

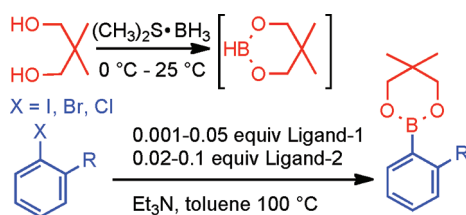
Neopentylglycolborylation of *ortho*-Substituted Aryl Halides Catalyzed by NiCl₂-Based Mixed-Ligand Systems

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NiCl₂-based mixed-ligand systems were shown to be very effective catalysts for the neopentylglycolborylation of aryl iodides, bromides, and chlorides bearing electron-rich and electron-deficient *ortho*-substituents. Although NiCl₂-based single-ligand catalytic systems were able to mediate neopentylglycolborylation of selected substrates, they were not as effective for all substrates, highlighting the value of the mixed-ligand concept. Optimization of the Ni(II)-catalyzed neopentylglycolborylation of 2-iodoanisole and methyl 2-iodobenzoate demonstrated that, while the role of ligand and coligand in the conversion of Ni(II) precatalyst to Ni(0) active catalyst cannot be ignored, a mixed-ligand complex is likely present throughout the catalytic cycle. In addition, protodeborylation and hydrodehalogenation were demonstrated to be the predominant side reactions of Ni(II)-catalyzed borylation of *ortho*-substituted aryl halides containing the electron-deficient carboxylate substituents. Ni(II) complexes in the presence of H₂O and Ni(0) are responsible for the catalysis of these side reactions.

Introduction

The versatility of aryl boronic acids,¹ boronate esters,¹ and potassium trifluoroborate salts,^{1–3} as synthetic precursors,^{4,5} catalysts,⁶ components in functional materials,^{7,8} and in medicine^{9,10} has driven the development of efficient methods for carbon–boron bond formation. The ultimate goal is to develop an efficient and cost-effective method for the synthesis of aryl–boron compounds that is tolerant toward all functional

groups and substitution patterns. The use of aryl Grignard or aryllithium species generated from aryl halides is most extensively employed in the synthesis of aryl boronic acids. However, this pathway is typically less tolerant to electrophilic or protic functionality than transition-metal-catalyzed approaches.¹

Among transition-metal-catalyzed borylation techniques, direct C–H borylation of aromatic compounds has attracted considerable attention in recent years. This is mostly due to its high atom-economy that results from the absence of arylhalide or pseudohalide synthetic intermediates. In 1999, Hartwig demonstrated the photochemical Cp*Re(CO)₃-catalyzed (where Cp* is 1,2,3,4,5-pentamethylcyclopentadiene)¹¹ and in 2000 the thermal Cp*Rh(η⁴-C₆Me₆)-catalyzed¹² direct aromatic C–H borylation of benzene using bis(pinacolato)diboron (B₂pin₂)^{13,14} as the

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boron source. Later, Marder¹⁵ reported a (Cp**RhCl*₂)₂ catalyst for direct aromatic C–H borylation of benzene, and Smith¹⁶ elaborated a very selective catalytic system from (Ind)Ir(COD) (where Ind is indenyl and COD is 1,5-cyclooctadiene) and bidentate phosphine ligands, both employing pinacolborane (HBpin) as an atom-efficient and cost-effective boron source. More recently, Hartwig and Miyaura have pioneered the use of the IMH catalyst, a combination of [Ir(COD)(OMe)]₂ and di-*tert*-butylpyridine (dtbpy), for the direct C–H borylation of arenes and heteroarenes using B₂pin₂^{17–22} or HBpin^{23,24} as the boron source. Direct C–H borylation exhibits regioselectivity dominated by steric interactions.^{18,25} Thus, *ortho*-substituted compounds are only produced as the major product when all *meta*- and *para*-positions are already substituted or specific *ortho*-directing groups^{26–28} are present.

Certain functional groups have been shown to mediate *ortho*-directed lithiation and facilitate subsequent C–B bond formation.^{29–31} Nevertheless, the most general approach for the synthesis of *ortho*-substituted arylboronic acids and esters has been the regiospecific Pd-catalyzed Miyaura borylation of aryl halides and triflates.^{32–37,38a} Early studies only presented sporadic examples of *ortho*-substituted aryl halide and triflate substrates.^{33–37,38a} Several recent Pd-catalyzed systems utilizing Buchwald-type^{39–41} biphenyl ligands have

demonstrated effective pinacolborylation of *ortho*-substituted aryl iodides,^{39,40} bromides,^{39,40} and chlorides^{40,42} using HBpin^{39,40} or B₂pin₂⁴² as boron sources. Additionally, a few systematic investigations on the Pd-catalyzed Miyaura pinacolborylation³⁹ and neopentylglycolborylation⁴³ of *ortho*-substituted substrates are available. Recently, Zhu and Ma^{44a} reported the CuI-catalyzed pinacolborylation of aryl iodides. This study includes four examples of *ortho*-substituted substrates. Subsequently, Marder et al. reported a Cu(I)/PBu₃-catalyzed borylation of aryl iodides and bromides utilizing 1.5 equiv of B₂pin₂ and bis(neopentylglycolato)diboron (B₂neop₂).^{44b} Good yields were obtained for the *ortho*-methoxy and *ortho*-methyl-substituted substrates investigated by Marder's group. However, aryl chlorides do not react under these conditions.

Previously, our laboratory has developed effective methods^{45–49} for the Ni(II)-catalyzed homo- and cross-coupling of aryl iodides, bromides, chlorides, mesylates, and tosylates and employed these reactions in the synthesis of building blocks for self-assembling dendrons and dendrimers and of other complex architectures.^{50–53} The use of Ni catalysis in aromatic borylation^{54–57} reduces cost by avoiding the use of precious metals but also harnesses the high reactivity of Ni toward less reactive aryl halides and pseudohalides, without the use of complex ligands. For Pd-catalyzed Miyaura borylation, tetraalkoxydiboron reagents are the most prevalent boron source.^{13,14,32,42,43,58a–58c,59–61} However, they suffer from high cost^{58b} and multistep synthesis.^{13,14,58a,59} In 2000, Tour⁵⁴ disclosed the first Ni(II)-catalyzed borylation

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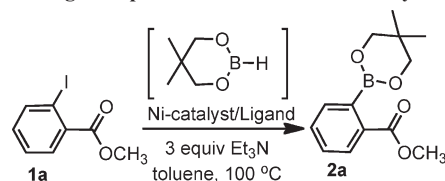
of 1,4-dibromobenzene and 1,3,5-tribromobenzene to produce nonhalogenated boronic acid additives for flame-retardant materials. Later, Mindiola developed a tridentate Ni(II) complex capable of transferring catecholborane to bromobenzene.⁶² Following these preliminary reports, in 2008, we elaborated the first general approach to Ni-catalyzed borylation⁵⁶ using in situ generated pinacolborane and neopentylglycolborane.^{37,63} The novel and extremely inexpensive boron source, neopentylglycolborane,^{58c} was prepared in situ. In situ prepared neopentylglycolborane is not purified, and therefore, the reaction mixture contains residual S(CH₃)₂. The S(CH₃)₂ does not affect Ni(II) species involved in the borylation but poisons the Pd(II)-catalyzed neopentylglycolborylation.⁵⁶ This Ni-catalyzed neopentylglycolborylation was successfully paired with sequential Ni-catalyzed⁵⁶ or complementary Pd-catalyzed^{57,64} cross-coupling, providing cost-effective access to a diversity of useful biaryl compounds. Although progress has been made to expand the scope of Ni-catalyzed neopentylglycolborylation, many substrates remain a challenge, including *ortho*-substituted aryl halides. In an earlier communication, NiCl₂(dppp)/dppp provided 100% conversion of the starting material for the neopentylglycolborylation of 2-bromotoluene.⁵⁶ However, the isolated yield was not determined.

The development of universal catalysts for the Ni(II)-catalyzed Suzuki–Miyaura cross-coupling⁴⁹ and effective neopentylglycolborylation of aryl chlorides⁵⁵ was achieved through the use of the mixed-ligand catalysts NiCl₂(dppp)/PPh₃ (dppp is 1,3-bis(diphenylphosphino)propane) and NiCl₂(dppp)/dppf [where dppf is 1,1'-bis(diphenylphosphino)ferrocene], respectively. In the previous studies and in the current one, we define a Ni(II)-based mixed-ligand catalytic system as having the following structure: Ni(II)X₂(ligand-1)/ligand-2 (where X is a halide or pseudohalide). In this report, X = Cl. Herein, the Ni(II)-catalyzed neopentylglycolborylation of *ortho*-substituted aryl iodides, bromides, and chlorides is investigated, and through the use of libraries of mixed-ligand Ni(II) catalysts, efficient and general reaction conditions are recommended.

Results and Discussion

Neopentylglycolborylation of Aryl Iodides. Preliminary experiments screening the Ni(II)-catalyzed neopentylglycolborylation of *ortho*-substituted aryl halides started with the aryl iodide methyl 2-iodobenzoate (Table 1) and a variety of catalysts. Ni(COD)₂/ligand catalytic system was shown previously to mediate the neopentylglycolborylation of all aryl halides,⁵⁷ and therefore, it was used to explore which aryl halide substrates are expected to be reactive under suitable NiCl₂-based catalysis. Therefore, in this study, Ni(COD)₂/ligand is not considered a mixed-ligand catalytic system. Ni(COD)₂/PCy₃ and Ni(COD)₂/dppp (Table 1, entries 1 and 2) are very effective for the *ortho*-neopentylglycolborylation of methyl 2-iodobenzoate, providing quantitative conversion and excellent yield. However, Ni(II)Cl₂-based catalysts are preferred on the basis of easier handling and preparation.

TABLE 1. Neopentylglycolborylation of Methyl 2-Iodobenzoate. Preliminary Screening for Optimum Combinations of Catalyst and Ligand



entry	catalyst (%)	ligand (%)	time (h)	convn ^a /yield ^b (%)
1	Ni(COD) ₂ (5)	dppp (10)	5	100/100 (88)
2	Ni(COD) ₂ (5)	P(Cy) ₃ (10)	4	100/100 (96)
3	NiCl ₂ (dppp) (5)	dppp (5)	4	100/100 (82)
4	NiCl ₂ (dppe) (5)	dppe (5)	5	28/28 (27) ^c
5	NiCl ₂ (dppp) (5)	dppe (5)	5	100/100 (80)
6	NiCl ₂ (dppp) (5)	PPh ₃ (10)	5	100/100 (81)
7	NiCl ₂ (dppp) (5)	dppf (10)	5	100/100 (97) ^c
8	NiCl ₂ (PPh ₃) ₂ (5)	dppp (10)	5	100/100 (78)

^aConversion determined by GC. ^bYield determined by GC. Isolated yield in parentheses. ^cIsolated yield for trifluoroborate.

NiCl₂(dppp)/dppp (Table 1, entry 3), the first catalyst developed for Ni-catalyzed neopentylglycolborylation,⁵⁶ while originally thought to be ineffective for *ortho*-substituents, was found to be effective for methyl 2-iodobenzoate. On the contrary, NiCl₂(dppe)/dppe [dppe is 1,2-bis(diphenylphosphino)ethane] (Table 1, entry 4) provided significantly lower yields than NiCl₂(dppp)/dppp, demonstrating once again the limited utility of dppe as ligand. However, the use of dppe as coligand to form the mixed-ligand catalyst NiCl₂(dppp)/dppe (Table 1, entry 5) provided a marked improvement in yield. Interestingly, other mixed-ligand systems NiCl₂(dppp)/PPh₃ and NiCl₂(PPh₃)₂/dppp (Table 1, entries 6 and 8) were also able to provide very good yields. However, a mixture of 5 mol % of NiCl₂(dppp) with 10 mol % of dppf coligand, the most efficient catalytic system discovered for the Ni(II)-catalyzed neopentylglycolborylation of *para*-substituted aryl chlorides⁵⁵ and aryl mesylates,⁶⁵ was also the most competent catalyst for this transformation (Table 1, entry 7).

It should be noted that the *ortho*-borylated compounds are almost exclusively viscous oils that, at the scale of these experiments, are more difficult to isolate and purify than the related crystalline *meta*- and *para*-borylated compounds.^{55–57,64} Their isolation was improved by converting the *ortho*-boronate esters to trifluoroborates.^{2,3} The conversion of aryl neopentylglycolboronates to aryltrifluoroborates was previously reported.⁵⁶ For specifically noted entries in Tables 1, 9, 10, and 12, the crude products were treated with KHF₂ to produce the crystalline potassium trifluoroborates,⁶⁶ and the resulting two-step isolated yields reported were in many cases significantly higher than the isolated yields of the one-step borylation.

Aryltrifluoroborates exhibit reactivity similar to that of arylboronate esters.^{2,3} Therefore, this two-step Ni-catalyzed trifluoroborylation serves as an effective solution to the isolation of oil-forming *ortho*-substituted aryl boronates.

The mixed-ligand systems composed of 5 mol % of NiCl₂(dppp) with 10 mol % of dppf, NiCl₂(dppp)/PPh₃, and NiCl₂(PPh₃)₂/dppp were universal and mediated the neopentylglycolborylation of electron-deficient (Table 2 entries

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TABLE 2. Neopentylglycolborylation of Aryl Iodides Containing Electron-Rich and Electron-Deficient *ortho*-Substituents

entry	substrate	catalyst (%)	ligand (%)	time (h)	2	convn ^a / yield ^b (%)
1		NiCl ₂ (dppp) (5)	dppf (10)	1	2b	100 / 100 (89)
2		NiCl ₂ (dppp) (5)	dppf (10)	5	2c	100 / 95 (71) ^c
3		NiCl ₂ (dppp) (5)	dppf (10)	24	2e	97 / 97 (78)
4		NiCl ₂ (dppp) (5)	dppf (10)	1	2f	100 / 100 (80)
5		NiCl ₂ (PPh ₃) ₂ (1)	dppp (2)	2	2f	100 / 100 (75)
6		NiCl ₂ (dppp) (1)	PPh ₃ (2)	2	2f	100 / 100 (76)
7		NiCl ₂ (dppp) (10)	PPh ₃ (20)	2	2f	100 / 100 (89)
8		NiCl ₂ (dppp) (10)	PPh ₃ (20)	2	2b	100 / 100 (97)
9		NiCl ₂ (dppp) (10)	PPh ₃ (20)	5	2e	100 / 100 (88)

^aConversion determined by GC. ^bYield determined by GC. Isolated yield in parentheses. ^cSelective monoborylated on iodide.

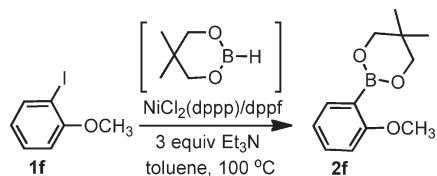
1, 2, and 8) and electron-rich (Table 2, entries 3–7 and 9) aryl iodides in 71–97% yield. In the case of 2-bromo-1-iodobenzene (Table 1, entry 2), a mixture of monoborylated and diborylated compounds was produced.

Screening for Optimum Combinations of Ni(II)-Based Catalysts and Mixed Ligands for the Neopentylglycolborylation of 2-Iodoanisole and 2-Iodomethyl benzoate. In a previous report, it was demonstrated that the catalyst loading level for the Ni(II)-catalyzed neopentylglycolborylation of *para*-substituted aryl iodides could be decreased to as low as 2 mol % without significantly decreasing the isolated yield.⁵⁷ As NiCl₂(dppp)/dppf has been identified as a universal catalyst for the neopentylglycolborylation of *ortho*-aryl iodides, it is necessary to ascertain the effect of catalyst loading on performance. The effect of catalyst loading on the NiCl₂(dppp)/dppf-catalyzed neopentylglycolborylation of electron-rich 2-iodoanisole was investigated (Table 3). Using 5% NiCl₂(dppp) and 10% dppf, a quantitative yield was obtained in 1 h (Table 3, entry 1). Even at 2% NiCl₂(dppp) and 4% dppf, the yield was as high as 91% after 1 h (Table 3, entry 3).

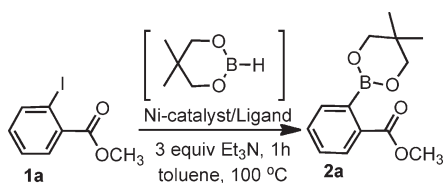
Decreasing catalyst loading to 1% NiCl₂(dppp) with 2% (dppf), or 0.5% NiCl₂(dppp) with 1% dppf, provided slightly

lower yields of 77 or 71% after 1 h, respectively. A similar study of catalyst loading was performed for electron-deficient methyl 2-iodobenzoate (Table 4). Using 5% NiCl₂(dppp) and 10% dppf, a quantitative yield was obtained in 1 h (Table 4, entry 1). At 3% NiCl₂(dppp) and 6% dppf, the yield remained good (80%) after 1 h (Table 4, entry 2). Further limiting catalyst loading to 2% NiCl₂(dppp) with 4% dppf, 1% NiCl₂(dppp), 2% NiCl₂(dppp), or 0.5% NiCl₂(dppp) with 1% dppf provided lower yields of 71, 61, and 8% after 1 h, respectively. However, higher yields for lower catalyst loading could be achieved with longer reaction times.

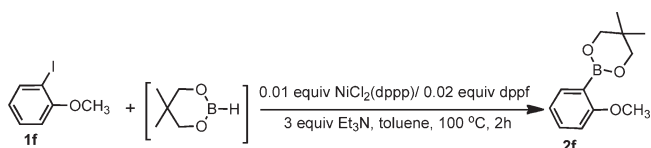
It is evident from the emergence of mixed-ligand catalysts in Ni(II)-catalyzed neopentylglycolborylation that the role of the catalyst and coligand is complex. A more comprehensive screening for optimum combinations of Ni(II)-based catalysts and mixed ligands for 2-iodoanisole (Table 5 and Figure 1, left) and methyl 2-iodobenzoate (Table 6 and Figure 1, right) utilizing a library of mixed-ligand systems at a loading level of 1 mol % of catalyst, 2 mol % of coligand (unless otherwise noted), and a reaction time of 2 h was conducted. These experiments were also compared with the catalyst Ni(COD)₂ that was used as standard for Ni(0)

TABLE 3. Neopentylglycolborylation of 2-Iodoanisole. Screening for Optimum Combinations of Catalyst and Mixed-Ligand Loading

entry	NiCl ₂ (dppp) (%)	dppf (%)	yield ^a (%)
1	5	10	100
2	3	6	90
3	2	4	91
4	1	2	77
5	0.5	1	71

^aYield determined by GC.**TABLE 4.** Neopentylglycolborylation of 2-Iodomethylbenzoate. Screening for Optimum Combinations of Catalyst and Mixed-Ligand Loading

entry	NiCl ₂ (dppp) (%)	dppf (%)	yield ^a (%)
1	5	10	100
2	3	6	80
3	2	4	71
4	1	2	61
5	0.5	1	8

^aYield determined by GC.**TABLE 5.** Neopentylglycolborylation of 2-Iodoanisole. Screening for Optimum Combinations of Catalyst and Mixed Ligand

catalyst	convn./yield ^a (%) for mixed ligands							
	no ligand	PCy ₃	PPh ₃	PTol ₃	dppf	dpe	dppp	dppb
NiCl ₂ (PPh ₃) ₂	0/0	11/11	44/44	33/33	12/12	9/9	97/97	57/57
NiCl ₂ (dppf)	0/0	6/6	5/5	6/6	3/3	3/3	33/33	23/23
NiCl ₂ (dpe)	15/15	15/15	10/10	30/30	7/7	1/1	2/2	36/36
NiCl ₂ (dppp)	86/86	86/86	97/97	95/95	100/100	6/6	42/42	69/69
NiCl ₂ (dppb)	7/7	10/10	18/18	15/15	25/25	5/5	6/6	7/7
Ni(COD) ₂	0/0	12/12	42/42	5/5	51/51	2/2	97/97	46/46
							84/84 ^d	

^aDetermined by GC. ^dMixture of 0.01 equiv of dppp and 0.01 equiv of dppf used as ligand.

species. In these experiments, 1,4-bis(diphenylphosphino)butane (dppb) and tri-*p*-tolylphosphine (PTol₃) were investigated in addition to the ligands already mentioned.

Interestingly, for 2-iodoanisole, NiCl₂(dppp) with no coligand is still a competent catalyst, achieving 86% yield in 2 h. The other catalysts were far less efficient in the absence of coligand. For Ni(COD)₂, NiCl₂(dppf), and NiCl₂(PPh₃)₂, no

product was obtained without coligand, suggesting that an active catalyst was not generated or was not stable under these conditions. NiCl₂(dppp) as catalyst exhibited superior performance to other catalysts under mixed-ligand conditions, with maximum yield (100%) in the presence of dppf coligand. This is the same Ni(II)-based mixed-ligand system that was most efficient for the neopentylglycolborylation of aryl chlorides.⁵⁵ Interestingly, while NiCl₂(dppp) with no coligand achieved 86% yield in 2 h, the use of excess dppp as “coligand” resulted in one of the lowest yields for NiCl₂(dppp) as catalyst (42%). It is possible that the resulting active Ni(0)(dppp)₂ complex readily adopts a relatively unstrained tetrahedral Ni(II)-bis-chelate structure that decreases the reactivity of the Ni(0) species toward oxidative addition.

Likewise, for NiCl₂(dppp), the use of other bidentate phosphine ligands such as dppe or dppb resulted in lower yields (6–69%) while the use of monodentate ligands PCy₃, PPh₃, or PTol₃ produced higher yields (86–97%). For all Ni catalysts composed of bidentate phosphine ligands, NiCl₂(dppp), NiCl₂(dppe), NiCl₂(dppb), and NiCl₂(dppf), lower yields were achieved when excess of ligand was employed as coligand than any of the corresponding mixed-ligand combinations. Therefore, it is not simply the concentration of ligand but also the combination of the mixed ligand that enables the superior catalytic performance. As reported previously⁵⁵ and demonstrated by the results from Table 5, reversing the ligand combination from NiCl₂(dppp)/dppf to NiCl₂(dppf)/dppp changes the reaction yield from 100 to 33%. All other combinations of NiCl₂(dppf) with various coligands resulted in even lower yields (0–23%). This trend reiterates that the benefit of dppf is achieved only as a coligand and that NiCl₂(dppf) is not an efficient catalyst. Therefore, at least in the case of bidentate ligands, where ligand exchange is more limited, there will be a notable difference when the precatalyst ligand and the coligand are reversed. Like in the case of NiCl₂(dppf), the remaining catalysts composed of a bidentate phosphine ligand, NiCl₂(dppe) and NiCl₂(dppb), exhibited generally poor yields. For NiCl₂(dppe), the highest yields were achieved using bidentate dppb as coligand (36%) or monodentate coligands such as PCy₃ (15%) or PTol₃ (30%). For NiCl₂(dppb) catalyst, optimum yields (18–25%) were obtained using either PPh₃ or dppf as coligand.

NiCl₂(PPh₃)₂ was the only catalyst based on a monodentate phosphine ligand that was investigated. The best yields were achieved for NiCl₂(PPh₃)₂/dppp (97%), NiCl₂(PPh₃)₂/dppb (57%), or NiCl₂(PPh₃)₂/PPh₃ (44%). Interestingly, extremely low yield was obtained for NiCl₂(PPh₃)₂/dppf (12%), despite the fact that dppf was the most efficient coligand for NiCl₂(dppp).

Switching the substrate to methyl 2-iodobenzoate (Table 6 and Figure 1, right) demonstrated similarities to the previous substrate as well as some intriguing differences. While yields were generally elevated as compared to 2-iodoanisole due to the presence of an activating electron-withdrawing group, NiCl₂(dppp) was once again demonstrated to be a privileged catalyst providing consistently the highest yields. Likewise, the universal mixed-ligand catalyst NiCl₂(dppp)/dppf provided quantitative yield. As before, NiCl₂(dppf) and NiCl₂(dppe) did not show good catalytic activity. Mixed- and non-mixed-ligand systems derived from NiCl₂(PPh₃)₂ also provided very high yields, but unlike with 2-iodoanisole, the mixed-ligand system NiCl₂(PPh₃)₂/dppp was not as effective as

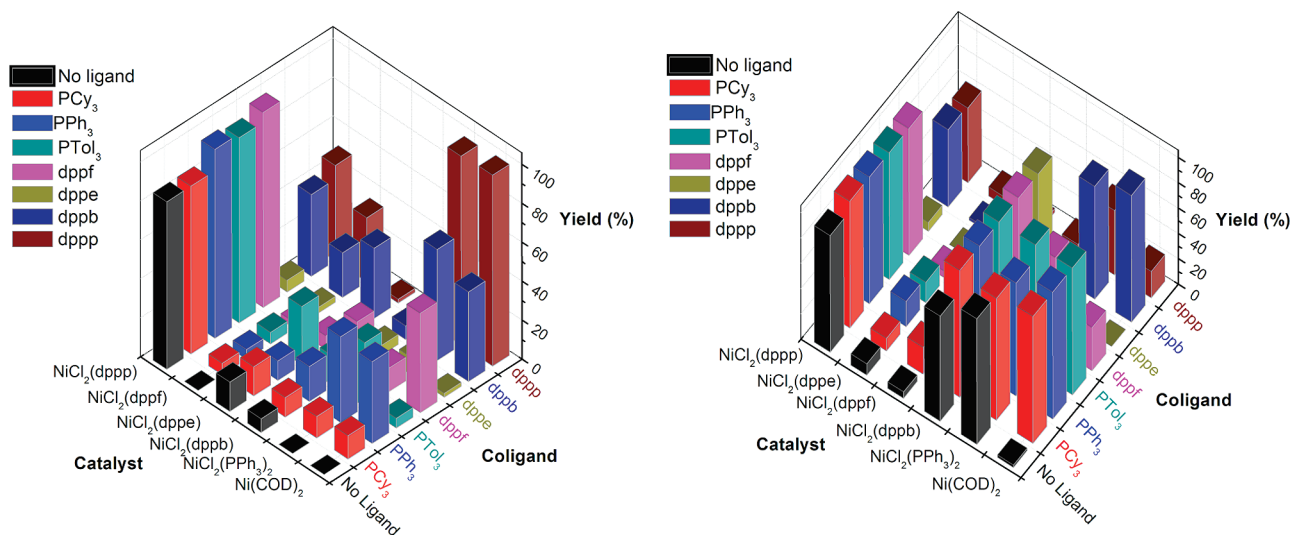
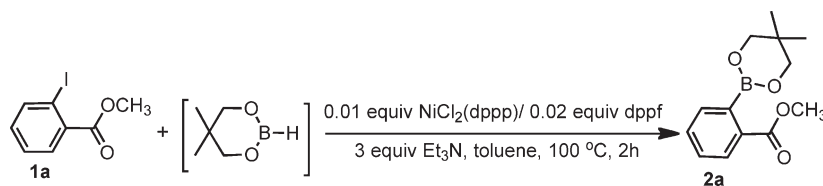


FIGURE 1. Three-dimensional representation of the effect of catalyst and mixed ligand on the yield of the Ni-catalyzed neopentylglycolborylation of 2-iodoanisole (left) and methyl 2-iodobenzoate (right).

TABLE 6. Neopentylglycolborylation of 2-Iodomethylbenzoate. Screening for Optimum Combinations of Catalyst and Mixed Ligand



catalyst	convn/yield ^a (%) for mixed ligands							
	no ligand	PCy ₃	PPh ₃	PTol ₃	dppf	dppe	dppp	dppb
NiCl ₂ (PPh ₃) ₂	99/99	96/96	89/89	100/100	71/71	1/1	51/51	100/89
NiCl ₂ (dppf)	9/9	10/10	20/20	16/16	5/5	0/0	7/7	2/2
NiCl ₂ (dppe)	5/5	21/21	3/3	5/5	2/2	0/0	3/3	8/8
NiCl ₂ (dppp)	100/92	100/100	100/100	100/100	100/100	7/7	59/59	61/61
NiCl ₂ (dppb)	100/83	100/100	100/100	100/100	72/72	0	85/66	100/89
Ni(COD) ₂	2/2	100/100	100/100	100/100	43/34	0	21/21	100/100

^aDetermined by GC.

other systems. Likewise, Ni(COD)₂/dppp, which was very effective for 2-iodoanisole, only provided 21% yield, while Ni(COD)₂ with PCy₃, PPh₃, PTol₃, or dppb provided quantitative yields (Table 6).

A high yield with dppb as a coligand was quite surprising, and intriguingly, yields for the neopentylglycolborylation of methyl 2-iodobenzoate using NiCl₂(dppb) as catalyst with and without coligands provided generally excellent yields. It is interesting to note that for methyl 2-iodobenzoate some catalyst systems provided a discrepancy between GC conversion and yield, which as it will be described in a subsequent section can be the result of protodeborylation or hydrodehalogenation side reactions.

It is apparent that the profile of catalytic activity changes from substrate to substrate. Fortunately, it seems that NiCl₂(dppp)-based catalysts and, in particular, the mixed-ligand system NiCl₂(dppp)/dppf are general catalysts for providing excellent to quantitative yield. However, dppf is a more expensive ligand and, in some scenarios, may be more difficult to remove during purification than simpler phosphine ligands. If price and catalyst separation become restrictive, a full catalyst screening is likely to provide alternate

catalysts that, while not universal, will be equally attractive for the substrate in question.

Neopentylglycolborylation of Aryl Bromides. Aryl bromides exhibit different trends in reactivity than aryl iodides. The mixed-ligand system NiCl₂(dppp)/dppf is still capable of mediating effective neopentylglycolborylation of electron-rich and sterically small 2-bromotoluene (Table 7, entry 12) and 2-bromoanisole (Table 8, entry 5). However, for bulkier or more electron-deficient *ortho*-substituents (Table 8, entries 1–4), NiCl₂(dppp)/dppf provides lower yields. For 2-bromotoluene, the mixed-ligand system NiCl₂(dppp)/PPh₃ (Table 7, entries 6 and 7) and the single-ligand system NiCl₂(dppp)/dppp (Table 7, entry 4) provide comparable yields to the mixed-ligand NiCl₂(dppp)/(dppf) (Table 7, entry 12). As in the case of aryl iodides, the model catalyst Ni(COD)₂/PCy₃ is relatively adept at mediating the borylation of electron-deficient aryl bromides (Table 7, entry 1) but is less reactive toward electron-rich substrates (Table 7 entries 2 and 3).

The large discrepancy between the conversion and yield of the NiCl₂(dppp)/dppp-catalyzed neopentylglycolborylation of methyl 2-bromobenzoate suggests that the bulky and electron-withdrawing *ortho*-carboxylates facilitate a side

TABLE 7. Neopentylglycolborylation of *ortho*-Substituted Aryl Bromides. Preliminary Screening for Optimum Combinations of Catalyst and Mixed Ligand

entry	substrate	catalyst (%)	ligand (%)	time (h)	2	convn ^a / yield ^b (%)
1		Ni(COD) ₂ (5)	P(Cy) ₃ (10)	19	2a	100 / 100 (85)
2		Ni(COD) ₂ (5)	P(Cy) ₃ (10)	17	2e	6 / 6
3		NiCl ₂ (dppp) (5)	dppp (5)	25	2a	76 / 9 (8) ^c
4		NiCl ₂ (dppp) (5)	dppp (5)	22	2e	78 / 78 (66)
5		NiCl ₂ (dppp) (5)	dppp (5)	15	2j	100 / 72 (42)
6		NiCl ₂ (dppp) (5)	PPh ₃ (10)	21	2e	56 / 56 (42)
7		NiCl ₂ (dppp) (10)	PPh ₃ (20)	19	2e	92 / 92 (69)
8		NiCl ₂ (dppp) (10)	PPh ₃ (20)	43	2f	100 / 100 (66)
9		NiCl ₂ (dppp) (1)	PPh ₃ (2)	48	2f	54 / 54 (35)
10		NiCl ₂ (PPh ₃) ₂ (1)	dppp (2)	40	2a	63 / 3
11		NiCl ₂ (PPh ₃) ₂ (1)	dppp (2)	43	2f	50 / 50 (40) ^c
12		NiCl ₂ (dppp) (5)	dppf (10)	24	2e	100 / 100 (69)

^aConversion calculated from GC. ^bYield determined by GC. Isolated yield in parentheses. ^cIsolated yield for trifluoroborate.

reaction, which can be attributed to either protodeborylation or hydrodehalogenation.

As it will be described in a later section, protodeborylation requires the presence of adventitious moisture and tends to occur only at extended reaction times. As the present experiments were conducted under rigorously dry conditions with short reaction times, hydrodehalogenation of the starting material is the most likely side reaction.

In addition to aryl neopentylglycolboronate esters, the single-ligand system NiCl₂(dppp)/dppp was able to mediate the effective monoborylation of pseudo-*ortho*-substituted 2-bromothiophene (Table 8, entries 6 and 7) and the diborylation of 2,5-dibromothiophene (Table 8, entry 8) in up to 97 and 83% recovered yield, respectively.

In light of the interest in thiophene-based derivatives for organic electronics, dendrimers, sensors, and other materials,

the synthesis of thiophene-based precursors for cross-coupling reactions (Table 8, entries 6–8) is of particular interest.⁶⁷ Therefore, we sought to investigate the neopentylglycolborylation of 2-bromothiophene. Excellent yield (93%) was obtained in 17 h for the neopentylglycolborylation of 2-bromothiophene (Table 8, entry 6) using 5 mol % of NiCl₂(dppp)/10 mol % of dppf as catalyst. Under these conditions, quantitative GC yield was obtained in 4.5 h using 5 mol % of NiCl₂(dppp)/10 mol % of dppf (Table 9, entry 1). Decreasing the catalyst loading to 3 mol % of NiCl₂(dppp)/6 mol % of dppf (Table 9, entry 2) provided 97% yield in 4.5 h and quantitative GC yield in 18 h. Further reduction in catalyst loading level to 2 mol % of NiCl₂(dppp)/4 mol % of dppf

(67) Rosen, B. M.; Wilson, C. J.; Wilson, D. A.; Peterca, M.; Imam, M. R.; Percec, V. *Chem. Rev.* **2009**, *109*, 6275–6540.

TABLE 8. Neopentylglycolborylation of *ortho*-Substituted Aryl Bromides

entry	substrate	catalyst (%)	ligand (%)	time (h)	2	convn ^a / yield ^b (%)
1		NiCl ₂ (dppp) (5)	dppf (10)	20	2a	100 / 21 (11)
2		NiCl ₂ (dppp) (5)	dppf (10)	44	2h	78 / 78 (66)
3		NiCl ₂ (dppp) (5)	dppf (10)	44	2g	36 / 36 (28) ^c
4		NiCl ₂ (dppp) (5)	dppf (10)	24	2c, 2d	57 / 57 (13) ^d
5		NiCl ₂ (dppp) (5)	dppf (10)	35	2f	100 / 100 (74) ^c
6		NiCl ₂ (dppp) (5)	dppf (10)	17	2i	100 / 100 (93)
7		NiCl ₂ (dppp) (5)	dppp (5)	17	2i	100 / 100 (97)
8		NiCl ₂ (dppp) (5)	dppf (10)	15	2j	100 / 86 (83)

^aConversion calculated from GC. ^bYield determined by GC. Isolated yield in parentheses. ^cIsolated yield for trifluoroborate. ^dMonoborylated/hydrodehalogenated/diborylated (3/7/1) **2d**, isolated yield for mixture mono- and hydrodehalogenated.

(Table 9, entry 3) or 1 mol % of NiCl₂(dppp)/2 mol % of dppf provided only 74 or 32% GC yield in 18 h, respectively.

Neopentylglycolborylation of Aryl Chlorides. In a previous report, the mixed-ligand system NiCl₂(dppp)/dppf was shown to be far superior to other single-ligand and mixed-ligand systems for the neopentylglycolborylation of aryl chlorides.⁵⁵ This system was also explored for the neopentylglycolborylation of *ortho*-substituted aryl chlorides.

For aryl chlorides, the steric bulk of the *ortho*-substituent appears to have the most profound effect on reactivity (Table 10). The highest yields were observed for aryl chlorides with small *ortho*-substituents regardless of whether they are electron-withdrawing or electron-donating, such as 2-chloroanisole (Table 10, entry 2), 1-chloro-2-fluorobenzene (Table 10, entry 5), 1,2-dichlorobenzene (Table 10, entry 6), 2-chlorotoluene (Table 10, entry 7), and 1-chloro-2-(trifluoromethyl)benzene (Table 10, entry 11).

Aryl chlorides with bulkier *ortho*-substituents such as 1-(benzyloxy)-2-chlorobenzene (Table 10, entry 1), methyl 2-chlorobenzoate (Table 10, entry 8), and (2-chlorophenyl)(phenyl)methanone (Table 10, entry 10) could only be borylated in low yield.

Likewise, 2-chlorophenol, which most probably is deprotonated under these reaction conditions could only be borylated

TABLE 9. Neopentylglycolborylation of 2-Bromothiophene. Screening for Optimum Combinations of Catalyst and Mixed-Ligand Loading

entry	NiCl ₂ (dppp) (%)	dppf (%)	yield ^a (%) at time (h)		
			2 h	4.5 h	18 h
1	5	10	98	100	100
2	3	6	91	97	100
3	2	4	67	67	74
4	1	2	26	26	32

^aYield determined by GC.

in low yield. In addition to *ortho*-substituted phenyl halides, NiCl₂(dppp)/dppf was able to mediate the neopentylglycolborylation of heteroaryl halides to provide, for example, pseudo-*ortho*-substituted 2-chlorothiophene (Table 10, entry 13) in 93% isolated yield.

In the previous section, the conditions for the Ni-catalyzed neopentylglycolborylation of 2-bromothiophene were optimized.

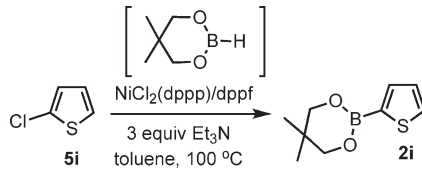
TABLE 10. Neopentylglycolborylation of *ortho*-Substituted Aryl Chlorides

entry	substrate	catalyst (%)	ligand (%)	time (h)	2	convn ^a / yield ^b (%)
1		NiCl ₂ (dppp) (5)	dppf (10)	23	2k	76 / 59 (45)
2		NiCl ₂ (dppp) (5)	dppf (10)	24	2f	96 / 96 (76)
3		NiCl ₂ (PPh ₃) ₂ (5)	dppp (10)	24	2f	51 / 51 (46)
4		NiCl ₂ (dppp) (5)	dppf (10)	24	2l	0 / 0
5		NiCl ₂ (dppp) (5)	dppf (10)	20	2b	66 / 66 (51)
6		NiCl ₂ (dppp) (5)	dppf (10)	26		83 / 78 (46) ^c
7		NiCl ₂ (dppp) (5)	dppf (10)	55	2e	100 / 100 (84)
8		NiCl ₂ (dppp) (5)	dppf (10)	24	2a	70 / 39 (26)
9		NiCl ₂ (PPh ₃) ₂ (1)	dppp (2)	22	2a	13 / 5 (4) ^d
10		NiCl ₂ (dppp) (5)	dppf (10)	24	2n	100 / 7
11		NiCl ₂ (dppp) (5)	dppf (10)	65	2h	62 / 62 (52)
12		NiCl ₂ (PPh ₃) ₂ (1)	dppp (2)	42	2h	5 / 5
13		NiCl ₂ (dppp) (5)	dppf (10)	20	2i	100 / 100 (93)

^aConversion determined by GC. ^bYield determined by GC. Isolated yield in parentheses. ^cMonoborylated and hydrodehalogenated/monoborylated (1/15), isolated yield for mixture of mono- and hydrodehalogenated products. ^dIsolated yield for trifluoroborate.

Here, a similar optimization was performed on 2-chlorothiophene (Table 11). Using, 5 mol % of NiCl₂(dppp)/10 mol % of dppf, the neopentylglycolborylation of 2-chlorothiophene (Table 11, entry 1) was more sluggish than for 2-bromothiophene, achieving quantitative GC yield only after 15 h. Decreasing catalyst loading level to 3 mol % of NiCl₂(dppp)/6 mol % of dppf (Table 11, entry 2) or 2 mol % of NiCl₂(dppp)/4 mol % of dppf (Table 11, entry 3) provided 87 (38 h) and 92% (43 h) GC yield, respectively. Further reduction in catalyst loading level to 1 mol % of NiCl₂(dppp)/2 mol % of dppf provided 58% GC yield in 43 h.

Investigation of Protodeborylation and Hydrodehalogenation Pathways Encountered during the Neopentylglycolborylation of Aryl Halides with NiCl₂-Based Mixed-Ligand Catalytic Systems. As discussed in the previous sections, the neopentylglycolborylation of aryl halides containing methylcarboxylates sometimes results in a notable discrepancy between GC yield and GC conversion. This suggests one or more side reactions. Fundamentally, four side reactions are possible: (1) hydrodehalogenation of aryl halide, (2) protodeborylation, (3) homocoupling of aryl halide, and (4) homocoupling of neopentylglycolboronate ester (Scheme 1).

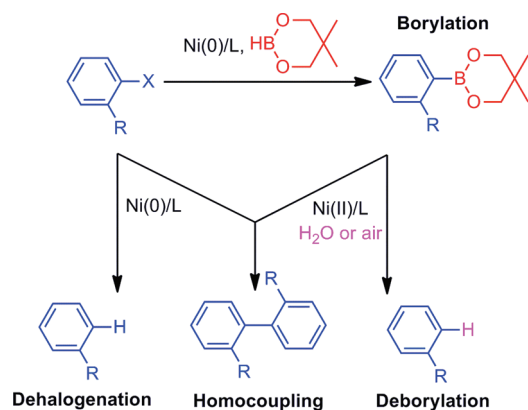
TABLE 11. Neopentylglycolborylation of 2-Chlorothiophene. Screening for Minimum Catalyst and Mixed-Ligand Loading


entry	NiCl ₂ (dppp) (%)	dppf (%)	yield ^a (%)				
			2 h	5 h	15 h	23 h	38 h
1	5	10	50	71	100	100	100
2	3	6	31	60	68	78	87
3	2	4	17	40	72 ^b	78	92 ^c
4	1	2	3	18	45 ^b	50	58 ^c

^aYield determined from GC. ^bGC at 18 h. ^cGC at 43 h.

On the basis of the mechanism proposed for the Pd-catalyzed borylation using pinacolborane,^{38a} it is assumed that, for Ni(II)-catalyzed borylation, borane/Et₃N mediates activation of Ni(II)Cl₂(Ligand) precatalyst to a Ni(0)(Ligand) active catalyst. If the mechanism of Ni-catalyzed borylation proceeds in a related way to the Pd-catalyzed mechanism, the aryl halide oxidatively adds to the Ni(0) active catalyst. Substitution of the Ni–halide bond with neopentylglycolborane followed by reductive elimination would produce the expected aryl neopentylglycolboronate ester product. However, at this time, it is not possible to exclude that a single-electron transfer (SET) mechanism could play some role in this reaction.^{38b} Kochi's^{38b} early work on Ni-catalyzed homocoupling established that a SET chain reaction can operate under certain reaction conditions. SET from Ni(0)/Ni(II) to Ar–X could result in hydrodehalogenation by the decomposition of the incipient radical anion into a radical that will become hydrogenated by chain transfer, and a halide anion, rather than through.

While the detailed mechanism of Ni(II)-catalyzed borylation is still uncertain, the discrepancy between conversion and yield was preliminarily attributed to the protodeborylation of the resulting boronate ester produced during the course of the reaction. Other studies have demonstrated the relative instability of electron-deficient *ortho*-boronic acids and esters toward protodeborylation.^{1,44b} In addition, Ni(II) salts have been shown to be extremely effective at accelerating protodeborylation of arylboronic acids.⁶⁸ An alternative explanation for the difference between yield and conversion could be provided by the direct hydrodehalogenation of the starting aryl halide mediated via SET from the Ni(0) catalyst and/or homocoupling side reactions. A model of protodeborylation side reaction was performed where methyl 2-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)benzoate was treated with 5 mol % of NiCl₂(dppp), Et₃N, in toluene at 100 °C in the absence of neopentylglycolborane and in the presence of 2 μL of H₂O (Figure 2a) or air (Figure 2b). Under these conditions, continuous protodeborylation was observed with time, achieving in 22 h 93% protodeborylation in the presence of water (Figure 2a) and 70% protodeborylation in the presence of air (compound B) and 7–30% homocoupling byproduct (compound C) (Figure 2b).

SCHEME 1. Possible Side Reactions for Ni-Catalyzed Borylation

GC analysis of the NiCl₂(dppp)/dppf-catalyzed neopentylglycolborylation of methyl 2-bromobenzoate and methyl 2-chlorobenzoate (Figure 2c,d) reveals an increased rate of protodeborylated/hydrodehalogenated byproduct formation and a much lower rate for the formation of borylated product.

In the case of NiCl₂(dppp)/dppf-catalyzed neopentylglycolborylation of methyl 2-bromobenzoate, the reaction reaches a maximum at 360 min, where 50% loss of starting material is observed corresponding to ~70% GC yield. Starting at 180 min, a major increase in the amount of hydrodehalogenated byproduct (compound B) is seen, while a maximum in the GC yield is observed. From 360 to 1440 min, the amount of product (compound A) decreases from 20% (maximum yield recorded at 360 min) to 10% GC yield, while the amount of hydrodehalogenated byproduct (compound B) increases correspondingly to 65%. These results demonstrate that during the most productive time domain of the reaction, the first 360 min, the rates of hydrodehalogenated byproduct and product formation are comparable. From 120 to 480 min, hydrodehalogenation and protodeborylation starts to compete with borylation, and from 480 min onward, protodeborylation is the most probable side reaction since a decrease of the of the GC yield is observed while the substrate consumption remains constant. NiCl₂(dppp)/dppf-catalyzed neopentylglycolborylation of methyl 2-chlorobenzoate is considerably slower than that of the corresponding bromide. In this case, the rate of protodeborylated/hydrodehalogenated byproduct formation is comparable with the rate of neopentylglycolborylation. Further investigation of the occurrence of protodeborylation showed no side reaction in the absence of Ni(II) catalyst when methyl 2-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)benzoate was treated with Et₃N in toluene at 100 °C for 24 h (Table 12, entry 1). Thus, Ni(II) species are capable of mediating the protodeborylation of arylneopentylglycolboronate esters with bulky, electron-deficient *ortho*-methylcarboxylate substituents. When the electron-deficient *ortho*-methylcarboxylate was replaced with the electron-deficient *ortho*-trifluoromethyl or with the electron-rich *ortho*-methoxy groups, no protodeborylation was observed under the same conditions even after 24 h (Table 12, entries 12 and 13).

Also, when the electron-deficient *ortho*-methylcarboxylate was replaced with a *para*-methylcarboxylate group, protodeborylation was not observed even after 24 h (Table 12, entry 14). These experiments demonstrate that only the *ortho*-methylcarboxylates mediate the protodeborylation and suggest that coordination of the Ni(II) catalyst by the carbonyl group of the

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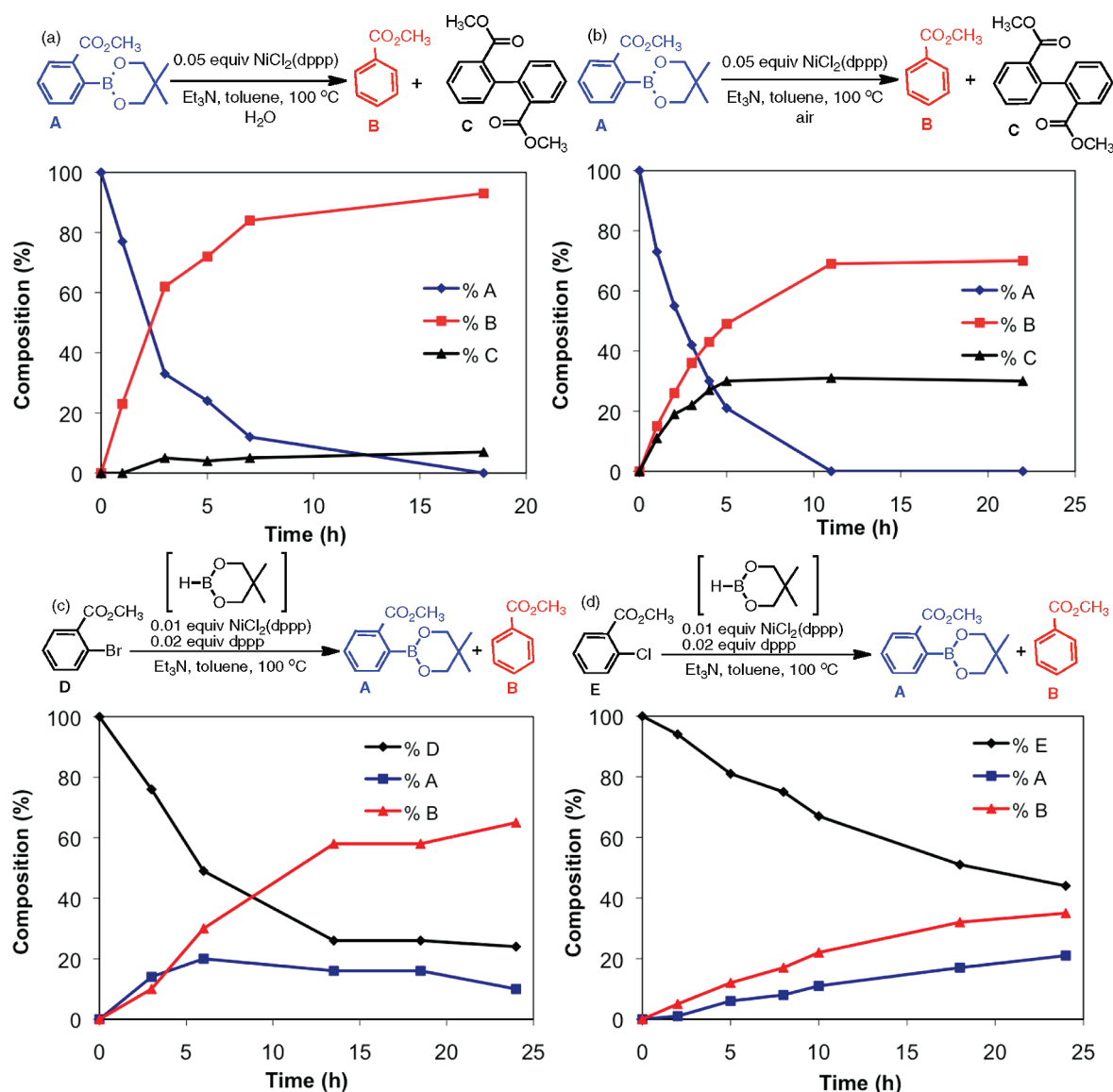


FIGURE 2. Evolution of starting material (compound A), protodeboronated product (compound B), and homocoupling byproduct (C) in the NiCl₂(dppp)-catalyzed protodeborylation of methyl 2-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)benzoate **2a** performed in water (a) and air (b). Evolution of starting material (compounds D and E), and protodeboronated side product (compound B) in the NiCl₂(dppp)/dppf-catalyzed neopentylglycolborylation of methyl 2-bromobenzoate (c) and methyl 2-chlorobenzoate (d).

carboxylate may have an important role in this reaction. This hypothesis is strongly supported by experiments where the methylcarboxylate unit in the *para*-position of the aryl group or noncoordinating electron-withdrawing groups such as -CF₃ in the *ortho*-position do not mediate protodeborylation (Table 12, entries 13 and 14).

The protodeboronation of arylboronic acids has been previously demonstrated to proceed through an acid- or base-catalyzed A-S_E2 mechanism in aqueous media.⁶⁹ This process

is accelerated by some metal cations,⁷⁰ such as Ni(II)⁶⁸ and Pd(II).⁷¹ Suzuki was the first to report the Pd-catalyzed homocoupling of arylboronic acids,⁷² while a more recent report suggests that hydridic palladium nanoparticles generated in situ from palladacycles mediate catalytic hydrodehalogenation of aryl halides or protodeboronation of arylboronic esters.⁷³ In the related electrophilic displacement reaction of arylboronic acids with hydrogen peroxide to generate phenols,⁷⁴ chelation with neopentylglycol did not have a catalytic effect.^{74c}

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TABLE 12. Investigation of the Protodeborylation under Different Reaction Conditions

entry	substrate	NiCl ₂ (dppp) (%)	dppf (%)	Et ₃ N	neopentyl glycolborane	additive	time (h)	convn ^a / yield ^b (%)
1		-	-	+	-	-	24	0 / 0
2		5	-	+	-	-	20	16 / 11 : 5 ^d
3		5	10	+	-	-	24	0 / 0
4		5	+	+	-	H ₂ O (18μL) ^c	20	98 / 98 : 0 ^d
5		5	-	+	-	air	22	100 / 70 : 30 ^d
6		5	-	+	+	-	24	0 / 0
7		5	10	+	+	-	24	0 / 0
8		-	10	+	-	H ₂ O (2μL) ^c	24	0 / 0
9		-	10	+	-	H ₂ O (4μL)	24	0 / 0
10		5	10	+	-	D ₂ O (18 μL)	24	100 / 100 (29) ^e
11		5	10	+	-	H ₂ O (2μL) ^c	24	0 / 0
12		5	10	+	-	H ₂ O (2μL)	24	0 / 0
13		5	10	+	-	H ₂ O (2μL)	24	0 / 0

^aConversion calculated from GC. ^bYield determined by GC. Isolated yield in parentheses. ^cEquivalent to 20% molar ratio. ^dHomocoupling byproduct. ^eWith 70% deuterium incorporation.

Furthermore, arylneopentylglycolboronates are relatively stable to hydrolysis,⁵³ and therefore, it is highly unlikely that the currently observed protodeborylation proceeds through an arylboronic acid intermediary.

Unfortunately, to the best of our knowledge, systematic investigations of the protodeborylation of arylboronate esters have not been reported in any prior publication. In the current study, it is evident that Ni(II) species catalyze the

TABLE 13. Investigation of the Hydrodehalogenation under Different Reaction Conditions

entry	substrate	catalyst %	ligand %	base	additive	solvent	time (h)	convn ^a / yield ^b (%)
1		Ni(COD) ₂ ^c (100)	-	-	-	toluene	26	100 / 0 : 100
2		-	-	Et ₃ N	Zn dust	toluene	26	11 / 11 : 0
3		Ni(COD) ₂ ^c (100)	dppp ^c (100)	Et ₃ N	-	toluene	1	100 / 0 : 100
4		NiCl ₂ (dppp) (5)	dppf (10)	Et ₃ N	Zn dust	THF ^c	5	100 / 96 : 4
5		NiCl ₂ (dppp) (5)	dppf (10)	Et ₃ N	Zn dust	THF-d ₈ ^d	10	100 / 96 (50) ^e : 4
6		NiCl ₂ (dppp) (5)	dppf (10)	Et ₃ N	Zn dust	toluene	7	100 / 55 : 45

^aConversion calculated from GC. ^bHydrodehalogenated:homocoupling products determined by GC, isolated yield in parentheses. ^cWith 1 equiv of Ni(COD)₂. ^dReaction temperature at 70 °C. ^eWith 14% deuterium incorporation.

protodeborylation of coordinating *ortho*-substituted arylboronates such as methyl 2-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)benzoate. The effects of catalyst, ligand, base, neopentylglycolborane, and water or air as additives to the reaction mixture were investigated.

Addition of 20% water to the reaction mixture containing both Ni(II) catalyst and the Et₃N base mediates almost quantitative protodeborylation in 18 h (Figure 2a), while in the absence of the Ni(II) catalyst, no protodeborylation product was observed (Table 12, entry 9). These experiments reiterate the role of the Ni(II) species in mediating protodeborylation of electron-deficient *ortho*-methylcarboxylate. Complete protodeborylation of methyl 2-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)benzoate and 70% deuterium incorporation was observed after addition of D₂O in the reaction mixture (Table 12, entry 11). It should be noted that, in the case of Cu(I)I-mediated borylation reported by Marder et al.,^{44b} hydrodehalogenation was also observed. In this study,^{44b} the addition of H₂O did not increase the amount of hydrodehalogenated side product. Likewise, the addition of D₂O did not result in deuteration of the side product, indicating that H₂O does not mediate protodeborylation in Cu(I)I-mediated borylation. On the other hand, reactions run in THF-d₆ resulted in 70% deuterium incorporation in the hydrodehalogenated side product. The mechanism outlined in their report does not explain the hydrodehalogenation side reaction, though Cu(0) nanoparticles were potentially implicated as the active catalyst. While not mentioned by the original authors,^{44b} these results are consistent with a radical mechanism of hydrodehalogenation, which could arise from a SET process mediated by either Cu(0) or Cu(I)I. Further work will be needed to

elucidate the mechanism of Ni(II)Cl₂-mediated protodeborylation. In addition, other Ni(II) species that are generated during the catalytic process may also be capable of mediating protodeborylation.

This study demonstrates that, when the yield of the product in Ni-catalyzed borylation of *ortho*-substituted carboxylates is low, improved yields may be achieved by reducing the reaction time of the borylation⁶⁵ or adjusting reaction conditions so as to minimize protodeborylation and hydrodehalogenation side reactions.

In light of Marder's results with Cu(I)I-mediated borylation, the hydrodehalogenation of 2-iodomethylbenzoate was investigated in the presence of either Ni(0) from Ni(COD)₂ (Table 13, entries 1 and 2) or generated in situ by the reduction of Ni(II) catalyst with Zn powder.⁴⁸ Quantitative homocoupling of aryl halide was obtained as a byproduct in the presence of Ni(COD)₂ catalyst in toluene, which is in agreement with other experiments.⁴⁸ However, Ni(0) generated in situ by the reduction of NiCl₂(dppp)/dppf with Zn powder in THF mediates almost quantitative hydrodehalogenation. Additionally, when the same experiment was performed in THF-d₈, 14% deuterium incorporation into the hydrodehalogenated product was observed. This suggests that a SET process that results in an aryl radical may operate under some borylation conditions.

Comparison with Previous Methods for *ortho*-Borylation. In this report, strategies for the Ni-catalyzed neopentylglycolborylation of *ortho*-substituted aryl chlorides, bromides, and iodides were elaborated. The expensive Pd catalysts and tetralkoxydiboron reagents were replaced with cost-effective

Ni catalysts and with the in situ prepared neopentylglycolborane. However, there are other methods in the literature for *ortho*-borylation, which may be more suitable for certain substrates.

The *ortho*-directing substituents can be used to achieve *ortho*-borylated products.^{26–31} Ir-, Re-, or Rh-catalyzed direct C–H borylation typically provides *para*- or *meta*-regioisomers, except in the presence of *ortho*-directing groups, and therefore^{26–28} represents an effective method for the synthesis of a limited pool of *ortho*-borylated arenes. Scattered examples of Pd-catalyzed borylation of *ortho*-substituted aryl halides are available in the literature.^{33–42} Pd(0)-catalyzed borylation of *ortho*-substituted aryl triflates using B₂pin₂ has been demonstrated for a limited set of substrates.^{33,38a} In these cases, no isolated yields were reported, and consequently, a comparison of efficacy cannot be made. Additionally, in the present case of Ni-catalyzed borylation, aryl triflates were not investigated due to the high costs of their preparation, which negates the economic advantages of Ni catalysis. Pd-catalyzed borylation of *ortho*-substituted aryl iodides^{36,38a,75} and bromides^{41,43,75} typically provides comparable yields to the present Ni-catalyzed approach, though in many cases with increased cost. Improved yields for certain substrates via Ni-catalyzed neopentylglycolborylation may be due to the decreased steric bulk of neopentylglycolborane versus pinacolborane.⁴³ The relatively low loading levels of cost-effective Ni catalysts and simple phosphine-containing ligands make Ni catalysis a particularly attractive method for the synthesis of *ortho*-substituted borylated derivatives starting from aryl iodides and selected aryl bromides and heteroaryl bromides. Recently, Buchwald reported a system for the Pd-catalyzed pinacolborylation of aryl chlorides using dicyclohexyl[2',4',6'-triisopropyl(1,1'-biphenyl)-2-yl]phosphine (XPhos) ligand and relatively high loading levels of B₂pin₂⁴² in dioxane, or using dicyclohexyl[2',6'-dimethoxy-(1,1'-diphenyl)-2-yl]phosphine (SPhos) ligand, pinacolborane, and triethylamine as solvent.⁴⁰ The Buchwald systems deliver superior performance in the borylation of many *ortho*-substituted aryl chlorides but are more expensive than the mixed-ligand systems reported here. In addition to Pd and Ni, Zu, Ma,^{44a} and Marder^{44b} reported Cu-catalyzed borylation of aryl halides which has been shown to be effective for *ortho*-methoxy and *ortho*-methyl-substituted aryl bromides and iodides but not for aryl chloride.

Conclusions

Efficient catalysts have been developed for the Ni-catalyzed neopentylglycolborylation of *ortho*-substituted aryl iodides, bromides, and chlorides. The mixed-ligand system NiCl₂(dppp)/dppf, previously developed for the Ni-catalyzed neopentylglycolborylation of a diverse array of aryl chlorides, and the mixed-ligand system NiCl₂(dppp)/PPh₃ were shown to be effective catalysts for the *ortho*-substituted aryl halides, demonstrating once again the value of the mixed-ligand concept. Preliminary experiments showed that electron-poor heterocycles such as 2-bromopyridines and pyrimidines were not successful in the neopentylglycolborylation under the same reaction conditions. Detailed optimization of the Ni-catalyzed neopentylglycolborylation of Ni-catalyzed borylation of 2-iodoanisole and methyl 2-iodobenzoate suggests that the generation of Ni(0) active

catalysts from Ni(II)Cl₂ precatalysts is highly dependent on the ligand and coligand, but also that a mixed-ligand catalyst is likely present in the active catalytic cycle. Additionally, it was demonstrated that protodeborylation and hydrodehalogenation are competitive side reactions of Ni-catalyzed neopentylglycolborylation of *ortho*-substituted derivatives containing carboxylates as electron-deficient substituents and that Ni(II)Cl₂(ligand) in the presence of H₂O and Ni(0), respectively, most probably mediates these processes. Further mechanistic and theoretical studies will be required to elucidate the structural benefits of mixed-ligand systems in various stages of the catalytic cycle.

Experimental Section

Preparation of Neopentylglycolborane. To a cooled solution (0 °C) of neopentylglycol (10.0 mmol, 2.0 equiv) dissolved in toluene (5 mL) was slowly added (CH₃)₂S·BH₃ (10.0 mmol, 2.0 equiv) via a syringe under nitrogen. After 30 min of stirring at 0 °C, the reaction mixture was allowed to warm to 23 °C and was left stirring at 23 °C until the gas evolution ceased (60–90 min). Neopentylglycolborane was used directly without further purification.

General Procedure for Neopentylglycolborylation. A Schlenk tube charged with the aryl chloride (5.0 mmol, 1.0 equiv) (for aryl chlorides, the reaction was conducted on 2.5 mmol scale), Ni catalyst (for the exact amount of catalyst and coligand, see Tables 1–8 in the text), (NiCl₂(dppp), NiCl₂(dppe), NiCl₂(dppb), NiCl₂(dppf), NiCl₂(PPh₃)₂, Ni(COD)₂) (0.5 mmol, 0.1–0.02 equiv), ligand (L: dppp, dppe, dppf, dppb, PPh₃, PCy₃, PTol₃) (0.5 mmol, 0.2–0.02 equiv), and a Teflon-coated stir bar was evacuated three times for 10 min under high vacuum and backfilled with N₂. Toluene (5 mL) and Et₃N (15.0 mmol, 3.0 equiv) were added to the reaction mixture at 23 °C. Freshly prepared neopentylglycolborane (10.0 mmol, 2.0 equiv in 5 mL of toluene) was added to the red colored suspension via syringe at 23 °C. The reaction mixture was heated to 100 °C (for NiCl₂(PPh₃)₂ catalyst, the reactions were performed at 80 °C to ensure catalyst stability), and the conversion was followed by GC. After 1–40 h (reaction time depends on the type of the chloro derivative and on the catalyst loading), maximum conversion was determined by GC and the reaction mixture was quenched via slow addition of a saturated aqueous ammonium chloride solution (10 mL). The quenched reaction mixture was washed three times with saturated aqueous ammonium chloride solution and extracted with ethyl acetate (50 mL). The combined organic layers were dried over anhydrous MgSO₄, filtered, and concentrated. The crude product was purified by silica gel chromatography or by recrystallization.

Methyl 2-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)benzoate (2a):⁴³ Colorless oil; ¹H NMR (500 MHz, CDCl₃) δ 7.9 (dd, *J* = 7.8, 0.8 Hz, 1H), 7.5 (m, 2H), 7.4 (dt, *J* = 7.8, 2.4 Hz, 1H), 3.9 (s, 3H), 3.80 (s, 4H), 1.1 (s, 6H); ¹³C NMR (126 MHz, CDCl₃) δ 169.4, 133.1, 132.3, 131.6, 129.0, 128.7, 72.9, 52.7, 32.2, 22.4.

2-(2-Fluorophenyl)-5,5-dimethyl-1,3,2-dioxaborinane (2b): Yellowish crystals, mp 37–40 °C (lit.³¹ 40 °C); ¹H NMR (500 MHz, CDCl₃) δ 7.7 (dt, *J* = 6.8, 1.7 Hz, 1H), 7.4 (m, 1H), 7.1 (t, *J* = 7.3 Hz, 1H), 7.0 (t, *J* = 8.8 Hz, 1H), 3.8 (s, 4H), 1.0 (s, 6H); ¹³C NMR (126 MHz, CDCl₃) δ 168.4 (d, *J* = 250 Hz), 136.5 (d, *J* = 8 Hz), 132.9 (d, *J* = 9 Hz), 123.8 (d, *J* = 3 Hz), 115.7 (d, *J* = 24 Hz), 72.7, 32.1, 22.2.

2-(2-Bromophenyl)-5,5-dimethyl-1,3,2-dioxaborinane (2c):⁷⁶ Colorless oil; ¹H NMR (500 MHz, CDCl₃) δ 7.6 (dd, *J* = 7.3, 1.7 Hz, 1H), 7.5 (dd, *J* = 7.9, 0.9 Hz, 1H), 7.3 (dt, *J* = 7.6, 1.0 Hz, 1H), 7.2 (dt, *J* = 7.6, 1.8 Hz, 1H), 3.8 (s, 4H), 1.0 (s, 6H); ¹³C NMR

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(126 MHz, CDCl₃) δ 135.7, 132.9, 131.4, 127.8, 126.6, 72.8, 32.2, 22.2.

1,2-Bis(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)benzene (2d): White crystals, mp 55–58 °C; ¹H NMR (500 MHz, CDCl₃) δ 7.6 (dd, *J* = 5.4, 3.3 Hz, 2H), 7.3 (dd, *J* = 5.4, 3.3 Hz, 2H), 3.8 (s, 8H), 1.1 (s, 12H); ¹³C NMR (126 MHz, CDCl₃) δ 132.5, 128.9, 72.9, 32.2, 22.3; HRMS (ES+) calcd for C₁₆H₂₄B₂O₄ (M⁺ + H) 303.1939, found 303.1947.

5,5-Dimethyl-2-(*o*-tolyl)-1,3,2-dioxaborinane (2e):⁷⁷ Colorless oil; ¹H NMR (500 MHz, CDCl₃) δ 7.7 (d, *J* = 7.3 Hz, 1H), 7.3 (dt, *J* = 7.4, 1.4 Hz, 1H), 7.1 (t, *J* = 7.5 Hz, 2H), 3.7 (s, 4H), 2.5 (s, 3H), 1.0 (s, 6H); ¹³C NMR (126 MHz, CDCl₃) δ 144.1, 135.0, 130.2, 130.1, 124.8, 72.4, 31.8, 22.6, 22.0.

2-(2-Methoxyphenyl)-5,5-dimethyl-1,3,2-dioxaborinane (2f): White solid, mp 39–41 °C (lit.⁷⁸ 41 °C); ¹H NMR (500 MHz, CDCl₃) δ 7.6 (dd, *J* = 7.2, 1.7 Hz, 1H), 7.4 (dt, *J* = 7.8, 1.8 Hz, 1H), 6.9 (dt, *J* = 7.3, 0.7 Hz, 1H), 6.9 (d, *J* = 8.3 Hz, 1H), 3.8 (s, 3H), 3.8 (s, 4H), 1.0 (s, 6H); ¹³C NMR (126 MHz, CDCl₃) δ 164.0, 136.1, 132.0, 120.6, 110.7, 72.8, 56.0, 32.1, 22.2.

5,5-Dimethyl-2-(2-(trifluoromethyl)phenyl)-1,3,2-dioxaborinane (2h):⁷⁹ Colorless oil; ¹H NMR (500 MHz, CDCl₃) δ 7.7 (d, *J* = 7.1 Hz, 1H), 7.4 (m, 1H), 7.6 (d, *J* = 7.6 Hz, 1H), 7.5 (m, 2H), 3.8 (s, 4H), 1.1 (s, 6H); ¹³C NMR (126 MHz, CDCl₃) δ 134.2, 133.5 (d, *J* = 31 Hz), 131.0, 129.6, 126.0 (d, *J* = 273 Hz), 125.6 (q, *J* = 5 Hz), 72.9, 32.1, 22.1.

5,5-Dimethyl-2-(thiophen-2-yl)-1,3,2-dioxaborinane (2i): White crystals, mp 91–92 °C (lit.⁵⁵ 91–92 °C); ¹H NMR (500 MHz, CDCl₃) δ 7.6 (dd, *J* = 3.5, 0.8 Hz, 1H), 7.6 (dd, *J* = 4.7, 0.8 Hz, 1H), 7.2 (dd, *J* = 4.7, 3.5 Hz, 1H), 3.8 (s, 4H), 1.0 (s, 6H); ¹³C NMR (126 MHz, CDCl₃) δ 136.0, 131.7, 128.4, 72.7, 32.4, 22.2.

2,5-Bis(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)thiophene (2j): White crystals, mp 156–157 °C (lit.⁸⁰ 156.5–157.5 °C); ¹H NMR (500 MHz, CDCl₃) δ 7.6 (s, 2H), 3.8 (s, 8H), 1.0 (s, 12H); ¹³C NMR (126 MHz, CDCl₃) δ 136.6, 72.7, 32.4, 22.3.

2-(2-(Benzyloxy)phenyl)-5,5-dimethyl-1,3,2-dioxaborinane (2k): White crystals, mp 79–81 °C; ¹H NMR (500 MHz, CDCl₃) δ 7.7 (dd, *J* = 7.3, 1.7 Hz, 1H), 7.5 (d, *J* = 7.2 Hz, 2H), 7.4 (m, 3H), 7.3 (t, *J* = 7.4 Hz, 1H), 7.0 (td, *J* = 7.3, 0.7 Hz, 1H), 6.9 (d, *J* = 8.3 Hz, 1H), 5.1 (s, 2H), 3.8 (s, 4H), 1.1 (s, 6H); ¹³C NMR (126 MHz, CDCl₃) δ 163.1, 138.1, 135.9, 131.9, 128.6, 127.7, 127.2, 121.7, 112.7, 72.8, 70.6, 32.1, 22.3; HRMS (CI+) calcd for C₁₈H₂₁BO₃ (M⁺) 296.1584, found 296.1601.

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2-(2-Chlorophenyl)-5,5-dimethyl-1,3,2-dioxaborinane (2m): Yellow crystals, mp 33–35 °C (lit.³¹ 36 °C); ¹H NMR (500 MHz, CDCl₃) δ 7.6 (dd, *J* = 7.4, 1.5 Hz, 1H), 7.3 (m, 2H), 7.2 (dt, *J* = 7.3, 1.3 Hz, 1H), 3.8 (s, 4H), 1.1 (s, 6H); ¹³C NMR (126 MHz, CDCl₃) δ 138.9, 135.8, 131.4, 129.8, 126.1, 72.9, 32.1, 22.2.

General Procedure for Aryl Trifluoroborate Synthesis. The trifluoroborates were prepared from the corresponding crude boronic esters according to literature procedures.⁶⁶ In a nalgene bottle were added a stir bar and the crude boronic ester (5 mmol, 1 equiv) dissolved in 12 mL of MeOH/H₂O (2:1). KHF₂ (15 mmol, 3 equiv) was added one portion over the reaction mixture, and the reaction mixture was stirred at room temperature overnight. The reaction mixture was transferred to a round-bottom flask and concentrated by rotary evaporation. The crude product was recrystallized from acetone to yield the corresponding trifluoroborate.

Potassium trifluoro(2-(methoxycarbonyl)phenyl)borate (3a):⁸¹ White powder, mp > 250 °C; ¹H NMR (500 MHz, DMSO-*d*₆) δ 7.5 (d, *J* = 7.3 Hz, 1H), 7.2 (m, 2H), 7.1 (dt, *J* = 7.4, 1.2 Hz, 1H), 3.7 (s, 3H); ¹³C NMR (126 MHz, DMSO-*d*₆) δ 172.2, 136.6, 132.7, 128.2, 125.7, 124.8, 51.2.

Potassium trifluoro(2-methoxyphenyl)borate (3f): White powder, mp > 250 °C (lit.⁸¹ > 230 °C); ¹H NMR (500 MHz, DMSO-*d*₆) δ 7.3 (d, *J* = 6.6 Hz, 1H), 7.0 (d, *J* = 7.4 Hz, 1H), 6.7 (m, 2H), 3.6 (s, 3H); ¹³C NMR (126 MHz, DMSO-*d*₆) δ 162.5, 131.2, 126.6, 119.1, 109.6, 54.7.

Potassium (2,6-difluorophenyl)trifluoroborate (3g): White powder, mp > 250 °C (lit.⁶⁶ > 250 °C); ¹H NMR (500 MHz, DMSO-*d*₆) δ 7.1 (m, 1H), 6.7 (m, 2H); ¹³C NMR (126 MHz, DMSO-*d*₆) δ 166.9 (dd, *J* = 242, 18 Hz), 127.6, 110.2 (dd, *J* = 31, 8 Hz).

Potassium trifluoro(2-(trifluoromethyl)phenyl)borate (3h): White powder, mp 195–200 °C (lit.⁸² 175–180 °C); ¹H NMR (500 MHz, DMSO-*d*₆) δ 7.7 (d, *J* = 6.1 Hz, 1H), 7.5 (d, *J* = 7.5 Hz, 1H), 7.4 (t, *J* = 7.0 Hz, 1H), 7.2 (d, *J* = 7.2 Hz, 1H); ¹³C NMR (126 MHz, DMSO-*d*₆) δ 134.1 (d, *J* = 3 Hz), 131.7 (d, *J* = 30 Hz), 129.8, 126.6 (d, *J* = 274 Hz), 125.4, 124.2 (q, *J* = 5 Hz).

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Supporting Information Available: ¹H NMR, ¹³C NMR, and HRMS data for new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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