not observed to any significant degree during the dehalogenation step (see Section 3), except in the case of the methylbenzoate derivative which gave the the desired product in only 37% yield in a 2.4:1 ratio.

Recently, in 2019, Maleczka Jr. and Smith III *et al.*[35] reported iridium-catalyzed C–H borylation of fluorobenzenes containing substituents. They optimized the selectivity by screening various bidentate nitrogen-based ligand in combination with [Ir(cod)OMe]$_2$ as a precataylst. Selected examples are shown in Scheme 7, for the fluorobenzenes containing Cl, Br, or I substituents at the *meta*-to-fluorine position. Notably, they observed that the least hindered C–H



X	L (ligand)	Isomer ratio at the 2 : 3 positions (GC)
Cl	dmadpm	11 : 1 (71% isolated yield)
	dtbpy	1.8 : 1 (99% isolated yield, solvent = hexane)
	bozo	1 : 3.3 (65% isolated yield)
Br	dmadpm	7 : 1 (71% isolated yield)
	dtbpy	7 : 1 (82% (3:1) isolated yield)
	bozo	1 : 1.8 (X = Br, in THF, 41% conversion)
I	dmadpm	14 : 1 (82% isolated yield)
	dtbpy	2.8: 1 (87% isolated yield)
	bozo	1 : 2.6 (X = I, in THF, 30% conversion)

Scheme 7. Selectivities of iridium-catalyzed C–H borylation[35]

borylation is favored for the hindered and electron rich ligands, while *ortho*-to-fluorine C–H borylation is favored for unhindered and weaker *σ*-donor ligands. Among ligands that have been screened, an electron rich and hindered ligand such as dmadpm (Scheme 7)' showed the highest selectivity for *meta*-to-fluorine C–H borylation, and was significantly more selective than dtbpy, which is the most common ligand for iridium catalyzed C–H borylation. Interestingly, *ortho*-to-fluorine selectivity can be achieved using a less hindered and weaker electron donating ligand such as bozo (bis(2-oxazolin-2-yl), even though the regioselectivity was not that high.

2.2.2. Platinum-Catalyzed C–H Borylation of Fluoroarenes

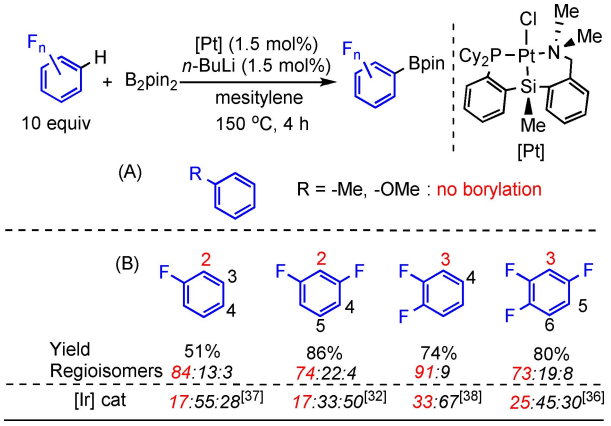
The iridium-catalyzed C–H borylation that targets a C–H bond *ortho* to a fluorine substituent requires steric repulsion from other substituents. In 2015, however, Iwasawa *et al.*[36] reported a platinum complex bearing a PSiN-pincer type ligand which catalyzes the C–H borylation of fluoroarenes with B_2pin_2 in the presence of *n*-butyllithium. Interestingly, this method is selective for the borylation of C–H bonds *ortho* to the fluorine substituent in good yield without the presence of steric protecting ancillary substituents. Notably, under these conditions, C–H borylation did not occur for unactivated arenes such as anisole and toluene (Scheme 8A). Interestingly, this method represents a useful alternative to the iridium-catalyzed systems for the borylation of C–H bonds that are *ortho* to fluorine substituents without the need of sterically-protecting substituents (Scheme 8B).[32,36–38]

In the same year, Tobisu and Chatani et al. reported a series of [Pt(NHC)(dvtms)] complexes (NHC = N-heterocyclic carbene; dvtms = divinyltetramethyldisiloxane) as catalyst precursors for the C–H borylation of arenes. These complexes are air stable and easy to prepare in two steps from $H_2[PtCl_6]$.[39] This study demonstrated that introducing NHC ligands gave turnover numbers (TON) up to 157 in reactions using ICy (1,3-bis(cyclohexyl)imidazolin-2-ylidene) as the ligand. Selected examples from the scope of these borylations revealed that introducing additional fluorine substituents increased the reactivity and selectivity in favor of generating *ortho*-directed borylated products (Scheme 9).

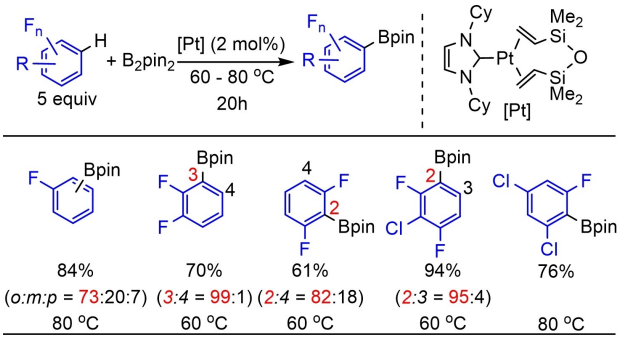
Selectivities observed in platinum-catalyzed C–H reactions reported by Iwasawa[36] and Tobisu and Chatani[39] were dictated by electronic effects, whereupon the most acidic arene C–H bonds *ortho* to the fluorine groups underwent borylation. This is in contrast with the iridium-catalyzed systems discussed previously which are governed predominantly by steric effects that target less sterically hindered C–H bonds.[29]

2.2.3. Cobalt-Catalyzed C–H Borylation of Fluorobenzenes

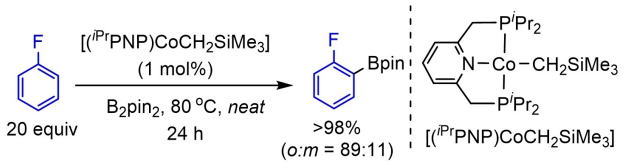
In 2014, Chirik *et al.* reported pincer-ligated cobalt alkyl complexes which catalyze the C–H borylation of arenes and heteroarenes.[40] Electron-rich arenes bearing only one substituent such as toluene and anisole are also viable substrates for C–H borylations but show less regioselectivity than the electron-deficient fluorobenzene, the only example reported employing a fluoroarene substrate. Using the complex [($^{i\text{Pr}}$PNP)$CoCH_2SiMe_3$] as a catalyst precursor for arene borylations, electron deficient substrates, including fluorobenzene, afforded products with higher selectivities. Borylation occurred *ortho* to the electron-withdrawing fluorine substituent with an *ortho* : *meta* ratio of 89:11 (Scheme 10), whereupon the fluorine substituent was believed to have an *ortho*-directing effect presumably due to the increased C–H acidity of the hydrogen substituents in the *ortho*-position.[41] In 2019, Chirik *et al.* reported that the *ortho*-to-fluorine selec-



Scheme 8. Platinum-catalyzed C–H borylation of fluoroarenes: (A) electron rich arene substrates; (B) fluorinated arene substrates.[36]



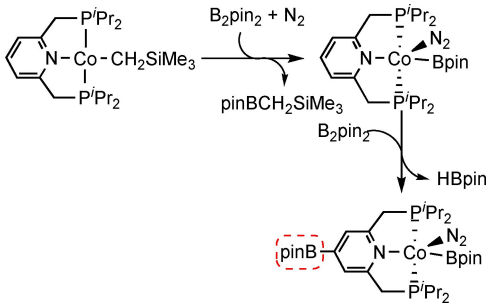
Scheme 9. Platinum-catalyzed C–H borylation of fluoroarenes.[39]



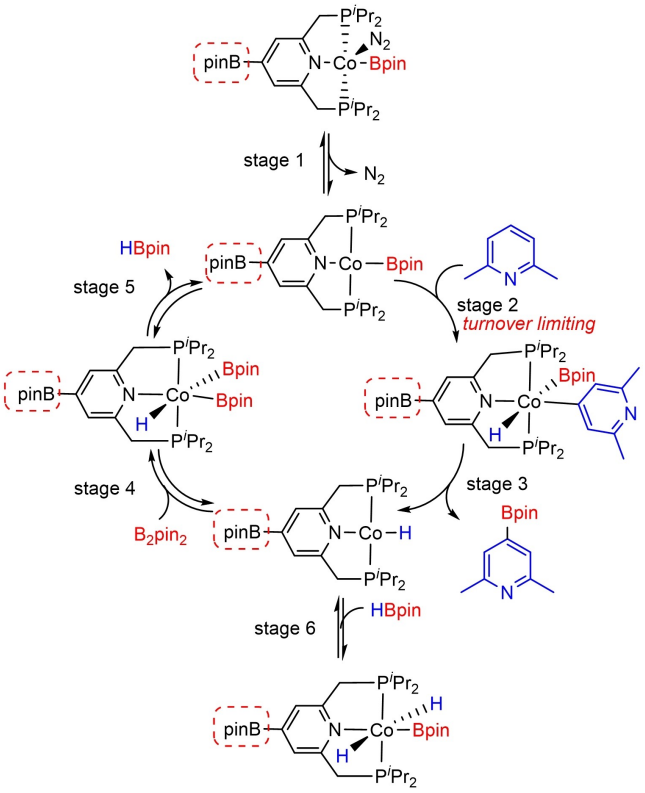
Scheme 10. C–H borylation of arenes using Chirik's first generation cobalt precatalyst.[40]

tivity is due to a lower barrier for the C(sp^2)–H oxidative addition of the fluorinated arenes to the Co(I) center compared to unactivated arenes such as toluene or *m*-xylene. Computational studies showed that the cobalt-aryl bond is strengthened with increasing number of *ortho*-fluorine substituents in the relevant intermediates of the ($^{i\text{Pr}}$PNP)Co-catalyzed C–H borylation.[42] This is in accordance with previous studies by Jones *et al.* and Eisenstein and Perutz *et al.* who showed a large *ortho*-fluorine effect on the strength of metal-aryl bonds.[43–45]

In 2016, Chirik *et al.* reported that treatment of the precatalyst [($^{i\text{Pr}}$PNP)CoCH$_2$SiMe$_3$] with B_2pin_2, under a N_2 atmosphere afforded [($^{i\text{Pr}}$PNP)Co(N_2)Bpin] along with N_2 coordination and the concomitant formation of Me_3SiCH_2Bpin (Scheme 11). Interestingly, excess B_2pin_2 led to C–H borylation at the 4-position of the pyridine moiety of the catalyst to give [4-Bpin-($^{i\text{Pr}}$PNP)Co(N_2)Bpin] as the resting state.[46] Using 2,6-lutidine as a substrate, Chirik proposed that the catalytic cycle involves a Co(I)/Co(III) pathway. Following N_2 dissociation from [4-Bpin-($^{i\text{Pr}}$PNP)Co(N_2)Bpin], C(sp^2)–H oxidative addition of the arene to a cobalt(I) boryl intermediate occurs to give a cobalt(III) hydrido boryl aryl intermediate (Scheme 12, stages 1 and 2). A subsequent B–C reductive elimination step releases the borylated product and the cobalt(I) hydride complex (Scheme 12, stage 3). Oxidative addition of B_2pin_2 and reductive elimination of HBpin closes the catalytic cycle (Scheme 12, stages 4 and 5). At higher conversions, when a substantial amount of HBpin is



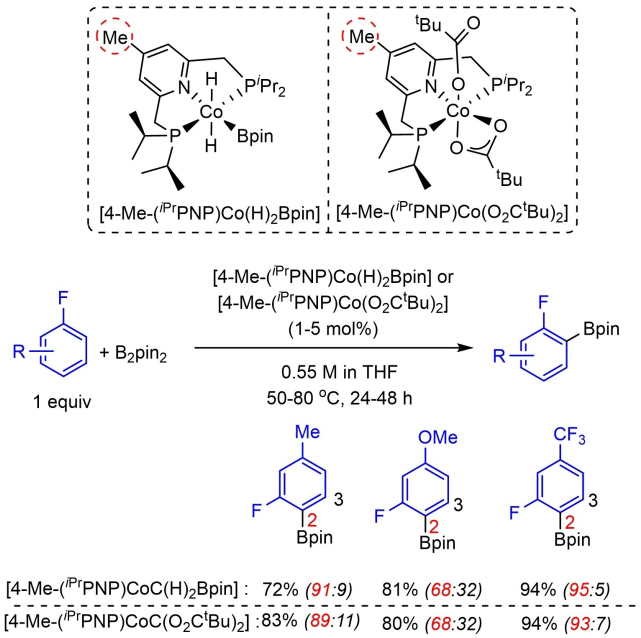
Scheme 11. Borylation occurred at the 4-position of the pyridine moiety of the cobalt catalyst that causes catalyst deactivation.[46]



Scheme 12. Proposed mechanism for the cobalt-catalyzed borylation of arenes with B_2pin_2.[46]

generated, oxidative addition of HBpin to the cobalt(I) hydride species occurs to generate the resting state [4-Bpin-($^{i\text{Pr}}$PNP)Co(H)$_2$Bpin] (Scheme 12, stage 6). Notably, with benzene or *N*-heteroarene substrates, Chirik *et al.* found that C(sp^2)–H oxidative addition of the arene ligand to the cobalt(I) boryl intermediate is the turnover-limiting step and that the process is irreversible. Interestingly, in 2019, they also reported that fluorination of the arene substrate activates the C(sp^2)–H bonds as the barrier for the oxidative addition is decreased and the process becomes reversible, hence this step is unlikely to be turnover-limiting.[42]

Catalyst C–H borylation occured at the 4-position of the pyridine ligand (Scheme 11) and is disadvantageous for the catalytic performance, as the metal center becomes less electron-rich and oxidative addition is inhibited upon borylation. This observation led to the development of a second generation of the Chirik cobalt precatalysts [4-Me-($^{i\text{Pr}}$PNP)Co(H)$_2$Bpin] and [4-Me-($^{i\text{Pr}}$PNP)Co(O_2C^tBu)$_2$] in which methyl substituents were located at the 4-position of the pyridine ligand to prevent ligand C–H borylation.[41] As shown in Scheme 13, the precatalysts [4-Me-($^{i\text{Pr}}$PNP)Co(H)$_2$Bpin] and [4-Me-($^{i\text{Pr}}$PNP)Co(O_2C^tBu)$_2$] are effective for the catalytic *ortho*-to-fluorine C–H borylation of substituted fluoroarenes using B_2pin_2 as the boron source and THF as the solvent (Scheme 13).

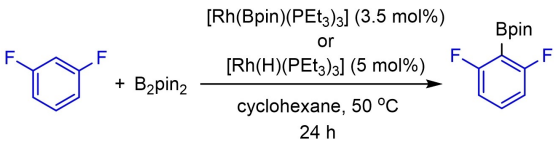


Scheme 13. Catalytic C–H borylation of fluoroarenes using Chirik's second generation cobalt precatalysts.[41]

Notably, this method is not viable for fluoroarene substrates containing bromo or chloro substituents (not shown).

2.2.4. Rhodium-Catalyzed C–H Borylation of Fluorinated Benzenes

In 2015, Braun *et al.*[47] developed a rhodium-catalyzed C–H borylation of arenes to generate boron-containing products *ortho* to two fluorine substituents using either B_2pin_2 or HBpin. For example, treatment of 1,3,5-trifluorobenzene or 1,3-difluorobenzene with excess B_2pin_2 in the presence of catalytic amounts of either $[Rh(PEt_3)_3(Bpin)]$ or $[Rh(PEt_3)_3H]$ in cyclohexane at 50 °C for 24 hours generated the corresponding C–H borylation products in good yield (Scheme 14). However, it should be noted that the C–H borylation performance was poor for heteroarene substrates. For example, reactions employing 2,3,5,6-tetrafluoropyridine as the borylation substrate and 5 mol% $[Rh(PEt_3)_3H]$ as the catalyst precursor gave 2,3,5,6-C_5NF_4Bpin in only 44% yield even after longer reaction times (7 days).



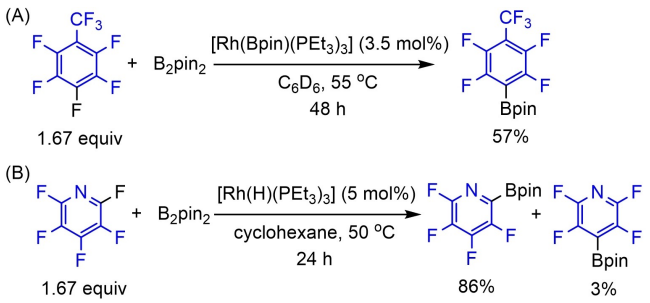
Scheme 14. Rhodium-catalyzed C–H borylation of 1,3-difluorobenzene.[47]

2.3. Catalytic C–F Borylation

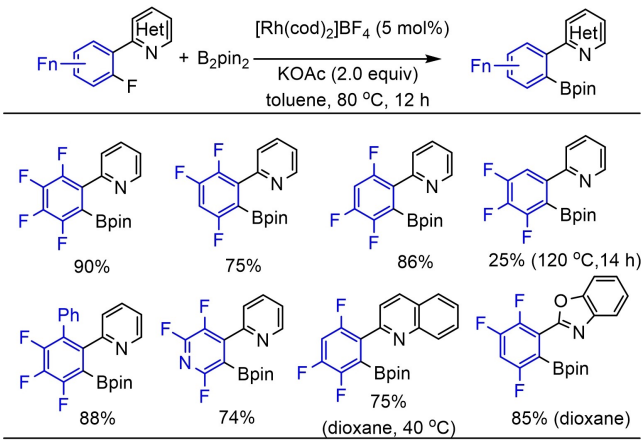
2.3.1. Rhodium-Catalyzed C–F Borylation of Fluoroarenes

Conversion of partially fluorinated arene compounds *via* C–F bond borylation is another option to generate fluoride-containing aryl boronate esters. In 2007, Marder and Perutz *et al.* reported the stoichiometric C–F borylation of fluoropyridines promoted by $[Rh(PMe_3)_3(SiPh_3)]$.[48] Inspired by these stoichiometric processes, Braun *et al.* demonstrated that Rh(I) complexes could be used for the catalytic C–F borylation of fluoroarenes,[47] pentafluoropyridine,[49] and hexafluoropropene.[50] The authors showed that adding 3.5 mol% of $[Rh(PEt_3)_3(Bpin)]$ into a mixture that contained 1,2,3,4,5-pentafluoro-6-(trifluoromethyl) benzene and B_2pin_2 in benzene at 55 °C for 2 days gave the C–F borylation product 4-Bpin-$C_6F_4(CF_3)$ in a yield of 57% (based on B_2pin_2) (Scheme 15A).[47] Under similar conditions, using 5 mol% $[Rh(PEt_3)_3(Bpin)]$ in cyclohexane, catalytic C–F borylation of pentafluoropyridine occurred at the 2-position to give C_5NF_4Bpin as the main product (86%) (Scheme 15B). Interestingly, when other fluoroarene substrates such as 1,3,5-trifluorobenzene or 1,3-difluorobenzene were employed, the authors observed that C–H borylation occurred instead of C–F borylation.

In 2015, Zhang *et al.* reported that the commercially available complex $[Rh(cod)_2]BF_4$ could be used as a precatalyst for the *ortho*-selective C–F borylation of 2-(fluorophenyl)pyridines with B_2pin_2. The reaction was conducted in the presence of potassium acetate as a base in toluene at 80 °C.[51] Notably, *ortho*-selective C–F borylation was directed by the *N*-heterocyclic substituent. As shown in Scheme 16, C–F borylation only occurred *ortho* to the pyridyl group in good to excellent yields. However, if the substrate has a hydrogen substituent *ortho* to the pyridyl group, such as 2-(2,3,4,5-tetrafluorophenyl)pyridine, C–H and C–F borylation both occurred, with products generated in 45% and 25% yields, respectively (Scheme 16). Preliminary mechanistic studies suggest that the toluene solvent acts as a hydrogen source for the formation of



Scheme 15. Rhodium-catalyzed C–F borylation of perfluorotoluene and perfluoropyridine.[47]

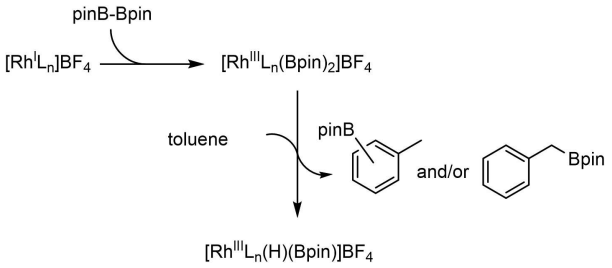


Scheme 16. Rhodium-catalyzed *ortho*-selective C–F borylation of polyfluoroarenes.[51]

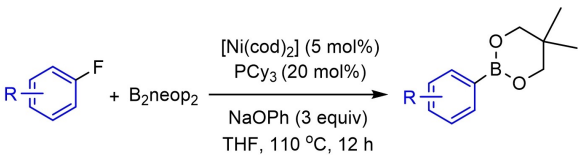
the rhodium hydride complex $[Rh^{III}L_n(H)(Bpin)]BF_4$ as a key intermediate to initiate the catalytic process (Scheme 17).

2.3.2. Nickel-Catalyzed C–F Borylation of Fluoroarenes

Several studies have been reported regarding the development of nickel-mediated C–F activation of arenes in stoichiometric processes.[1,2,52–55] However, effective catalytic borylations of these substrates using nickel catalysts were reported only recently by Martin *et al.* (Scheme 18).[56] In this initial study, a combination of $[Ni(cod)_2]$ and PCy_3 (tricyclohexylphosphine) as a precatalyst system was effective to promote the



Scheme 17. Generation of $[Rh^{III}L_n(H)(Bpin)]BF_4$ as a key intermediate in the catalytic process.[51]

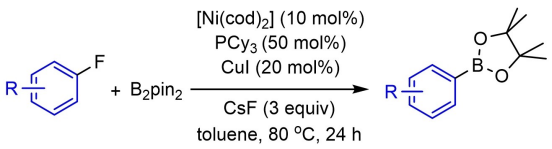


Scheme 18. Nickel-catalyzed C–F borylation of aryl fluorides with B_2neop_2.[56]

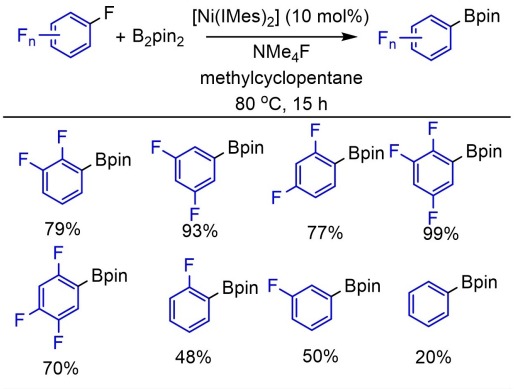
C–F borylation of fluorinated aryls with B_2neop_2 (neop = neopentyl glycolato) to give products in up to 81% yield. However, employing B_2pin_2, instead of B_2neop_2, resulted in no borylation products. Soon after, Niwa and Hosoya *et al.* used B_2pin_2 as the boron source and employed nickel and copper cocatalyst systems to borylate the C–F bond of fluoroarenes in up to 99% yield (Scheme 19).[57] However, they did not examine polyfluorinated substrates. As a result, this reaction furnished non-fluorinated aryl boronate esters.

In 2016, Radius and Marder *et al.* employed an NHC-nickel complex as a precatalyst for the C–F borylation of partially fluorinated arenes using B_2pin_2. Optimal conversions were achieved using $[Ni(IMes)_2]$ (IMes = 1,3-dimesitylimidazolin-2-ylidene) in the presence of tetramethylammonium fluoride (NMe_4F) in methylcyclopentane at 80–100 °C (Scheme 20).[58] A mechanistic pathway was proposed based on experimental studies (Scheme 21), whereupon the initial reaction of $[Ni(IMes)_2]$ with fluoroarene proceeds *via* oxidative addition of the C–F bond to give *trans*-$[Ni(IMes)_2(Ar_F)F]$. Then, the presence of NMe_4F (or CsF) led to a fluoride adduct with B_2pin_2 which promoted boryl transfer to the Ni(II) complex to give *trans*-$[Ni(IMes)_2(Ar_F)(Bpin)]$ along with $[F_2Bpin]^-$. Finally, rapid reductive elimination occurred to provide Ar_F-Bpin and regenerate $[Ni(IMes)_2]$.

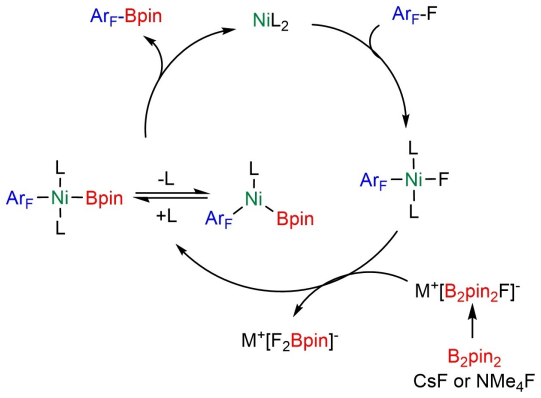
Noteworthy is that these nickel-catalyzed C–F borylations require high temperatures to facilitate the rate-determining transmetalation step, although C–F oxidative addition to $[Ni(IMes)_2]$ proved facile at room



Scheme 19. Nickel/copper-catalyzed defluoroborylation of fluoroarenes with B_2pin_2.[57]

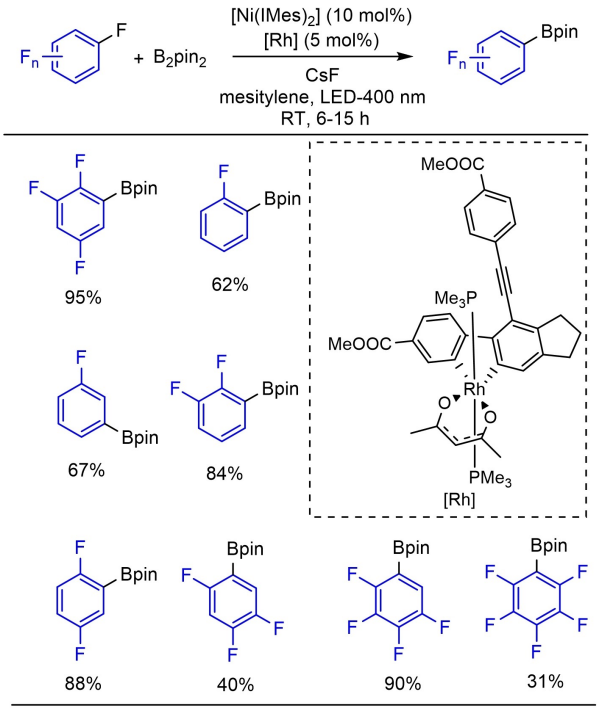


Scheme 20. Thermal-catalytic C–F borylation of fluoroarenes using a Ni precatalyst.[58]



Scheme 21. Proposed mechanism for the thermal-catalytic C–F borylation of fluoroarenes using an NHC–Ni catalyst.[58]

temperature. It is interesting to note that a rhodium biphenyl complex could be used as a triplet sensitizer to enhance the transmetalation with B_2pin_2 to the nickel(II) complex. The reaction was conducted in the presence of visible light (400 nm) using CsF as a base, and proved effective for the C–F borylation of polyfluoroarenes at room temperature (Scheme 22).[59] In the absence of the rhodium complex, the intermediate complex *trans*-[Ni(IMes)$_2$(Ar$_F$)F] decomposed quickly under irradiation in the presence of B_2pin_2. Interestingly, this decomposition pathway could be



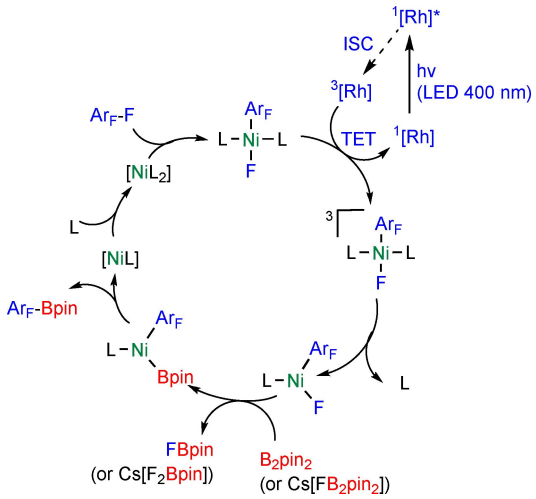
Scheme 22. Photocatalytic C–F borylation of fluoroarenes using a dual Ni/Rh catalyst.[59]

circumvented by indirect excitation of the triplet states of the nickel(II) complex *via* the photoexcited rhodium biphenyl complex. Triplet energy transfer (TET) accelerated the transmetalation step and thus the whole borylation process. The proposed mechanism suggested that the long-lived triplet excited state of the rhodium complex functions as the photosensitizer that provides facile TET to *trans*-[Ni(IMes)$_2$(Ar$_F$)F], facilitating dissociation of one of the NHC ligands (Scheme 23). The resulting 3-coordinate nickel complex reacts with B_2pin_2, or its anionic adduct Cs[FB$_2$pin$_2$], to give [Ni(IMes)(Ar$_F$)(Bpin)] which was proposed to be followed by rapid reductive elimination releasing the borylated arene products and [Ni(IMes)].

Thermal[58] and photocatalytic[59] C–F borylation procedures have subsequently been developed that are selective and efficient in generating fluorinated aryl pinacol boronate products. However, those C–F borylation methods were not able to generate C_6F_5Bpin from C_6F_6 in any appreciable yields.[55] As these methods require the use of a strong base, protodeboronation may be responsible for the low yields.

2.4. Catalytic C–X Borylation (X = Cl, Br, I, OTf)

The transition metal-catalyzed C–X (X = Cl, Br, I, OTf) borylation reaction provides another option for introducing boronate ester groups selectively into fluorinated aryl halides or triflates.[60–70] Masuda *et al.* reported that [Pd(dppf)Cl$_2$] (dppf = 1,1′-bis(diphenylphosphino)ferrocene) acts as an active catalyst precursor for the C–X borylation of aryl halides and triflates with B_2pin_2 in the presence of excess of Et_3N.[68] Masuda's methodology was attempted by Cammidge *et al.* for the borylation of aryl triflates in

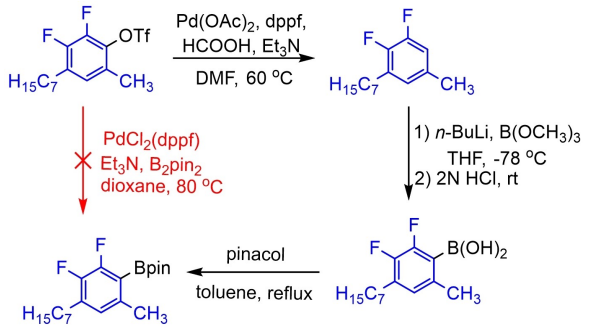


Scheme 23. Proposed mechanism for the photocatalytic C–F borylation of fluoroarenes using [Rh]/[Ni(IMes)$_2$] via triplet energy transfer (TET).[59]

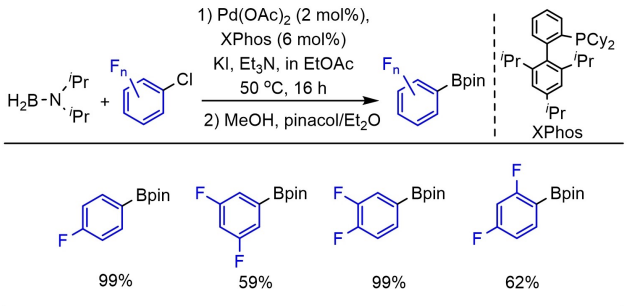
which the C–OTf bond was *ortho* to a C–F and a C–CH_3 bond; however, no reaction was observed under these conditions (Scheme 24). To generate the desired boronate ester, Cammidge *et al.* resorted to using an *ortho* lithiation method, demonstrating the challenges associated with some transition metal-catalyzed C–OTf borylation reactions.[69]

Several examples of transition metal-catalyzed C–X borylation reactions generating products with the C–B moiety located *ortho*, *meta*, and *para* to the fluorine substituents have been reported.[58,63–67,69] For example, in 2014, Pucheault *et al.* reported a palladium-catalyzed C–Cl borylation in the synthesis of aryl boronate ester derivatives using aryl(amino) boranes in good to excellent yields (Scheme 25). However, attempts to generate di *ortho*-fluorinated aryl boronates were not examined.[66]

Earlier attempts to use transition metal-catalyzed C–X (X = Cl, Br, I) borylations to generate aryl-Bpin products containing two *ortho*-fluorine substituents all proved unsuccessful. For example, in 2012, Molander *et al.* reported the borylation of aryl-X (X = Br, Cl, I, OTf) with $B_2(OH)_4$ using the second generation Buchwald precatalyst XPhosPd–G2 (Scheme 26), followed by the conversion of the borylated aryl boronic acid products into potassium trifluoroborate analogues. This method is effective to generate



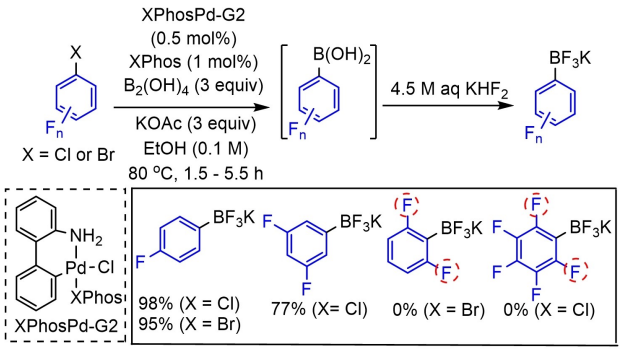
Scheme 24. Transition metal-catalyzed C–OTf borylation vs. lithiation to synthesize *ortho*-fluorinated aryl boronates.[69]



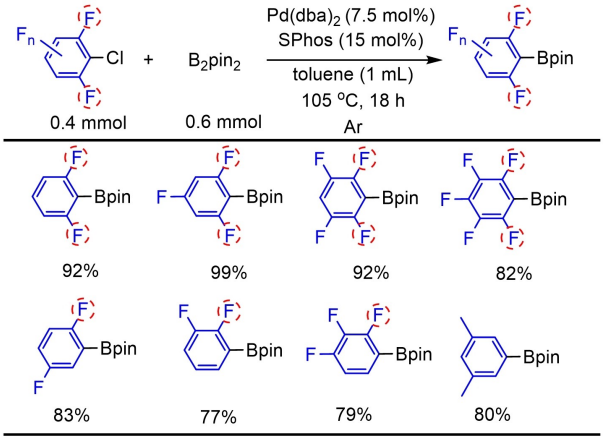
Scheme 25. Palladium-catalyzed C–Cl borylation to construct fluorinated aryl boronate esters.[66]

borylated products in good to excellent yields; however, notably, the reaction failed for aryl-X substrates, in which the C–X bond is flanked by two C–F bonds, e.g., 2-bromo-1,3-difluorobenzene and 1-chloro-2,3,4,5,6-pentafluorobenzene (Scheme 26).[70] These reactions were typically conducted in the presence of stoichiometric amounts of base, but the resulting products are unstable under these conditions resulting in considerable amounts of protodeboronated fluoroarene species.

Very recently, Radius and Marder *et al.* reported the palladium catalyzed C–Cl borylation of fluorinated aryl chlorides containing two *ortho*-fluorine substituents using a combination [$Pd(dba)_2$] (dba = dibenzylideneacetone) with SPhos (2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl) as the precatalyst, and B_2pin_2 as the boron source.[71] Notably, this reaction was conducted under base-free conditions thus preventing the base-sensitive borylated product, di-*ortho*-fluorinated aryl-Bpin, from decomposing. As shown in Scheme 27, these conditions are effective to catalyze C–Cl borylation of aryl chlorides containing two, one,



Scheme 26. C–X borylation to construct fluorinated arylboronates using the precatalyst XphosPd–G2.[70]

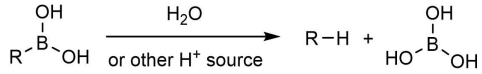


Scheme 27. Base-free palladium-catalyzed C–Cl borylation of fluorinated aryl chlorides.[71]

or no *ortho*-fluorine substituents giving good to excellent yields.

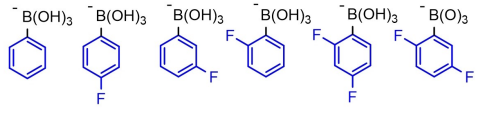
3. Protodeboronation of Fluorinated Aryl Boronates

Before going into detail about the catalytic applications of fluorinated aryl boronates, it is important to discuss the stability issue associated with these compounds. One major problem involves the protodeboronation of fluorinated aryl boronic acids, which is accelerated in compounds containing *ortho*-fluorine substituents. As mentioned above, protodeboronation involves protonolysis of the boron group to give a new aryl C–H bond (Scheme 28). The influence of *ortho*-fluorine substituents on the protodeboronation of aryl boronic acids was initially reported by Kuivila *et al.* in 1963, who studied the rate of protodeboronation of fluorinated aryl boronates at pH 6.5 at 90 °C in aqueous malonate buffer (Table 1).[72] It was concluded that: (i) in the case of mono fluoride substrates the rates of protodeboronation decreased in the order of *ortho* > *para* > *meta*; (ii) for difluoro-substituted aryl boronic acids, protodeboronation rates were faster for *ortho-meta*-substituted substrates as opposed to those in the *ortho-para*-positions; and (iii) that $C_6F_5B(OH)_2$, which involved all *ortho*-, *meta*-, and *para*-fluorine positions, had the highest rates of protodeboronation.

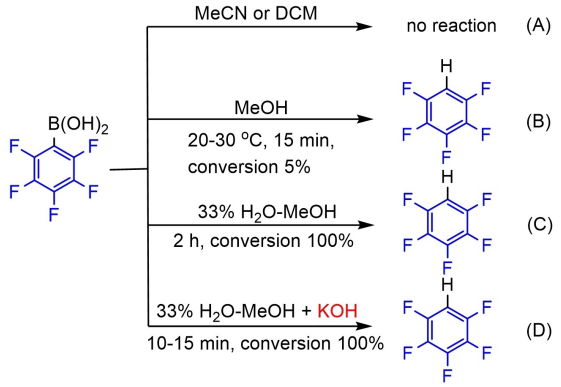


Scheme 28. A general protodeboronation reaction.

Table 1. Effect of fluorine substituents on the relative rates of protodeboronation of aryl boronic acids.[26,72]



k_{rel}	1.0	1.4	0.3	11	--	--	Kuivila, 1963
k_{rel}	1.0	1.4	0.98	243	616	1548	Lloyd-Jones, 2017



Scheme 29. Protodeboronation of $C_6F_5B(OH)_2$: (A) in acetonitrile or dichloromethane; (B) in methanol; (C) in 33% H_2O-methanol; (D) in 33% H_2O-methanol + KOH.[73]

In 2002, Frohn and Adonin *et al.* also reported the protodeboronation of fluorinated aryl boronic acids.[73] In this study, they found that $C_6F_5B(OH)_2$ was stable in MeCN and dichloromethane, but was less stable in methanol at 20–30 °C with about 5% conversion to the decomposition product per 15 minutes (Scheme 29). Moreover, the protodeboronation rate of $C_6F_5B(OH)_2$ was faster in a 33% H_2O-MeOH solvent mixture and the process was complete within 2 hours to give C_6F_5H. The addition of KOH increased the rate of protodeboronation so that the reaction was complete within 10–15 minutes.

Protodeboronation of $C_6F_5B(OH)_2$ was immediate and occurred exothermically in a mixture of D_2O-pyridine at room temperature within 3–5 minutes (Table 2, entry 1). Not surprisingly, when the aryl boronic acid contained only one *ortho*-fluorine group, protodeboronation occurred considerably more slowly than with substrates containing two *ortho*-fluorine groups (Table 2, entries 2, 4 and entries 8, 9). Notably, with no *ortho*-fluorine substituent, protodeboronation did not occur for electron deficient compounds such as 3,4,5-$C_6F_3H_2B(OH)_2$ even after 180 minutes at high temperatures (Table 2, entry 7).

Lloyd-Jones *et al.*[26] studied the mechanism, supported by experimental and computational evidence, for the protodeboronation of aryl boronic acid containing *ortho*-fluorine substituents. They disclosed that protodeboronation occurs *via* a C–B heterolysis of a trihydroxy organoboronate intermediate ($[M]^+[ArB(OH)_3]^-$), which notably does not require water in this step. This is followed by a proton transfer from water

Table 2. Total conversion of polyfluorophenyl-$B(OH)_2$ into deuteropolyfluorobenzenes (ArD) in 9% D_2O-pyridine (v/v).[73]

Entry	Compound	T (°C)	Time of conversion (min)
1	$C_6F_5B(OH)_2$	25	< 3–5
2	2,3,4,5-$C_6F_4HB(OH)_2$	100	50
3	2,3,4,6-$C_6F_4HB(OH)_2$	32	210[a]
4	2,3,4,6-$C_6F_4HB(OH)_2$	100	15
5	2,3,5,6-$C_6F_4HB(OH)_2$	32	60
6	2,4,6-$C_6F_3H_2B(OH)_2$	100	90
7	3,4,5-$C_6F_3H_2B(OH)_2$	100	180, no reaction
8	2,4-$C_6F_2H_3B(OH)_2$	100	1140 (19 hours)[b]
9	2,6-$C_6F_2H_3B(OH)_2$	100	150

[a] Conversion 82%.
[b] Conversion 53%.

to generate the hydrolyzed product (Scheme 30A). Protodeboronation of 2,6-difluorophenyl boronic acid is rapid due to the *ortho*-fluorine substituents stabilizing an *ipso*-aryl carbanion with delocalization of the negative charge ($n\rightarrow\sigma^*_{C(2)\text{-}C(3)}$ and $n\rightarrow\sigma^*_{C(6)\text{-}C(5)}$) into the C(2)–F and C(6)–F bonds and, hence, the accompanying rehybridization increases the s-character at the carbanion (C1) (Figure 6). Furthermore, their kinetic studies showed that unimolecular heterolysis of the aryl boronate ester to give boric acid is the rate-limiting step (Scheme 30A). However, unlike di-*ortho*-fluoro substituted aryl boronic acids, the rate limiting step of protodeboronation in electron-rich aryl boronic acids was observed to be proton transfer from a molecule of water followed by cleavage of the C–B bond to generate boric acid (Scheme 30B). Twenty isomers of $C_6F_{5-n}H_nB(OH)_2$ were studied with half-lives ($t_{1/2}$) that measured spanning 9 orders of magnitude, from <3 miliseconds to 6.5 months, showing that *ortho*-fluorinated aryl boronic acids accelerated protodeboronation, with $C_6F_5B(OH)_2$ displaying the fastest rate.

Interestingly, Perrin *et al.* reported that many typical electron-deficient aryl boronic acids, including fluorinated derivatives, are stable in acidic solutions of 0.1 M HCl.[74] Under aqueous basic conditions (200 mM hydroxide), aryl boronic acids that contain di-*ortho*-substituted electron withdrawing groups such as fluoride, chloride, bromide, and trifluoromethyl groups, are unstable towards protodeboronation (Scheme 31).

Carrow *et al.* studied the influence of triethylamine and/or water with respect to the stability of C_6F_5Bpin and $C_6F_5B(OH)_2$ towards protodeboronation.[75] Notably, triethylamine was used as received and contains trace amounts of water. In this study, they measured the yield of C_6F_5H that was generated from the protodeboronation of $C_6F_5B(OH)_2$ and C_6F_5Bpin solutions in THF-triethylamine and treated with various numbers of equivalents of water. As shown in Chart 1, in the presence of triethylamine (0.5 equivalent), C_6F_5Bpin is much more stable than $C_6F_5B(OH)_2$. Thus, it can be concluded that C_6F_5Bpin is more stable than its boronic acid analogue in anhydrous basic solution.

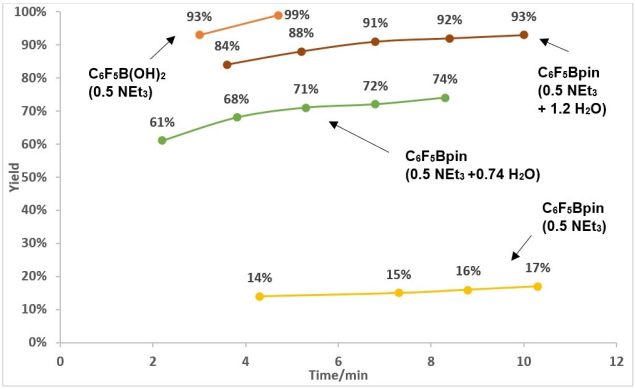
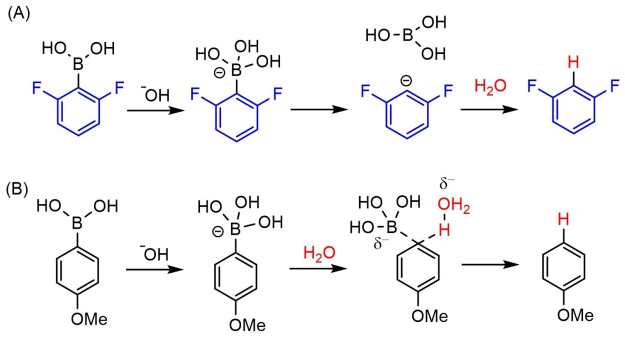


Chart 1. Yield of C_6F_5H that resulted from protodeboronation of $C_6F_5B(OH)_2$ or C_6F_5Bpin determined by ^{19}F NMR spectroscopy.[75]



Scheme 30. Mechanism of the base-catalyzed protodeboronation of (A) 2,6-difluorinated aryl boronic acid vs. (B) 4-anisyl boronic acid.[26]

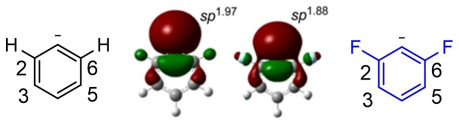
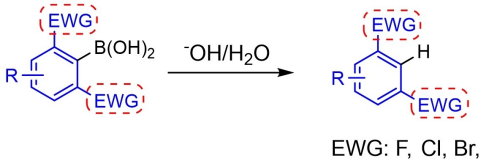
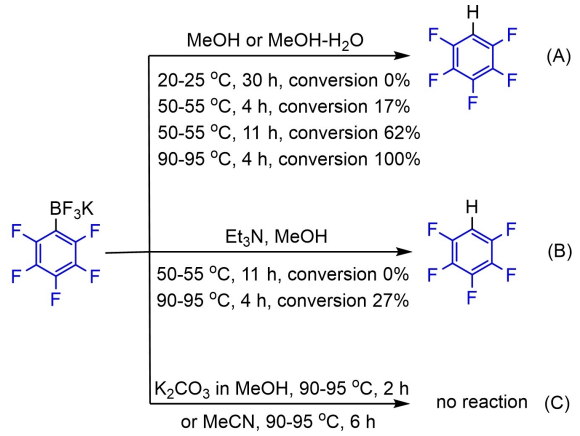


Figure 6. NLMO analyses of non-fluorinated and 2,6-difluorinated aryl anions which will be generated by C–B heterolysis of their corresponding trihydroxy aryl boronates. Adapted with permission.[26] Copyright 2017, American Chemical Society.

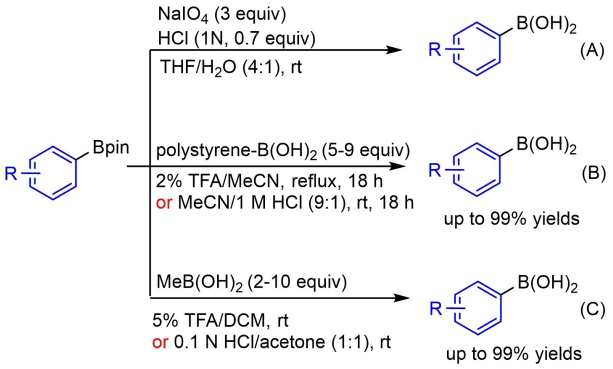
Adonin *et al.* investigated the protodeboronation of potassium polyfluoroaryltrifluoroborate salts (Ar_F-BF_3K).[76] Unlike $C_6F_5B(OH)_2$, which is prone towards protodeboronation at 20–30 °C (ca. 5% conversion within 15 minutes), $C_6F_5BF_3K$ was stable over 30 hours upon treatment with methanol or aqueous methanol at 20–25 °C (Scheme 32A). However, this salt slowly protodeboronated at elevated temperatures such as 50–55 °C (17% and 62% after 4 and 11 hours, respectively) or 90–95 °C (conversion was complete after 4 hours) (Scheme 32A). Interestingly, protodeboronation could be reduced by addition of base, such as Et_3N or K_2CO_3 (Scheme 32B). It should be noted that protodeboronation did not occur when $C_6F_5BF_3K$ was treated with K_2CO_3 in methanol or in weakly basic



Scheme 31. Base-promoted protodeboronation of electron-poor 2,6-disubstituted aryl boronic acids.[74]



Scheme 32. Protodeboronation of $C_6F_5BF_3K$ in methanol: (A) without base; (B) with Et_3N; and (C) with K_2CO_3 or MeCN.[76]



Scheme 33. Conversion of aryl pinacol boronates to their boronic acid analogues via oxidative hydrolysis (A) or transesterification with polystyrene boronic acid (B) or methyl boronic acid (C).[79–82]

solvents such as MeCN (Scheme 32C). In addition, opposite results were found under acidic conditions. Frohn *et al.* had previously reported that $C_6F_5BF_3K$ was readily protodeboronated within 6 hours in 40% HF_{aq} at elevated temperatures (85–95 °C).[77]

In summary, under aqueous basic conditions *ortho*-fluorine groups are known to promote the protodeboronation of aryl boronates (except for trifluoroborate salts). Furthermore, $C_6F_5B(OH)_2$, which contains fluorine substituents at all positions, is remarkably unstable with respect to this decomposition pathway and remains a challenging substrate for use in organic synthesis.

4. Applications of Fluorinated Aryl Boronates in Organic Synthesis

4.1. Intermediates for the Introduction of Functional Groups

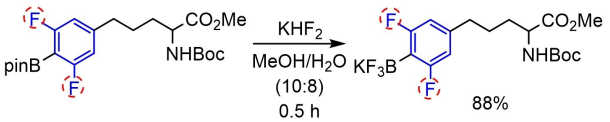
4.1.1. Conversion of Fluorinated Aryl Boronate Esters to Boronic Acids or Trifluoroborate Salts

The reactivity of organoboron compounds is dictated by the substituents bound to the boron atom and, hence, the resulting Lewis acidity of the compound. For example, aryl pinacol boronate esters are less reactive than aryl boronic acids or trifluoroborate analogues as substrates for the copper-catalyzed C–N cross-coupling of aryl amines[78,79] or C–O coupling with phenols.[79] The conversion of aryl pinacol boronate esters to their boronic acid analogues has been reported *via* oxidative hydrolysis[79,80] or transesterification with excess polystyrene boronic acid[81] or methyl boronic acid.[82] In general, these methods are conducted under acidic conditions in the presence of trifluoroacetic acid (TFA) or HCl (Scheme 33). However, these methodologies have not yet been examined for aryl boronate ester substrates containing *ortho*-fluorine substituents.

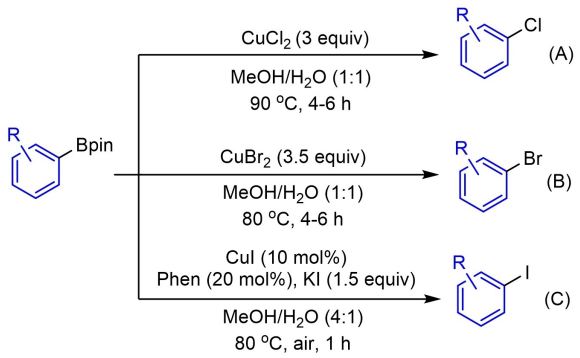
Organotrifluoroborates are reportedly more stable to air and moisture than their boronic acid or ester counterparts.[83–86] The conversion of aryl boronate esters to the corresponding trifluoroborate analogues is readily accomplished with the addition of potassium hydrogen difluoride (KHF_2).[80,87] As shown in Scheme 34, the method is viable for the conversion of aryl pinacol boronates containing two *ortho*-fluorines in high yields.

4.1.2. Conversion of Fluorinated Aryl Boronate Esters to Aryl Halides

Aryl halides are among the most important intermediates in organic synthesis. Reliable methods to convert aryl boronate esters to aryl chlorides or bromides *via* addition of stoichiometric amounts of $CuCl_2$ or $CuBr_2$ (Scheme 35A and B) have been reported.[88] However, addition of CuI to aryl boronate esters under these conditions did not afford the corresponding aryl iodides. Subsequent research found that a reliable method to generate these aryl iodides is the addition of stoichiometric amounts of potassium iodide (KI) as the source of iodide along with a combination of 10 mol% CuI and 20 mol% of phenanthroline at 80 °C (Scheme 35C).[89] Hartwig, *et al.* were able to carry out a tandem iridium-catalyzed borylation/copper-catalyzed iodination of aryl pinacol boronates with sub-



Scheme 34. Conversion of a 2,6-fluorinated aryl pinacol boronate to its trifluoroborate analogue.[87]

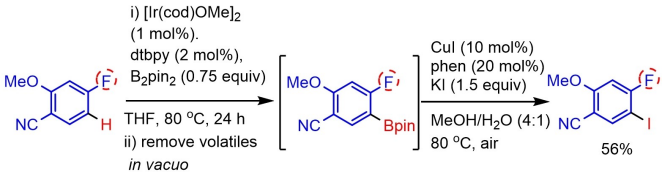


Scheme 35. Conversion of aryl pinacol esters to aryl halides.[88,89]

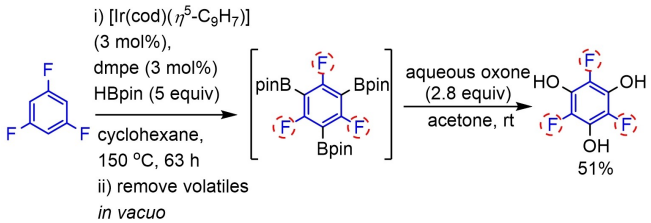
strates involving only one *ortho*-fluorine substituent (Scheme 36).[89]

4.1.3. Conversion of Fluorinated Aryl Boronate Esters to Phenols

Phenols are important building blocks in organic synthesis, having diverse applications in areas such as polymer and pharmaceutical chemistry.[90] A reliable method to generate aryl hydroxyl compounds is *via* oxidation of aryl boronate esters using aqueous oxone. Indeed, Maleczka Jr. and Smith III *et al.* combined the oxidation of aryl pinacol boronate esters as a second step after an initial iridium-catalyzed borylation. Notably, this method is efficient for the generation of phenols in which the C–OH bond is flanked by two C–F bonds (Scheme 37).[91]



Scheme 36. One pot C–H borylation and iodination of an *ortho*-fluorinated aryl pinacol boronate ester.[89]



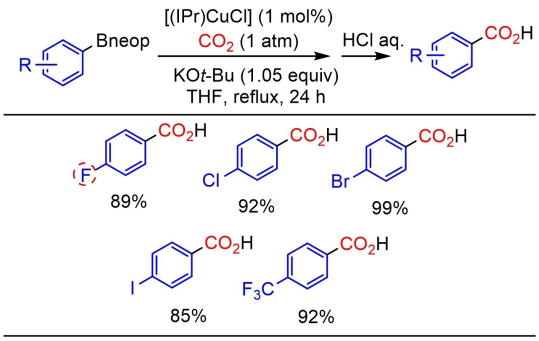
Scheme 37. Iridium-catalyzed borylation/oxidation of fluorinated arenes.[91]

4.1.4. Conversion of Fluorinated Aryl Boronate Esters to Corresponding Carboxylic Acids

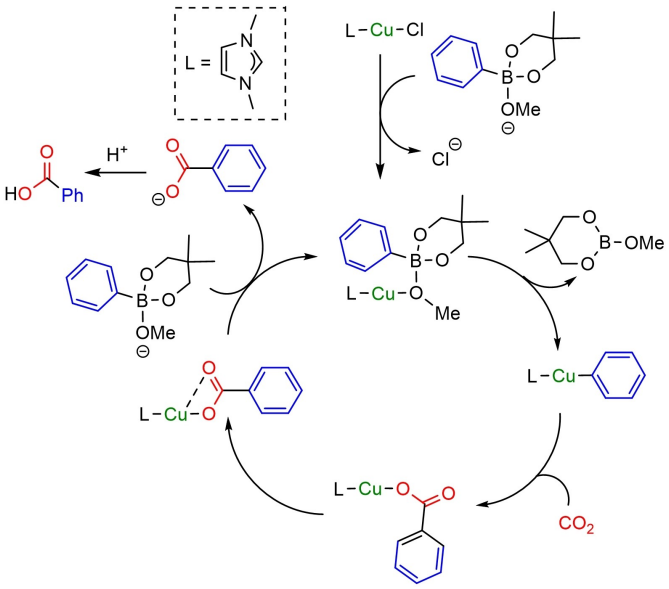
Carbon dioxide is an important feedstock in the chemical industry and is used in the construction of medicinal, agricultural, and specialty chemicals.[92] In 2008, Hou *et al.* reported the carboxylation of aryl-Bneop derivatives, using an NHC-copper complex as the catalyst.[93] Thus, [(IPr)CuCl] (IPr = 1,3-bis(2,6-diisopropylphenyl)-imidazolin-2-ylidene) is efficient to catalyze the carboxylation of aryl-Bneop, in the presence of CO_2 (balloon), KO*t*-Bu as the base, in THF solution, under reflux for 24 hours, followed by addition of 1 M hydrochloric acid solution. Appreciable yields can also be obtained using a catalyst system formed *in situ* from a combination of Cu(I) or Cu(II) salts such as CuCl, CuBr, $CuCl_2$ or $Cu(OAc)_2$ with protonated NHC ligands such as IPr·HCl or IMes·HCl. As shown in Scheme 38, these conditions are efficient for aryl-Bneop derivatives bearing electron-withdrawing substituents such as fluorine, chlorine, bromine, iodine, and CF_3 at the *para*-position to generate the corresponding carboxylation products in good to excellent yields. However, challenging *ortho*-fluorinated aryl-Bneop substrates were not examined.

In 2010, Lin, Marder, *et al.* reported DFT calculations on the mechanism of the above reaction using [(NHC)Cu(OMe)] as a model complex and phenyl-Bneop as the substrate.[94] They proposed that the catalytic carboxylation occurs *via* three major steps (Scheme 39): (i) base-assisted transmetallation of phenyl-Bneop with [(NHC)CuCl] to give [(NHC)CuPh]; (ii) rate determining insertion of CO_2 into the Cu–Ph bond to give [(NHC)Cu-OC(O)Ph]; and, finally (iii) this intermediate reacts with the alkoxy adduct of phenyl-Bneop to release the benzoate product and regenerate the catalyst.

The carboxylation of fluorinated aryl-Bneop derivatives was also reported by Nolan *et al.* in 2014 using an NHC-nickel complex as the catalyst.[95] Among the nickel complexes examined for this reaction, [Ni-

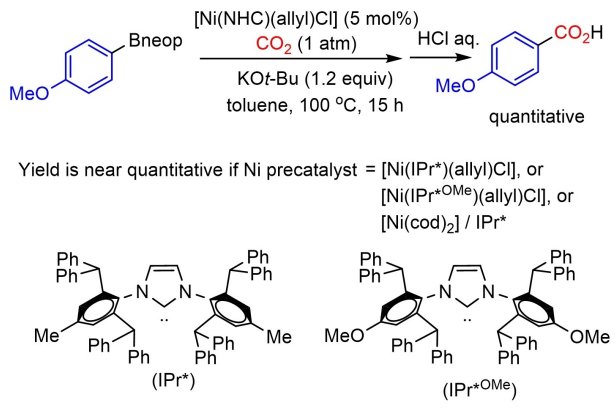


Scheme 38. Scope of the copper-catalyzed carboxylation of electron-deficient aryl-Bneop compounds.[93]

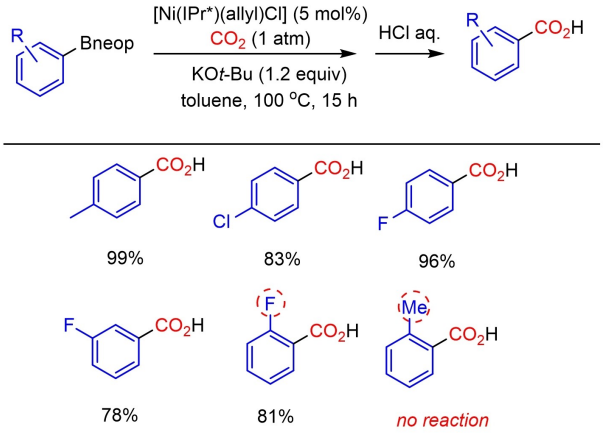


Scheme 39. Proposed mechanism of the copper-catalyzed carboxylation of phenyl-Bneop.[94]

(IPr*)(allyl)Cl] and [Ni(IPr*^{OMe})(allyl)Cl] were found to give carboxylation products in near quantitative yields (Scheme 40). It should be noted that the reaction can be conducted using a catalyst system formed *in situ* from [Ni(cod)$_2$] and IPr*. Reactions are viable for aryl-Bneop derivatives bearing electron-rich or electron-poor substituents to give the corresponding carboxylation products in good to excellent yields (Scheme 41). However, this method was not effective for aryl-Bneop derivatives bearing sterically bulky substituents at the *ortho*-position. Interestingly, no reaction was observed using other aryl boron reagents such as boronic acids, pinacolates, or potassium trifluoroborates. It was suggested that the addition of a strong base, such as KO*t*-Bu, accelerated the trans-



Scheme 40. Optimized conditions for nickel-catalyzed carboxylations.[95]

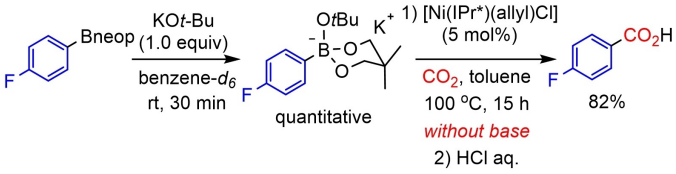


Scheme 41. The scope of nickel-catalyzed carboxylations.[95]

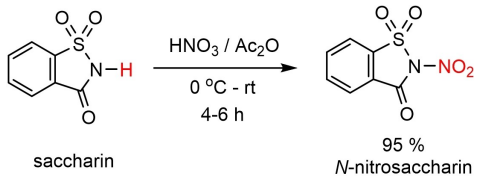
metalation step and the overall reaction of 4-fluorophenyl-Bneop (Scheme 42). Further carboxylation of the aryltrialkoxyborate gave the corresponding carboxylic acid in good yield even without the addition of base.

4.1.5. Conversion of Fluorinated Aryl Boronates to Nitro Arenes

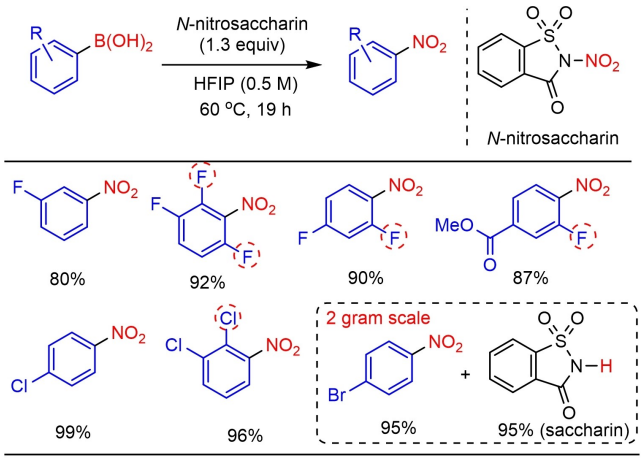
Nitroaromatic compounds are highly useful synthons in pharmaceutical chemistry.[96] Although no examples of the conversion of aryl boronate esters into their nitroaromatic counterparts have been reported, these useful compounds can be prepared using aryl boronic acids[97] or trifluoroborate salts.[98] Recently, Katayev *et al.* reported the conversion of aryl boronic acids into their nitro analogues using non-metal, recyclable, and bench-stable nitrating reagents, such as *N*-nitrosaccharin.[97] *N*-Nitrosaccharin was readily synthesized from the reaction of a saccharin solution in acetic anhydride with nitric acid (Scheme 43). The reaction of electron-deficient aryl boronic acids with 1.3 equivalents of *N*-nitrosaccharin in 0.6 M hexafluoroisopropanol at 60 °C for 19 hours gave the corresponding aromatic nitro compounds in good to excellent yield (Scheme 44). Notably, high conversion was also observed for unstable and challenging substrates such as aryl boronic acids containing two *ortho*-fluorine



Scheme 42. The role of KOtBu in transmetalation reactions of aryl-Bneop compounds.[95]



Scheme 43. Synthesis of N-nitrosaccharin.[97]



Scheme 44. Ipso-Nitration of aryl boronic acids using N-nitrosaccharin as the nitrating reagent.[97]

groups and the reaction could be scaled up to the gram level.

4.1.6. Conversion of Fluorinated Aryl Boronates to Cyanoarenes

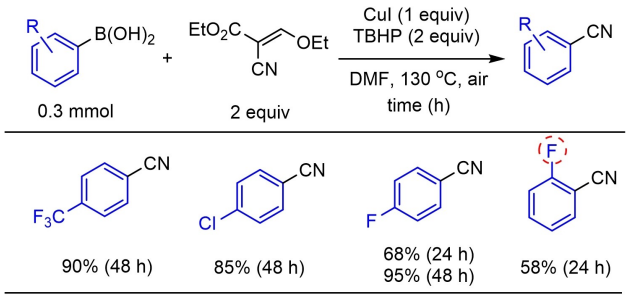
Introducing cyano groups into drug candidates frequently improves the pharmacodynamics and pharmacokinetics of the molecules.[99] In 2012, Hartwig *et al.* reported that an iridium-catalyzed arene C–H borylation, followed by a copper-mediated cyanation using $Zn(CN)_2$ and a stoichiometric amount of a base, such as CsF, afforded the corresponding desired cyano products.[100] In 2013, Han *et al.* showed that a combination of Cu_2O/*N,N*′-dimethylethylenediamine (DMEDA) catalyzed the cyanation of aryl pinacol boronate esters in the presence of trimethylsilyl cyanide (TMSCN).[101] In 2006, Liebeskind *et al.* reported the palladium-catalyzed/copper-mediated cyanation of aryl boronic acids with benzylthiocyanate as a CN source.[102] In 2016, Senanayake *et al.* reported a low loading $[Rh(cod)Cl]_2$-catalyzed cyanation of aryl boronic acids with dimethylmalononitrile (DMMN) in the presence of a stoichiometric amount of base, such as Cs_2CO_3.[103] The cyanation of *ortho*-fluorinated aryl boronic acids was reported by Qi *et al.* in 2016.[104] In this study, the cyanation of aryl boronic acids was achieved using 2 equivalents of ethyl (ethoxymethylene)cyanoacetate as the CN source in the presence of 1 equivalent of copper iodide and 2 equivalents of *tert*-butyl hydroperoxide (TBHP) as the oxidant. As shown in Scheme 45, these reactions tolerated aryl boronic acid substrates bearing electron-withdrawing substituents such as trifluoromethyl, chlorine, and fluorine at the *ortho*- or *para*-positions to give cyanoarenes in excellent yields after 48 hours. However, the cyanation of aryl boronic acids bearing two *ortho*-fluorine groups was not examined.

4.1.7. Methyl Esterification of Fluorinated Aryl Boronates

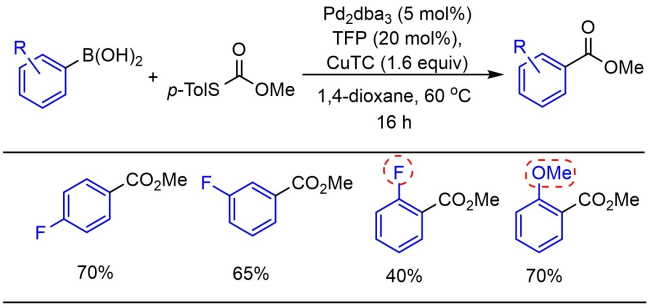
Aryl carboxylate esters are another important class of compounds in organic synthesis and pharmaceutical chemistry.[105] The esterification of fluorinated aryl boronates was initially reported by Xu and Dai *et al.*[106] In this study, *O*-methyl *S*-*p*-toluenyl thiocarbonate was used as the methoxy carbonylation reagent. A catalytic amount of $[Pd_2(dba)_3]$/TFP (TFP = tri(2-furyl)phosphine) was used as the catalyst system, in the presence of stoichiometric amounts of copper(I) thiophene-2-carboxylate (CuTC). Previously, CuTC salts were proposed in the Liebeskind-Srogl cross-coupling reaction to have a role in forming a strong Cu–S bond with the thioester, thus accelerating the transmetalation step with the palladium catalyst.[107] As shown in Scheme 46, the reaction is viable for aryl boronic acids bearing a fluorine substituent in either the *para*- or *meta*-position. In general, reactions using *ortho*-electron-donating substituents gave higher yields that those containing electron-withdrawing substituents.

4.1.8. Conversion of Fluorinated Aryl Boronates to Aldehydes

Compounds containing an aldehyde group are important synthons in organic synthesis as they can readily be transformed into a plethora of functional groups. For example, Vemuravenib, which is used for treat-

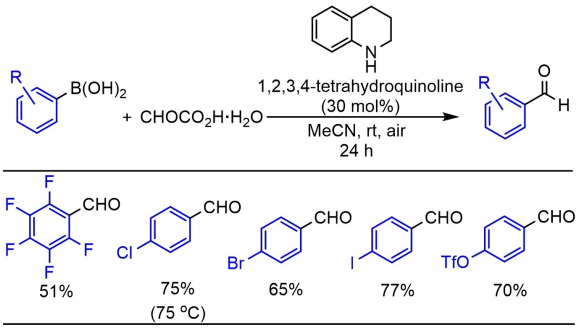


Scheme 45. Copper-promoted cyanation of aryl boronic acids with ethyl (ethoxymethylene)cyanoacetate as the cyanating agent.[104]

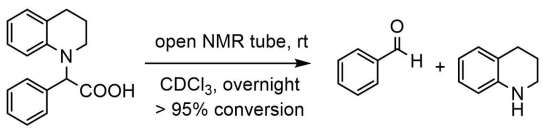


Scheme 46. Palladium-catalyzed esterification of aryl boronic acids.[106]

ment of late-stage melanoma, and Sitagliptin, which is a promising antidiabetic candidate, are synthesized from fluorinated benzaldehyde derivatives (Figure 1).[1] In 2017, Wang *et al.* reported a method to convert aryl boronic acids to aldehydes in the presence of glyoxylic acid monohydrate and 1,2,3,4-tetrahydroquinoline acting as an organocatalyst.[108] This method was successful using the challenging substrate, $C_6F_5B(OH)_2$, to give 2,3,4,5,6-pentafluorobenzaldehyde in a fair yield (51%). Interestingly, this reaction was tolerant of aryl boronic acids bearing reactive groups such as *para*-chlorine, bromine, iodine, and triflate (Scheme 47). The reaction was proposed to involve a Petasis intermediate, whereupon independent synthesis of this species followed by treatment with $CDCl_3$ in air afforded benzaldehyde quantitatively (Scheme 48).



Scheme 47. Amine-catalyzed formylation of aryl boronic acids with glyoxylic acid.[108]



Scheme 48. Conversion of a Pestasis intermediate to give benzaldehyde.[108]

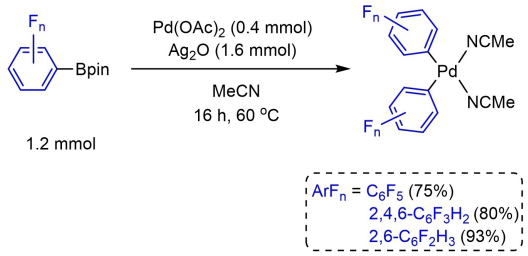
4.2. Homocoupling Reaction

4.2.1. Palladium-Catalyzed Homocoupling of Polyfluorophenyl Boronate Esters

In transition metal catalysis, reductive elimination is an important step to release the coupled products.[109,110] Indeed, two electronic effects play an important role in the reductive elimination of $[ML_2(Ar)(Ar')]$ complexes containing group-10 metals to form biaryl compounds Ar–Ar′. Reductive elimination is favorable if the ancillary ligands are weak electron donors or strong π-acceptors.[111] Furthermore, the rate of reductive elimination of Ar–Ar′ from these complexes decreases in the order $Ar_{rich}–Ar'_{poor} > Ar_{rich}–Ar'_{rich} > Ar_{poor}–Ar'_{poor}$ (Ar_{rich} = electron rich aryl; Ar_{poor} = electron poor aryl). Moreover, reductive elimination of very electron poor diaryls, such as $C_6F_5–C_6F_5$, is challenging owing to the strong metal–C_{aryl} bonds.[112-114]

In 2011, Menezes and Oliveira *et al.* reported optimized conditions for the homocoupling of potassium aryl trifluoroborates salts in aqueous media.[115] However, if the aryl groups contain two *ortho*-fluorine substituents, homocoupling products were not observed. In 2020, Radius and Marder *et al.*[116] reported an efficient palladium-catalyzed homocoupling reaction of aryl pinacol boronates containing two *ortho*-fluorine groups. Reactions conducted in noncoordinating solvents such as toluene, benzene, or *m*-xylene were found to promote reductive elimination in the absence of ancillary ligands or coordinating solvents. Indeed, reactions conducted in weakly coordinating solvents were impeded by the formation of stable complexes of the type *cis*-$[PdL_2(Ar_F)_2]$.

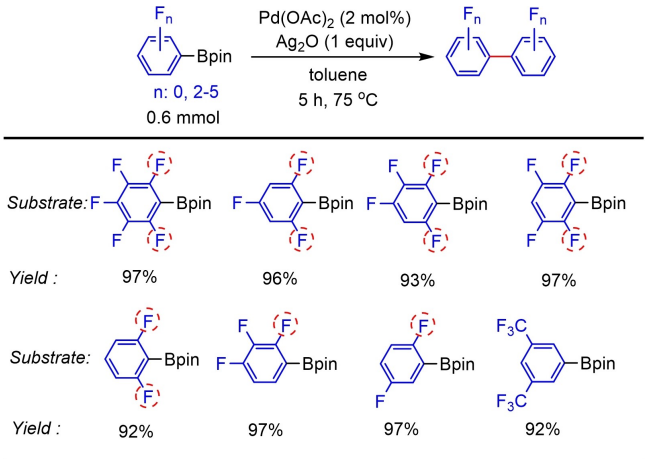
In this same investigation, the palladium-catalyzed homocoupling of fluorinated aryl-Bpin compounds was conducted in the presence of stochiometric amounts of silver oxide, which acted not only as an oxidant but also had a role in facilitation of the transmetalation step (see Section 4.3.3 for the role of Ag_2O in transmetalation). Only reactions of aryl–Bpin compounds containing one *ortho*-fluorine group proved successful. Further investigation showed that stoichiometric reactions of C_6F_5Bpin, 2,4,6-trifluorophenyl–Bpin, and 2,6-difluorophenyl–Bpin with palladium acetate in MeCN once again resulted in the formation of the stable complexes *cis*-$[Pd(NCMe)_2(C_6F_5)_2]$, *cis*-$[Pd(NCMe)_2(2,4,6\text{-}C_6F_3H_2)_2]$, and *cis*-$[Pd(NCMe)_2(2,6\text{-}C_6F_2H_3)_2]$, respectively (Scheme 49). Thus, it was concluded that: (i) reductive elimination from $[PdL_2(Ar)_2]$ is problematic if the aryl ring contains two *ortho*-fluorines; and (ii) the use of weakly coordinating solvents, such as MeCN, generate stable complexes that shut down the homocoupling reaction. Therefore, the use of 'noncoordinating' arene solvents such as toluene, benzene, or *m*-xylene was required for the homocoupling of $2,6\text{-}C_6F_{2+n}H_{3-n}$Bpin



Scheme 49. Synthesis of *cis*-[Pd(NCMe)$_2$(Ar$_{Fn}$)$_2$].[116]

in excellent yields as long as no stronger coordinating solvents or ligands are present (Scheme 50).

DFT calculations at the B3LYP–D3/def2-TZVP/6-311 + g(2d,p)/IEFPCM // B3LYP–D3/SDD/6-31 g**/IEFPCM level of theory were performed, which indicated an exergonic process and lower barrier (< 21 kcal/mol) for the reductive elimination of [Pd(C$_6$F$_5$)$_2$] complexes bearing arene ligands, compared to stronger coordinating solvents or ancillary ligands (acetonitrile, THF, SMe$_2$, and PMe$_3$), which showed not only an endergonic process, but also required high energy barriers (> 34 kcal/mol). The reductive elimination from [Pd(η^n-arene)(C$_6$F$_5$)$_2$] has a low barrier due to: (i) ring slippage of the arene ligand as the hapticity changes from η^6 in the reactant to η^n (n ≤ 3) in the transition state and the product, which led to less σ-repulsion; and (ii) more favorable π-back-bonding from [Pd(Ar$_F$)$_2$] to the arene ligand in the transition state. These findings support the experimental results, which showed that the palladium-catalyzed homocoupling of 2,6-difluoro-aryl-Bpin derivatives is efficient in aromatic solvents.



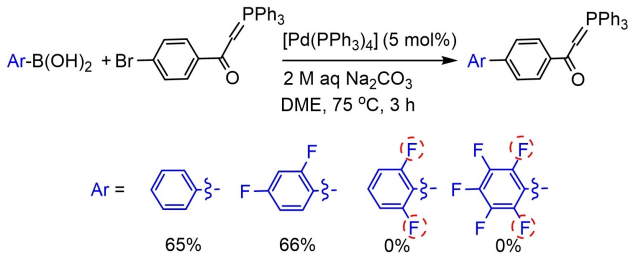
Scheme 50. Palladium-catalyzed homocoupling of fluorinated aryl pinacol boronates in toluene.[116]

4.3. Suzuki-Miyaura Cross-Coupling

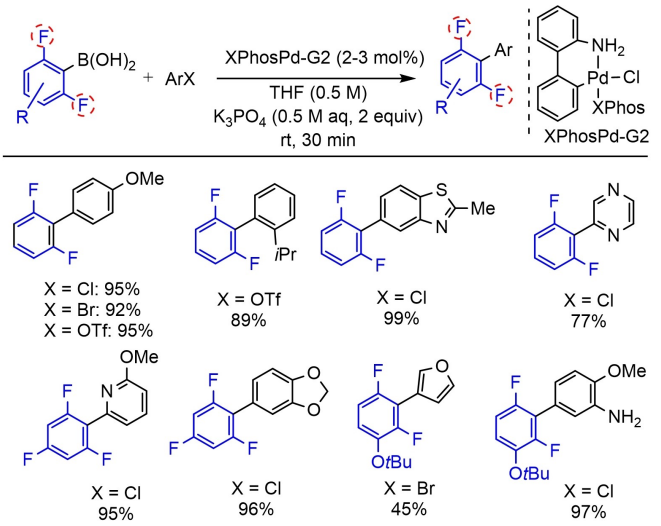
4.3.1. Palladium-Catalyzed Suzuki-Miyaura Cross-Coupling to Polyfluorophenyl Boronic Acids and Esters

The Suzuki-Miyaura cross-coupling reaction is well known as one of the most important methodologies for generating a C–C bond and has been widely utilized in the synthesis of natural products and in materials chemistry, including large-scale production.[117–119] However, employing fluorinated aryl boronates that contain two *ortho*-fluorines in this reaction has been challenging.[120–124] For example, Thiemann *et al.* reported optimized conditions for the palladium-catalyzed Suzuki-Miyaura cross-coupling of 4-bromobenzoylmethylidenetriphenylphosphorane with fluorine-containing aryl boronic acids in good yields in some cases (Scheme 51).[122] However, under these conditions, if the aryl boronic acids had two *ortho*-fluorines, e.g., 2,6-difluorophenylboronic acid and pentafluorophenylboronic acid, the corresponding cross-coupled products were not observed. The reaction was only efficient for aryl boronic acid compounds bearing one *ortho*-fluorine.

In 2010, Buchwald *et al.* showed that the rate of transmetalation was accelerated by an increased number of fluorine substituents and that compounds containing *ortho*-fluorine groups displayed the highest activities.[125] The precatalyst XPhosPd–G2 (Scheme 52) provided an active XPhosPd(0) species which underwent oxidative addition *in situ* and enhanced the cross-coupling rate. The rate of protodeboronation of polyfluorophenyl boronic acids was impeded by employing 0.5 M K$_3$PO$_4$ in THF at room temperature. These reactions were efficient for the Suzuki-Miyaura cross-coupling of 2,6-difluorophenylboronic acids derivatives with aryl bromides, chlorides, and triflates, but poor yields were observed using aryl iodides. The protodeboronation of 2,3,6-trifluorophenylboronic acid was rapid and poor yields were observed. This observation was supported by Lloyd-Jones *et al.* who showed that aryl boronic acids containing fluorine substituents at both the *ortho*- and



Scheme 51. Palladium-catalyzed cross-coupling of phosphoranes with aryl boronic acids.[122]

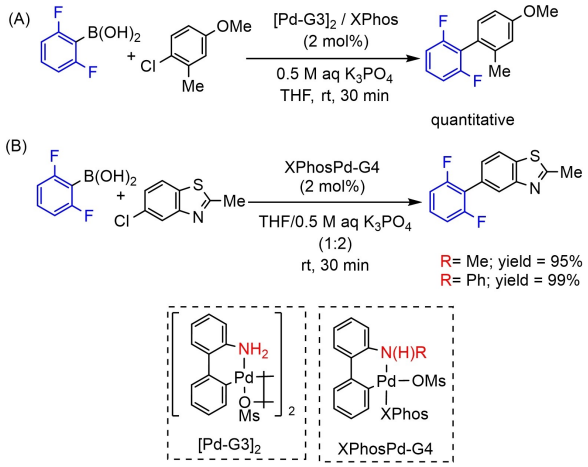


Scheme 52. Buchwald Pd–G2 precatalyst for Suzuki-Miyaura cross-coupling of polyfluorophenylboronic acids with aryl halides.[125]

meta-positions were susceptible to rapid protodeboronation.[26]

Later, Buchwald *et al.* replaced the precatalyst Pd–G2 with Pd–G3, by exchanging the chloride ligand at Pd–G2 with a noncoordinating methanesulfonate ligand (MS).[126] However, activation of the precatalyst LPd–G3 to generate LPd(0) often resulted in a carbazole byproduct that reacted with the starting materials and made the isolation of products challenging (Scheme 53). It is important to note that there is a significant health risk associated with NH_2-aminobiphenyl impurities in pharmaceuticals.[127]

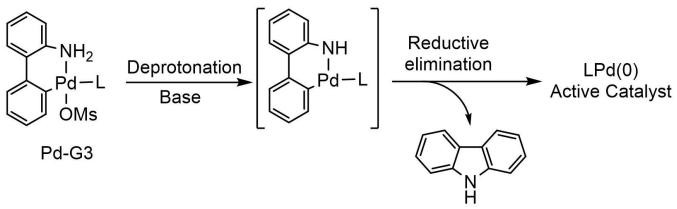
Further development generated precatalysts *via* the replacement of the NH_2-aminobiphenyl ligand of Pd–G3 with *N*-methyl or *N*-phenyl analogues to generate Pd–G4.[128] Similar to Pd–G2, XPhos was also reported to be the optimal ligand in reactions with the dimer of Pd–G3 or the monomer of Pd–G4 for the Suzuki-Miyaura cross-coupling of 2,6-difluorophenyl boronic acid with aryl halides. Under these conditions, cross-coupled products were afforded in excellent yields (Scheme 54).[126,128]



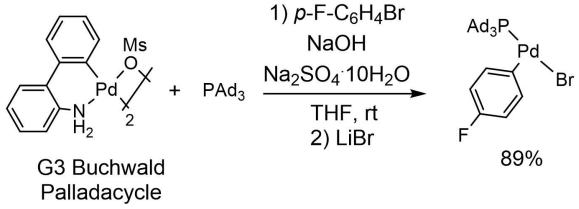
Scheme 54. Buchwald (A) Pd–G3 or (B) Pd–G4 precatalysts for the cross-coupling of 2,6-difluorophenyl boronic acids with aryl chlorides.[126,128]

In 2018, Carrow *et al.* synthesized a series of unsaturated complexes of the type [Pd(L)(Ar)X], including [Pd(PAd_3)(*p*-FC_6H_4)Br] (Carrow precatalyst; PAd_3 = tri(1-adamantyl)phosphine), which was found to be an efficient 'on-cycle' precatalyst.[75] This system allowed for the Suzuki-Miyaura cross-couplings of highly fluorinated aryl boronic acids with aryl or heteroaryl bromides and proved to be faster than the competing protodeboronation degradation pathway. The synthesis of the precatalyst proceeded *via* a room temperature reaction of the G3 Buchwald palladacycle with 1-bromo-4-fluorobenzene (Scheme 55). The catalytic process initially occurred *via* deprotonation of the PAd_3-palladacycle G3 using sodium hydroxide, which led to the C–N reductive elimination of carbazole and the generation of an active species [Pd(PAd_3)]. The Pd(0) species generated is then believed to be trapped by 1-bromo-4-fluorobenzene, undergoing oxidative addition to give [Pd(PAd_3)(*p*-FC_6H_4)Br]. It is important to note that this T-shaped precatalyst is stable in air, under moisture, and on silica gel, which allows its easy purification *via* flash chromatography.

Treating a mixture containing $C_6F_5B(OH)_2$ with 1-bromo-4-fluorobenzene, 1 mol% of [Pd(PAd_3)(*p*-FC_6H_4)Br] with 1.1 equivalent of Et_3N at room temper-



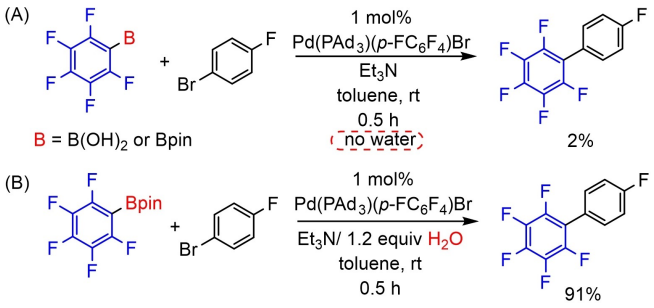
Scheme 53. Activation of the Buchwald Pd–G3 precatalyst.[126]



Scheme 55. Synthesis of Pd(PAd_3)(p-FC_6F_4)Br.[75]

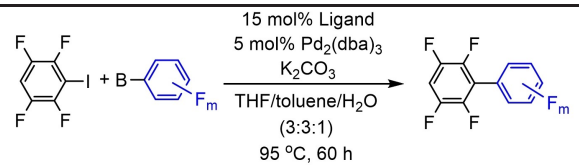
ature, afforded the corresponding cross-coupled product in only 2% yield (Scheme 56A). However, for reactions employing C_6F_5Bpin, an increased yield of 91% was obtained upon addition of 1.2 equivalents of water to the mixture (Scheme 56B). Unlike C_6F_5Bpin, which is more stable to wet triethylamine, $C_6F_5B(OH)_2$ decomposes within minutes to give C_6F_5H in 99% yield (see Section 3, Chart 1). Thus, the authors proposed that careful addition of water may facilitate a fast equilibration between boronic acid and its ester analogues, the former being more reactive for transmetalation and the later being more stabile to protodeboronation. Notably, using insoluble salts such as $Na_2SO_4{\cdot}10H_2O$ as a source of water which can be released slowly in the reaction gave the highest yield in 93%. On the other hand, reactions with $C_6F_5B(OH)_2$ were still ineffective. These optimized conditions are appropriate for coupling various fluorinated aryl boronic acids or esters with aryl bromides and hetero aryl bromides in good yields.

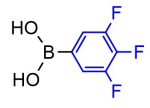
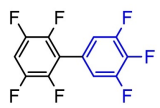
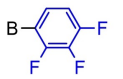
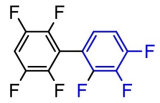
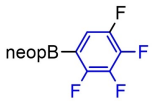
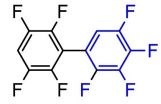
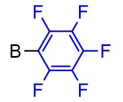
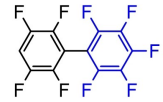
In 2017, Bulfield and Huber reported methods for the synthesis of polyfluorinated biphenyls, with fluorine substituents being present in both coupling partners.[123] They employed a combination of 5 mol% of $[Pd_2(dba)_3]$ and 15 mol% of a phosphine ligand to couple fluorinated aryl boronates with fluorinated aryl halides. The reactions required K_2CO_3 as a base and long reaction times of 60 hours at 95 °C. They also selected different phosphine ligands to optimize each cross-coupling reaction that employed different fluorine substituents on aryl boronates and aryl halides. Selected examples are shown in Table 3 for the cross-coupling of 1,2,4,5-tetrafluoro-3-iodobenzene with different aryl boronates and ligands. Overall, aryl boronic acids that contain one *ortho*-fluorine group such as 2,3,4-trifluorophenyl boronic acid are still more difficult to undergo cross-coupling reactions than analogues with no *ortho*-fluorine groups, such as 3,4,5-trifluorophenyl boronic acid (Table 3, entries 1 and 2). However, better yields were obtained when neopentyl glycol boronic esters (Bneop) and (*N*-methyliminodiacetic acid) boronate (BMIDA) analogues were used (Table 3, entry 2). The most electron deficient substrate, however, pentafluorophenyl boronic acid, or its trifluoroborate salt analogue were not viable under these conditions. (Table 3, entry 4).



Scheme 56. Precatalyst $[Pd(PAd_3)(p\text{-}FC_6H_4)Br]$ for cross-coupling of $C_6F_5B(OH)_2$ or its C_6F_5Bpin with $(p\text{-}FC_6H_4)Br$: (A) without water; or (B) with addition of water.[75]

Table 3. Palladium-catalyzed Suzuki-Miyaura cross-coupling to achieve polyfluorinated biaryls.[123]



B-Ar_F	Product	Optimized yield (Ligand)
		98% (CyJohnPhos)
		28%, B: $B(OH)_2$ (XPhos); 84%, B: Bneop (DavePhos); 80%, B: BMIDA (CyJohnPhos)
		62% (DavePhos)
		0%, B: $B(OH)_2$; < 5%, B: BF_3^- salt

In 2012, Hartwig *et al.* reported a method to synthesize fluorinated biaryls *via* a one-pot, two-step process, i.e., iridium-catalyzed C–H borylation of fluoroarenes followed by Suzuki-Miyaura cross-coupling using a simple palladium catalyst (*vide supra*).[33] Using this method, borylation occurred selectively *ortho* to the fluorine substituent due to its small size and the steric repulsion of other bulkier substituents such as methoxy, carboxylate, and chloride groups, etc. Buchwald *et al.*[125,126,128] and Carrow *et al.*[75] showed that highly reactive palladium precatalysts were needed to employ unstable substrates such as 2,6-difluoroaryl boronic acid. Interestingly, in a further report, Hartwig *et al.* demonstrated that a combination of 1 mol% of $[Pd(dba)_2]$ and equimolar Q-phos (1,2,3,4,5-pentaphenyl-1′-(di-*tert*-butylphosphino)ferrocene) was sufficient to catalyze effectively the Suzuki-Miyaura cross-coupling of *in situ* generated 2,3-difluoroaryl and 2,6-difluoroaryl pinacol boronate esters with aryl bromides. The Suzuki-Miyaura cross-coupling reaction was conducted in the presence of K_3PO_4 as a base in a mixture of dioxane and water (10:1), at 50 °C for 18 h.

As shown in Scheme 57, the cross-coupled products were generated in good yields.

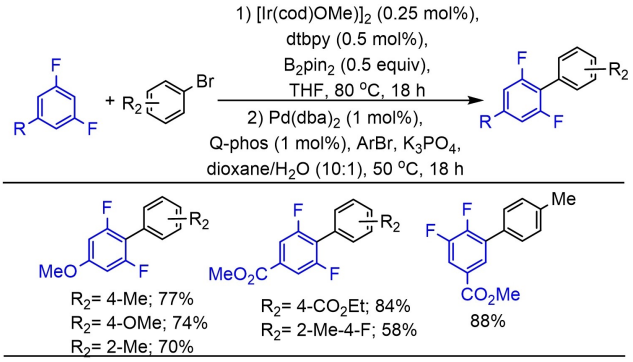
The Lewis acidity of the boron atom is important for the reactivity of organoboron compounds in cross-coupling reactions. In 2007, Suginome *et al.* introduced protected analogues of aryl boronates, namely aryl-Bdan (dan = naphthalene-1,8-diaminato) derivatives, for which the C–B bond is less reactive due to the reduced Lewis acidity of the boron atom.[129] In 2020, Saito *et al.*[130] and Tsuchimoto *et al.*[131] reported a method to apply aryl-Bdan compounds in Suzuki-Miyaura cross-coupling reactions. Indeed, Saito *et al.*[130] reported examples of different polyfluorophenyl-Bdan derivatives, especially C_6F_5Bdan, that were coupled without difficulty with aryl iodides using a combination of common palladium catalyst precursors such as $[Pd_2(dba)_3]\cdot CHCl_3$ and ligands such as XPhos. The reactions were conducted in the presence of a 1 M solution of KO*t*-Bu/THF, in toluene, at 70 °C for 24 hours to give cross-coupled products in good yields (Scheme 58). Under these conditions, the addition of water inhibits the palladium-catalyzed cross-coupling process of aryl-Bdan with the aryl iodide. In contrast, Carrow *et al.*[75] previously reported that the addition of water was required to improve the performance of the palladium-catalyzed cross-coupling of aryl pinacol boronates with aryl bromides (Scheme 56).

It should be mentioned that Cammers-Goodwin *et al.* showed that $C_6F_5B(OH)_2$ is susceptible to nucleophilic attack at its *para*-carbon atom to replace the *para*-fluoro-substituent with potassium *tert*-butoxide (KO*t*-Bu).[132] However, the method described by Saito *et al.*[130] above used excess strong base, such as a 1 M solution of KO*t*-Bu in THF, but, interestingly, attack at the *para*-carbon was not mentioned.

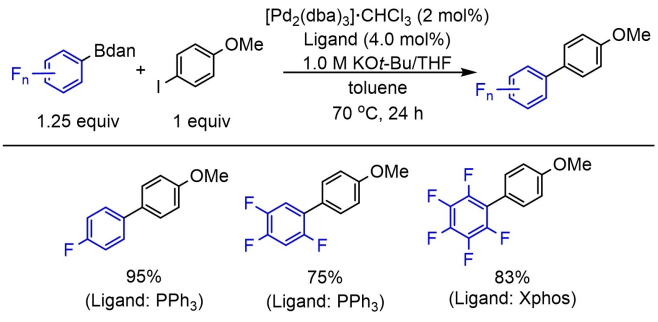
4.3.2. Palladium-Catalyzed Suzuki-Miyaura Cross-Coupling of Polyfluorophenyl Borate Salts

In 2003, Frohn and Adonin *et al.*[133] reported the application of lithium polyfluorophenyltrimethoxyborates Ar_F–$B(OMe)_3Li$ in Suzuki Miyaura cross-coupling reactions under base-free conditions. They observed optimal yields using $C_6F_5B(OMe)_3Li$ and 4-fluoroiodobenzene along with 10 mol% of $[Pd(PPh_3)_4]$ as a catalyst (Scheme 59). However, the same conditions were not effective for other Ar_F–$B(OMe)_3Li$ substrates containing hydrogen substituents, but the yields could be improved using 10 mol% of $[Pd(OAc)_2]$ as the catalyst precursor and DME as the solvent. The authors showed that fluorinated aryl-$B(OMe)_3Li$ compounds were more reactive and gave better yields than their potassium trifluoroborate salt analogues.[134] Notably, the yield of the cross-coupled product from the reaction of $C_6F_5B(OMe)_3Li$ with 4-fluoroiodobenzene was improved by the addition of stochiometric amounts of silver oxide.

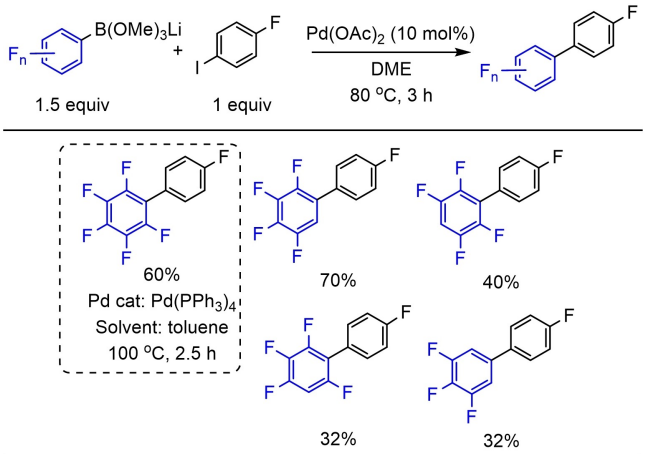
In 2003, Molander *et al.*[135] reported an effective method using a low loading of $[Pd(dppf)Cl_2]\cdot CH_2Cl_2$ to catalyze the Suzuki-Miyaura cross-coupling of aryl halides with potassium heteroaryltrifluoroborate salts. These authors demonstrated that 2,6-difluorophenyl-



Scheme 57. Iridium-catalyzed C–H borylation / palladium-catalyzed cross-coupling of fluoroarenes with aryl bromides.[33]



Scheme 58. Palladium-catalyzed Suzuki-Miyaura cross-coupling of polyfluoroaryl-Bdan and aryl iodide.[130]



Scheme 59. Palladium-catalyzed cross-coupling of fluorinated aryl-$B(OMe)_3Li$ with 4-fluoroiodobenzene.[133]

BF_3K was a viable substrate in the reaction (Scheme 60A), but also that this method was less effective in reactions employing $C_6F_5BF_3K$ (Scheme 60B).

4.3.3. Silver Oxide-Assisted Palladium-Catalyzed Suzuki-Miyaura Cross-Coupling Reaction of Fluorinated Aryl Boronic Acids or Borate Salts

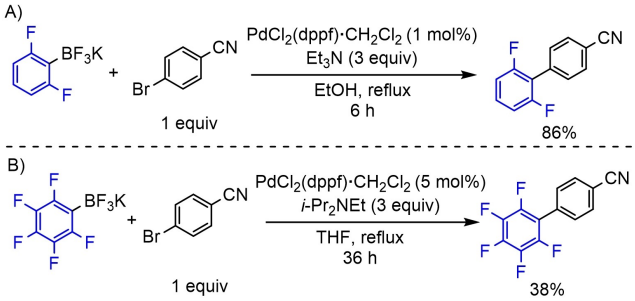
In 1987, Kishi *et al.*[136] reported that rates of the palladium-catalyzed Suzuki-Miyaura cross-coupling reaction are 30 times faster in the presence of silver oxide (Ag_2O) compared to those reactions using common bases such as potassium hydroxide. In 2003, Osakada *et al.*[137] showed that the reaction of $[Pd(PEt_3)_2(C_6F_5)I]$ with Ag_2O in toluene-water gave the stable complex $[Pd(PEt_3)_2(C_6F_5)OH]$ with concomitant formation of silver iodide (AgI). Furthermore, $[Pd(PEt_3)_2(C_6F_5)OH]$ underwent transmetalation with 4-methoxyphenylboronic acid followed by reductive elimination to give the corresponding fluorinated biphenyl product. Thus, it was suggested that Ag_2O replaces the halide ligand (X) in $[PdL_2(Ar)X]$ with an OH ligand, to give an hydroxy-palladium species that has a higher affinity for transmetalation.

As Ag_2O is known to accelerate the transmetalation of arylboronates (*vide supra*), this phenomenon was exploited to accelerate the Suzuki-Miyaura cross-coupling with, e.g., 2,6-difluoro-substituted arylboronate substrates. In 2005, Korenaga *et al.* employed 3 mol% of $[Pd(PPh_3)_4]$ as a catalyst precursor, and CsF as a base, to achieve the cross-coupling of $C_6F_5B(OH)_2$ with iodobenzene in DME at 70 °C (Scheme 61A).[138] It should be noted that using KO*t*-Bu as a base also accelerated this reaction, but it gave the byproduct *p*-(*t*-BuO)–C_6F_4–C_6H_5 in 30% yield (Scheme 61B). It is known that the *para*-position of pentafluorophenyl is susceptible to nucleophilic attack to replace the *para*-fluoro-substituent at $C_6F_5B(OH)_2$ with an alkoxide base.[132]

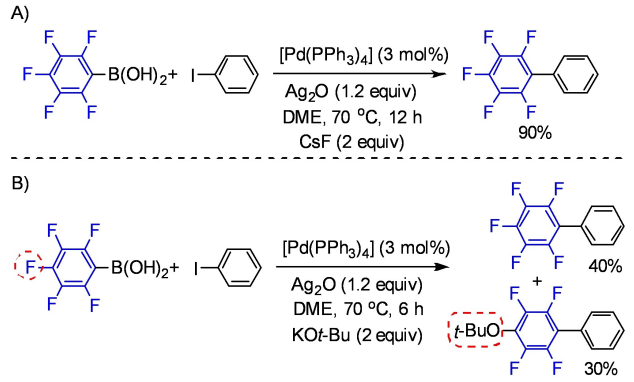
Furthermore, Korenaga *et al.*[138] reported optimized conditions for the use of aryl bromide instead of aryl iodide substrates and demonstrated that a combination of 2.5 mol% of $[Pd_2(dba)_3]$ and 6 mol% of P(*t*-Bu)$_3$ in DMF, at 100 °C, for 12 hours, gave the cross-coupled products in fair to good yields (Scheme 62). Overall, electron-rich aryl bromides afforded the cross-coupled products in more than 90% yield and were consequently more favorable compared to electron-poor aryl bromides. However, sterically hindered electron-rich aryl bromides, such as 2-methyl-phenylboronic acid, gave the cross-coupled product in only 54%. Less efficient cross-coupling was found employing phenyl chloride or triflate instead of the analogous bromide to give the corresponding products in 39% and 4% yield, respectively.

In 2005, Takimiya *et al.* reported the Suzuki-Miyaura cross-coupling reaction employing heteroarenes, such as 2-bromothiophene derivatives with $C_6F_5B(OH)_2$.[139] For example, using pentafluorophenyl boronic acid with 2-bromothiophene with 8 mol% $[Pd(PPh_3)_4]$ along with an excess of K_3PO_4 and Ag_2O, led to the cross-coupled product in moderate yield (Scheme 63).

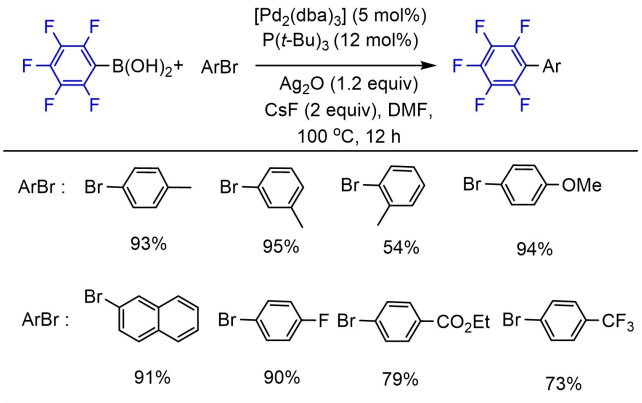
In 2002, Frohn and Adonin *et al.*[140] reported optimized conditions for the Suzuki-Miyaura cross-



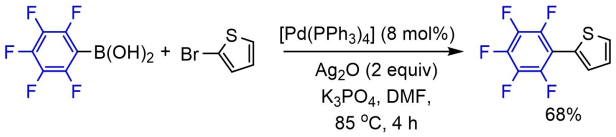
Scheme 60. Palladium-catalyzed cross-coupling of potassium fluorinated-aryltrifluoroborates with 4-bromobenzonitrile.[135]



Scheme 61. Ag_2O-assisted palladium-catalyzed cross-coupling of $C_6F_5B(OH)_2$ with iodobenzene.[138]



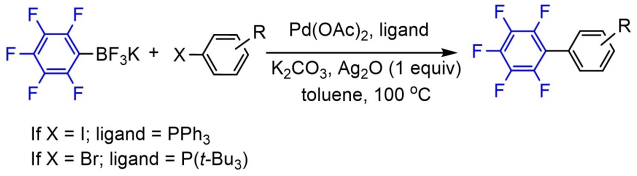
Scheme 62. Ag_2O-assisted palladium-catalyzed cross-coupling of $C_6F_5B(OH)_2$ with aryl bromides.[138]



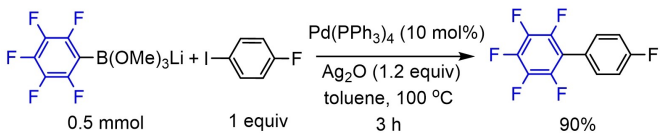
Scheme 63. Palladium-catalyzed cross-coupling of pentafluorophenyl boronic acid with 2-bromothiophene.[139]

coupling of potassium pentafluorophenyltrifluoroborate ($C_6F_5BF_3K$), which was chosen as it is more stable in the presence of base compared to its boronic acid analogue. Thus, a combination of 10 mol% of [Pd(OAc)$_2$], 20 mol% of PPh_3, and 2 equivalents of K_2CO_3 catalyzed the Suzuki-Miyaura cross-coupling of $C_6F_5BF_3K$ with aryl iodides in toluene at 100 °C within 3 hours. However, this reaction only gave the corresponding products in good yields in the presence of stoichiometric amounts of Ag_2O (Scheme 64). In 2015, Adonin *et al.* extended his method to cross-couple $C_6F_5BF_3K$ with aryl bromides.[141] In 2003, Frohn and Adonin *et al.* employed $C_6F_5B(OMe)_3Li$ instead of its $-BF_3K$ analogue and, interestingly, in this case sufficient yields were obtained without the presence of base, but stochiometric amounts of Ag_2O were necessary (Scheme 65).[133]

As mentioned in section 4.2, the palladium-catalyzed homocoupling of aryl pinacol boronates to generate symmetrical fluorinated biaryls with two *ortho*-fluorines in each ring must be conducted in arene solvents to reduce the energy barrier of the reductive elimination step.[116] It was previously mentioned in section 4.3.2 and Table 3 that Bulfield and Huber reported optimized conditions for constructing polyfluorobiphenyls *via* Suzuki-Miyaura cross-coupling of fluorinated aryl-boronic acid derivatives and fluorinated aryl halides, using a combination of [$Pd_2(dba)_3$] and phosphine ligands in good to excellent yields;[123]



Scheme 64. Palladium-catalyzed cross-coupling of $C_6F_5BF_3K$ with aryl iodides and bromides.[140.141]



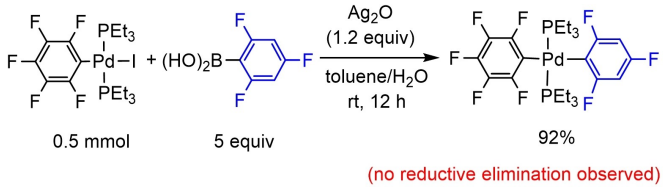
Scheme 65. Palladium-catalyzed cross-coupling of $C_6F_5B(OMe)_3Li$ with 1-fluoro-4-iodobenzene.[133]

however, the reaction failed to couple pentafluorophenyl boronic acid derivatives with 1,2,4,5-tetrafluoro-3-iodobenzene (Table 3, entry 4). Moreover, Osakada *et al.* reported the reaction of *trans*-[$Pd(PEt_3)_2(C_6F_5)I$] with 2,4,6-$C_6F_3H_2B(OH)_2$ in the presence of an excess of Ag_2O to give *trans*-[$Pd(PEt_3)_2(C_6F_5)$(2,4,6-$C_6F_3H_2$)] in 92% yield, but no reductive elimination product was observed (Scheme 66).[137]

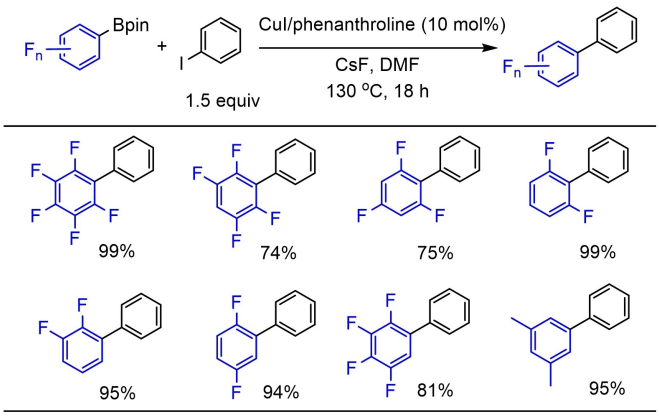
4.3.4. Copper-Catalyzed Suzuki-Miyaura Cross-Coupling of Fluorinated Aryl Boronic Esters

As described in sections 4.3.1–4.3.3, the palladium-catalyzed Suzuki-Miyaura cross-coupling of fluorinated aryl boronic acids requires one of the following methods to achieve acceptable to good yield: (i) a stoichiometric amount of silver oxide; (ii) a highly reactive palladium precatalyst such as second, third, and fourth generation Buchwald precatalysts or Carrow precatalysts; (iii) a one pot-two step iridium-catalyzed C–H borylation of fluoroarenes with B_2pin_2 followed by a palladium-catalyzed Suzuki-Miyaura cross-coupling reaction; or (iv) *via* protection of the boron using more stable moieties such as Bdan (*vide supra*). Several reports employing economically-viable and earth-abundant low toxicity metals, such as copper, as catalyst systems have been of recent significant interest for Suzuki-Miyaura cross-coupling reactions.[142–149] Thus, Radius and Marder reported the copper-catalyzed Suzuki-Miyaura cross-coupling of highly fluorinated aryl boronic esters with aryl halides.[17] A combination of 10 mol% copper iodide and 10 mol% phenanthroline with CsF as a base proved effective in the cross-coupling of fluorinated aryl pinacol boronates with aryl iodides to generate cross-coupled products in good to excellent yields (Scheme 67).

This method was also applicable to polyfluorophenyl borate salts such as pentafluorophenyl-BF_3K. Notably, slightly lower yields were obtained when employing 2,4,6-trifluorophenyl–Bpin and 2,3,5,6-tetrafluorophenyl–Bpin due to the formation of C–H arylation byproducts. It is known that C–H bonds that are flanked by two C–F bonds have a high acidity and can be directly arylated.[150–152] However, these results showed that C–Bpin groups are more reactive than C–H bonds within the arylation target. Cross-coupling



Scheme 66. Synthesis of *trans*-[$Pd(PEt_3)_2(C_6F_5)$(2,4,6-$C_6F_3H_2$)].[137]



Scheme 67. Copper-catalyzed cross-coupling of polyfluorophenyl–Bpin with phenyl iodide.[17]

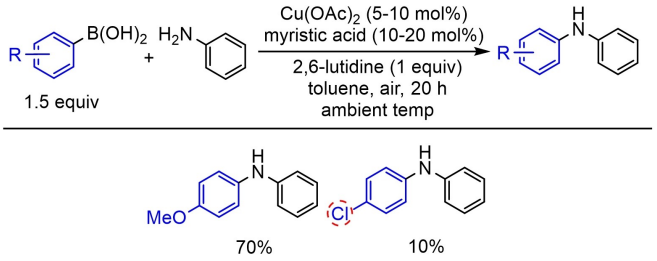
of aryl bromides instead of aryl iodides with polyfluoroaryl–Bpin is also possible if an increased amount of the CuI/phenanthroline catalyst in a mixture of DMF and toluene (1:1) is used.

4.4. C–N Cross-Coupling

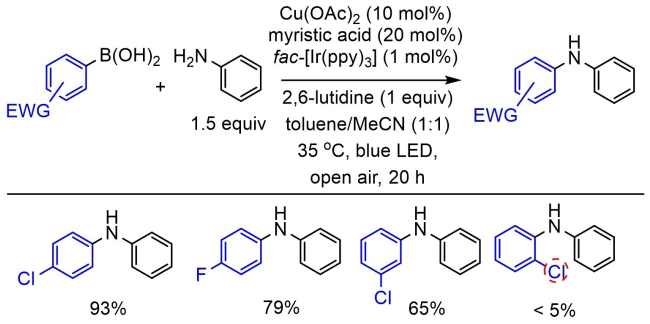
4.4.1. Copper-Catalyzed Chan-Evans-Lam C–N Cross-Coupling of Fluorinated Aryl Boronic Acids with Amines

Aromatic amines are widely utilized as important compounds in agrochemical[153] and pharmaceutical science.[154] A C–N cross-coupling reaction of aryl amines with aryl boronic acids or esters is a powerful way to approach the corresponding diarylamines, known as Chan-Evans-Lam cross-coupling reactions.[155–157] It should be mentioned that Chan-Evans-Lam cross-couplings to form C–N bonds are conveniently conducted using a copper catalyst system at room temperature, providing an advantageous route compared with cross-couplings of aryl halides using commonly employed yet commercially expensive, palladium precatalysts that required high temperatures for the reaction to go to completion.[158,159] In 2001, it was reported that the optimal conditions for the copper-catalyzed Chan-Evans-Lam cross-coupling of aryl amines with aryl boronic acids could be achieved in the presence of a low loading of added myristic acid along with stoichiometric amounts of 2,6-lutidine.[160] However, the reaction was not effective for aryl boronic acids bearing electron-withdrawing substituents such as chloride (Scheme 68).

In 2015, Kobayashi *et al.* optimized these conditions using copper(II) acetate as a catalyst and a *fac*-[Ir(ppy)$_3$] complex as a photocatalyst in the presence of blue LEDs and 2,6-lutidine as a base.[161] As shown in Scheme 69, this method is viable for the C–N cross-coupling employing aryl boronic acids bearing electron-withdrawing substituents such as chlorine or fluorine at the *para*-position and, not unexpectedly, was better than those with electron-withdrawing halides at the *meta*- or *ortho*-positions. Thus, solving this problem in C–N cross-coupling of anilines with aryl boronic acids bearing *ortho*-chlorine or *ortho*-fluorine might require conducting the reactions under base-free condition to slow down the protodeboronation.

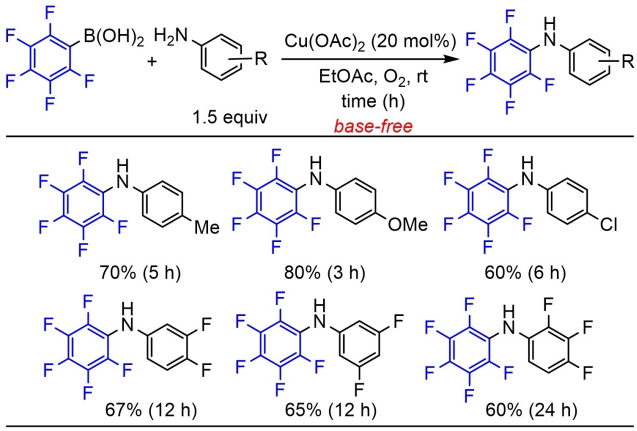


Scheme 68. Copper(II)-catalyzed N-arylation of aryl boronic acids with anilines.[160]



Scheme 69. Visible light-mediated C–N coupling of electron-deficient aryl boronic acids and aniline.[161]

However, prior to Kobayashi's report, in 2008, Su *et al.* reported the copper-catalyzed *N*-arylation reaction of pentafluorophenyl boronic acid with aniline.[162] The optimized reaction was conducted using copper(II) acetate as a precatalyst under an oxygen atmosphere and notably base-free conditions. As shown in Scheme 70, the cross-coupling reaction was tolerant of anilines containing aryl rings bearing electron-rich or electron-poor moieties, and the cross-coupled products were generated in moderate to good yields. It is important to note that the reaction failed in the presence of bases such as Et$_3$N or pyridine, due to the problematic protodeboronation issue. The reaction also failed when using a copper(I) precatalyst, such as copper iodide instead of a copper(II) catalyst, or in the absence of oxygen. It should be mentioned here that aside from the desired cross-coupling products, the reactions were contaminated by minor byproducts of

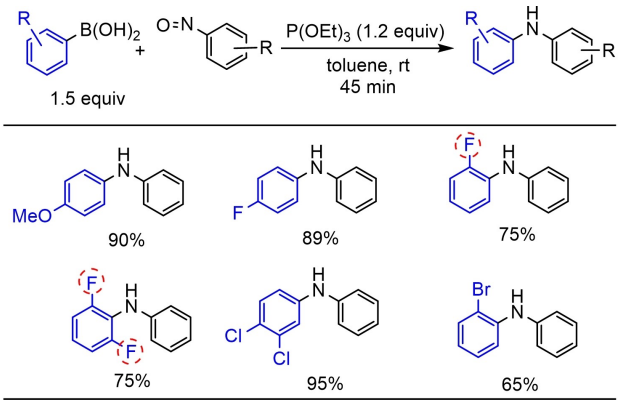


Scheme 70. Cu(II)-catalyzed N-arylation of $C_6F_5B(OH)_2$ with anilines.[162]

protodeboronation and homocoupling of pentafluorophenyl boronic acid. Interestingly, employing alkyl amines instead of anilines generated *N*-alkyl-2,2',3,3',4',5,5',6,6'-nona-fluorobiphenyl-4-amines in moderate yields (not shown).

4.4.2. Phosphine-Mediated Chan-Evans-Lam C–N Cross-Coupling of Fluorinated Aryl Boronic Acids with Nitrosoarenes

Another option to synthesize unsymmetrical diarylamines is *via* C–N cross-coupling of aryl boronic acids with nitrosoarenes. In 2018, Csákÿ *et al.* reported the coupling of aryl boronic acids with nitrosoarenes under transition metal-free and neutral (base-free) conditions.[163] Reactions were mediated by $P(OEt)_3$ in toluene to generate unsymmetrical diarylamines in fair to excellent yields at room temperature (Scheme 71). However, the desired coupling product was not observed when aryl pinacol boronates or potassium



Scheme 71. Phosphine-mediated C–N cross-coupling of aryl boronic acids with nitrosoarenes.[163]

trifluoroborates were used in place of the boronic acid analogues. The reaction tolerated sensitive substrates such as aryl boronic acids containing two *ortho*-fluorines, as base-free conditions slowed the decomposition protodeboronation pathways.

4.5. C–O Cross-Coupling

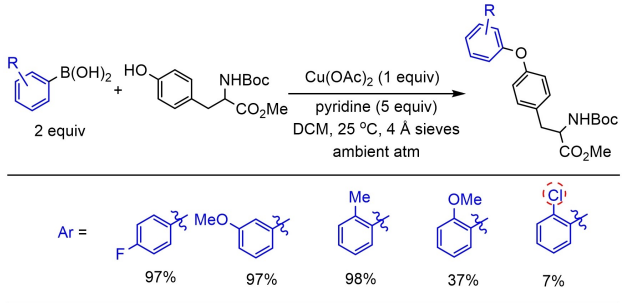
4.5.1. Challenges in the Chan-Evans-Lam C–O Cross-Coupling of ortho*-Electron-Withdrawing-Substituted Aryl Boronic Acids and Phenols to Form Diaryl Ethers*

In 1998, Evans *et al.* reported the synthesis of diaryl ethers *via* copper-promoted C–O cross-coupling of aryl boronic acids with phenols.[164] Reactions were conducted in the presence of 1 equivalent of [Cu(OAc)$_2$], 5 equivalents of pyridine using 4 Å molecular sieves in dichloromethane in air at 25 °C. Products were generated in good to excellent yields for aryl boronic acids bearing electron-donating groups at the *ortho*-, *meta*-, or *para*-positions (Scheme 72). Reactions were also viable for aryl boronic acids bearing electron-deficient substituents, such as fluorine, at the *para*- or *meta*-positions. However, the reaction was not effective if the electron-deficient substituent was at the *ortho*-position (7% yield) and the predominant pathway was, once again, derived from protodeborylation.

4.6. C–C(O) Cross-Coupling

4.6.1. Palladium-catalyzed C–C(O) Cross-Coupling of Fluorinated Aryl Boronic Acids and N*-(Aryl-carbonyloxy)phthalamides*

Aryl ketones are important aromatic compounds that have found many applications in medicinal chemistry.[1] In 2014, Sun *et al.* reported the C–C(O) cross-coupling of *N*-(aryl-carbonyloxy)phthalamides with aryl boronic acids.[165] These reactions were catalyzed by a low loading of [Pd(OAc)$_2$] and an NHC ligand that was formed *in situ* from a triazole-based



Scheme 72. Cu-promoted C–O cross-coupling of aryl boronic acids with phenol derivatives.[164]

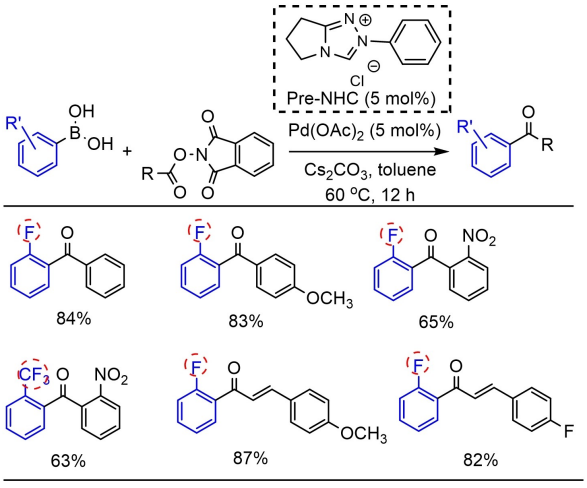
NHC precursor. As shown in Scheme 73, the reaction was viable for unstable substrates such as *ortho*-fluorinated aryl boronic acids giving moderate to good yields. Aryl boronic acids bearing other electron-withdrawing substituents, such as trifluoromethyl groups, were also effective in this reaction. The chemistry was extended to *N*-(alkenylcarbonyloxy) phthalamides, which coupled with *ortho*-fluorinated aryl boronic acids in good yield. The authors proposed a mechanism which involves the oxidative addition of *N*-(aryl-carbonyloxy)phthalamides, followed by transmetalation with the boronic acid, and subsequent reductive elimination to release the cross-coupled products.

4.6.2. Copper-Catalyzed C–C(O) Cross-Coupling of Fluorinated Aryl Boronic Acids and Thiol Esters (Liebskind-Srogl Cross-Coupling)

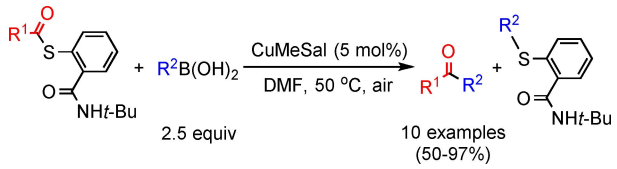
In 2007, Liebskind *et al.* reported the copper-catalyzed cross-coupling of organoboronic acids with thiol esters in air using 5 mol% of Cu(I)-3-methylsalicylate (Cu-MeSal) under base-free condition, to generate ketones as cross-coupled products in moderate to excellent yields (Scheme 74).[166] It should be mentioned that previous Liebskind-Srogl cross-coupling reactions required palladium precatalysts along with stoichiometric amounts of copper(I) carboxylate as a mediator, whereupon the copper(I) salt was thought necessary to facilitate the transmetalation step from boron to palladium.[107] Further investigation suggested that the copper(I) ion generates a thermodynamically stable Cu–SR species. Liebskind intuitively realized that this Cu–SR bond could be activated in the presence of the second equivalent of the organoboronic acid, thus generating a catalytically-active Cu(I) species.

The catalytic mechanism was proposed based on the presence of O_2, which initially led to oxidation of Cu(I) to Cu(II)/(III) (Scheme 75, stage 1), followed by coordination of the organoboronic acid and the release of the cross-coupled product (Scheme 75, stages 2 and 3). Finally, the Cu–SR bond is activated in the presence of an excess of the organoboronic acid, thus regenerating the Cu(I) intermediate and continuing the catalytic process (Scheme 75, stage 4).

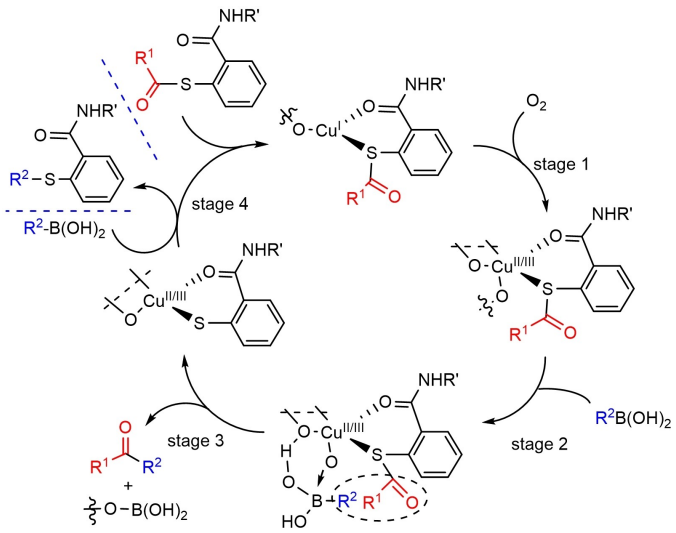
This reaction was effective for a wide range of aryl boronic acids that are not stable to basic conditions, including those containing *ortho*-fluorine substituents.[167] The scope of this study was expanded to include the synthesis of peptidyl ketones, which are important compounds in the development of molecular therapeutics (Scheme 76). This reaction also proved successful using *ortho*-brominated aryl boronic acids without effecting the bromide substituent. Notably, the authors mentioned that neither the formation of oxidative homocoupling products of the aryl boronic acids nor the racemization of the monopeptidyl ketones was detected.



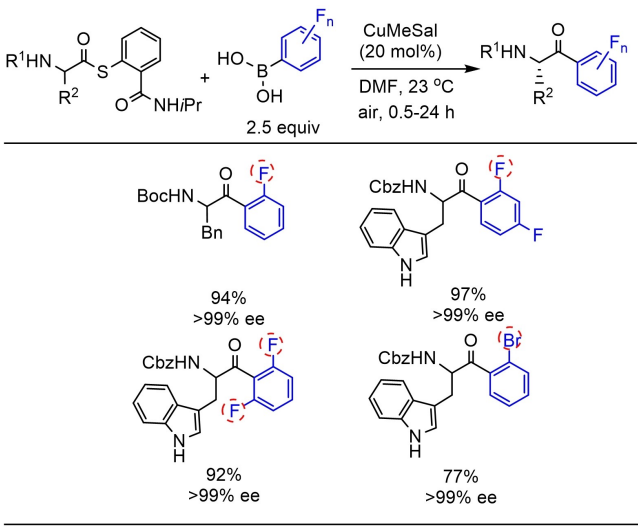
Scheme 73. Pd-NHC-catalyzed C–C(carbonyl) cross-coupling to synthesize diaryl ketones.[165]



Scheme 74. Copper-catalyzed cross-coupling of thiol esters and boronic acids.[166]



Scheme 75. Proposed mechanistic pathway for the copper-catalyzed cross-coupling of thiol esters and boronic acids in aerobic conditions.[166]

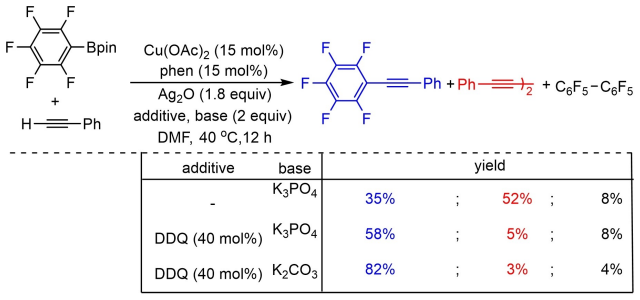


Scheme 76. Copper-catalyzed cross-coupling of peptidyl thiol esters and boronic acids, where Sal = 3-methylsalicylate.[167]

4.7. C–C(alkyne) Cross-Coupling

4.7.1. Copper-Catalyzed Oxidative Cross-Coupling of Fluorinated Aryl Boronates with Terminal Alkynes

Marder and Radius *et al.* reported that a combination of [$Cu(OAc)_2$] with phenanthroline effectively catalyzed the oxidative cross-coupling of highly fluorinated aryl-Bpin compounds with terminal alkynes under mild conditions.[168] The reaction of pentafluorophenyl-Bpin with ethynylbenzene using 1.8 equivalents of Ag_2O as the oxidant and 2 equivalents of K_3PO_4 gave the homocoupled alkyne compound as the major product (Scheme 77). Interestingly, the use of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) reduced the amount of alkyne homocoupling and increased the desired cross-coupled product. The authors proposed that DDQ functions as an electron-transfer mediator. Using K_2CO_3 as the base proved the most efficient and gave cross-coupling products in good yield.



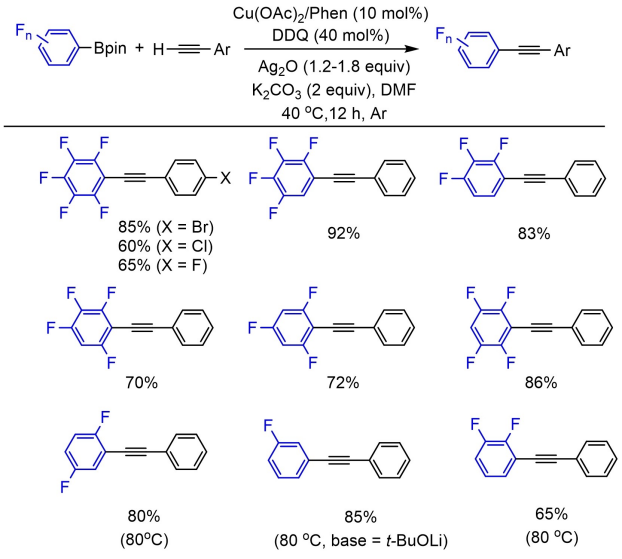
additive	base	yield		
-	K_3PO_4	35%	52%	8%
DDQ (40 mol%)	K_3PO_4	58%	5%	8%
DDQ (40 mol%)	K_2CO_3	82%	3%	4%

Scheme 77. Optimization reaction of copper-catalyzed oxidative cross-coupling of fluorinated aryl-Bpin with terminal alkynes.[168]

A number of polyfluorinated aryl-Bpin compounds containing *ortho*-fluorine substituents proved to be viable substrates under these reaction conditions and gave rise to the corresponding cross-coupled products in moderate to good yields. This reaction was also successful using electron-deficient ethynylbenzenes bearing bromine, chlorine, and fluorine groups at the *para*-position (Scheme 78). Unfortunately, no desired products were observed for reactions with 4-nitrophenyl and 4-cyano-phenylalkyne (not shown).

5. Conclusion and Perspective

As naturally occurring sources of aryl fluorides have not yet been identified, this class of molecules must be generated through chemical synthesis. Fluorinated aryl boronates, important synthons for the generation of these important fluoroarenes, can be synthesized in stoichiometric or catalytic processes using different methods, such as C–H, C–F, and C–X (X = Cl, Br, I, OTf) borylations. Under aqueous basic conditions, protodeboronation of fluorinated aryl boronic acids can be problematic only if the aromatic group contains *ortho*-fluorine substituents. Pentafluorophenyl boronic acid combines di-*ortho*-, di-*meta*-, and *para*-fluorine substituent groups that promote the protodeboronation and it is by far the most challenging substrate to be applied in organic synthesis. This protodeboronation issue has now been solved in many cases, and thus polyfluorinated aryl boronates, especially those containing *ortho*-fluorine substituents, can be converted to chlorides, bromides, iodides, phenols, carboxylic acids, nitro groups, cyanides, methyl esters and aldehyde analogues. Boron-containing substrates can be imple-



Scheme 78. Scope of the copper-catalyzed oxidative coupling of polyfluorophenyl with terminal alkynes.[168]

mented in many cross-coupling reactions, such as in the Suzuki-Miyaura cross-coupling with aryl halides, the Chan Evans-Lam C–N cross-coupling with aryl amines or nitrosoarenes, C–C(O) cross-coupling reactions with *N*-(aryl-carbonyloxy)phthalamides or thiol esters (Liebskind-Srogl cross-coupling), and the oxidative cross-coupling with terminal alkynes. The difficult reductive elimination step from highly stable complexes of the type $[PdL_2(2,6\text{-}C_6F_{2+n}H_{3-n})_2]$ frequently impedes these reactions and is the next challenge to be addressed in the homocoupling of 2,6-di-fluorinated aryl pinacol boronates. Progress has been made in this area by employing arene solvents and non-coordinating ligands. Future work will certainly focus on using economically and less toxic methodologies to generate this remarkably useful family of compounds.

Acknowledgments

Y.P.B. thanks the Indonesia Endowment Fund for Education (LPDP) for a PhD scholarship. S.A.W. is grateful to the Natural Sciences and Engineering Council of Canada for funding. T.B.M. and U.R. thank the Julius-Maximilians-Universität Würzburg and the Deutsche Forschungsgemeinschaft (DFG) for support. Open Access funding enabled and organized by Projekt DEAL.

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