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$NiCl_2(PMe_3)_2$-Catalyzed Borylation of Aryl Chlorides

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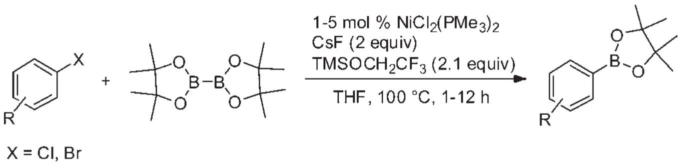
ABSTRACT



The cross-coupling of aryl chlorides and bis(pinacolato)diboron was achieved using $NiCl_2(PMe_3)_2$ catalyst in the presence of metal 2,2,2-trifluoroethoxide. The catalyst smoothly provided the desired products regardless of a variety of functional groups and substituted positions.

Arylboronic acids and their derivatives are important building blocks in organic synthesis.[1] In particular, their application in transition-metal-catalyzed carbon–carbon and carbon–heteroatom bond formation renders them one of the most useful synthetic tools in both academic laboratories and industry.[2] The traditional syntheses of arylboron compounds have technical problems and are limited in functional group tolerance.[1] In the past two decades, two efficient methods for the synthesis of arylboronic esters *via* transition-metal-catalyzed carbon–boron bond formation have been developed. One is Rh- or Ir-catalyzed direct C–H borylation of arenes,[3,4] and the other is Pd-,[5] Ni-,[6] or Cu-catalyzed[7] substitutional borylation of aryl halides. Direct C–H borylation is generally *meta*- or *para*-oriented under typical conditions due to the steric hindrance of the substituent at the *ortho*-position. In contrast, the borylation of substrates with functional groups such as hydrosilyl[4a,b] and carbonyl[4c–f] occurs only at the *ortho*-position of these groups through *ortho*-metalation. Therefore, direct C–H borylation is not always applicable for the synthesis of desired arylboronic esters. On the other hand, substitutional borylation should proceed only at the carbon–halogen bond and can provide the desired products from appropriate aryl halides. Pd-catalyzed borylation was achieved with even aryl chlorides by the use of electron-rich and bulky[5b–e,g] or silica-supported[5m] ligands, while Cu-catalyzed borylation was limited to aryl bromides and iodides.[7] The development of widely available Ni catalysts for substitutional borylation is a recent topic in the field of cross-coupling reactions. In the past few years, Percec and Murata independently developed Ni-catalyzed borylation using dialkoxyborane.[6b–h] Although this borylation proceeds smoothly with aryl halides and mesylates, it has some limitations with respect to functionalized substrates. Therefore, we have been interested in the development of Ni-catalyzed borylation with improved substrate scope. Herein, we report the $NiCl_2(PMe_3)_2$-catalyzed borylation of a wide range of functionalized aryl chlorides, including sterically challenging substrates using bis(pinacolato)diboron in the presence of metal 2,2,2-trifluoroethoxide.

Table 1 shows the results of the Ni-catalyzed borylation of methyl 4-chlorobenzoate, **1a**, using K_3PO_4 as a base.

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(1) *Boronic Acids*; Hall, D. G., Ed.; Wiley-VCH: Weinheim, Germany, 2005.

(2) For selected reviews, see: (a) Liu, C.; Zhang, H.; Shi, W.; Lei, A. *Chem. Rev.* **2011**, *111*, 1780. (b) Partyka, D. V. *Chem. Rev.* **2011**, *111*, 1529. (c) Rosen, B. M.; Quasdorf, K. W.; Wilson, D. A.; Zhang, N.; Resmerita, A. M.; Garg, N. K.; Percec, V. *Chem. Rev.* **2011**, *111*, 1346. (d) Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, *41*, 1461. (e) Molander, G. A.; Ellis, N. *Acc. Chem. Res.* **2007**, *40*, 275. (f) Corbet, J.-P.; Mignani, G. *Chem. Rev.* **2006**, *106*, 2651.

(3) For recent reviews, see: (a) Hartwig, J. F. *Chem. Soc. Rev.* **2011**, *40*, 1992. (b) Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890.

(4) (a) Robbins, D. W.; Boebel, T. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 4068. (b) Boebel, T. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 7534. (c) Yamazaki, K.; Kawamorita, S.; Ohmiya, H.; Sawamura, M. *Org. Lett.* **2010**, *12*, 3978. (d) Kawamorita, S.; Ohmiya, H.; Sawamura, M. *J. Org. Chem.* **2010**, *75*, 3855. (e) Ishiyama, T.; Isou, H.; Kikuchi, T.; Miyaura, N. *Chem. Commun.* **2010**, *46*, 159. (f) Miyaura, N. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 1535.

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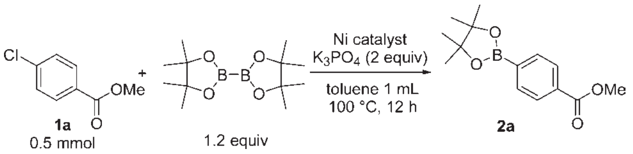
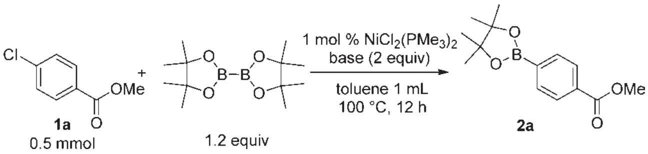
Table 1. Screening of Ni Complexes



entry	catalyst (mol %)	additive (mol %)	yield of **2a**[a] (%)	yield of methyl benzoate[a] (%)
1	NiCl$_2$(dppp) (10)	–	33	14
2	NiCl$_2$(dppp) (5)	dppf (10)	5	29
3[b]	NiCl$_2$(dppp) (5)	dppf (10)	1	0
4	NiCl$_2$(PCy$_3$)$_2$ (10)	–	13	12
5	NiCl$_2$(PPh$_3$)$_2$ (10)	–	6	64
6	NiCl$_2$(dmpe) (10)	–	12	74
7	NiCl$_2$(dppm) (10)	–	22	1
8	NiCl$_2$(dppe) (10)	–	5	6
9	NiCl$_2$(dppf) (10)	–	8	40
10	NiCl$_2$(PMe$_3$)$_2$ (10)	–	74	0
11	NiCl$_2$(PMe$_3$)$_2$ (5)	–	73	2
12	NiCl$_2$(PMe$_3$)$_2$ (1)	–	39	6

[a] GC yield based on a calibrated internal standard. [b] K$_3$PO$_4$ (1.0 mmol) was replaced by NEt$_3$ (1.5 mmol).

Table 2. Effect of the Base on the Ni-Catalyzed Borylation



entry	base	additive (mol %)	yield of **2a**[a] (%)	yield of methyl benzoate[a] (%)
1	Na$_3$PO$_4$	–	16	0
2	K$_2$CO$_3$	–	24	2
3	Cs$_2$CO$_3$	–	33	6
4	AcOK	–	0	0
5	PhOK	–	19	15
6	*t*-BuOK	–	18	7
7	K$_3$PO$_4$	H$_2$O (200)	0	0
8	K$_3$PO$_4$	EtOH (200)	27	13
9	K$_3$PO$_4$	CF$_3$CH$_2$OH (200)	88	12
10	CsF	TMSOCH$_2$CF$_3$ (300)	90[c]	3
11[b]	CsF	TMSOCH$_2$CF$_3$ (210)	99[c]	0
12[b]	CsF	–	32	12
13[b]	–	TMSOCH$_2$CF$_3$ (210)	0	0

[a] GC yield based on a calibrated internal standard. [b] Toluene (1 mL) was replaced by THF (0.5 mL). [c] Isolated yield.

NiCl$_2$(dppp)/NEt$_3$ is known as an efficient catalyst for the borylation of aryl halides using dialkoxyboranes.[6b–i] Moreover, NiCl$_2$(PCy$_3$)$_2$/inorganic base catalyzes the borylation of aryl carbamates using bis(neopentylglycolato)-diboron.[6a] However, these Ni catalyst systems were not effective for this borylation (entries 1–4). Conventional Ni-phosphine complexes such as NiCl$_2$(dmpe), NiCl$_2$-(PPh$_3$)$_2$, NiCl$_2$(dppm), NiCl$_2$(dppe), and NiCl$_2$(dppf) also exhibited poor activity (entries 5–9). In contrast, NiCl$_2$(PMe$_3$)$_2$ catalyzed the borylation in good yield (entries 10 and 11). Nevertheless, the yield declined to 39% with 1 mol % of NiCl$_2$(PMe$_3$)$_2$.

Our next investigation surveyed bases to achieve satisfactory yields for the borylation with only 1 mol % of NiCl$_2$(PMe$_3$)$_2$. The results are summarized in Table 2. Inorganic bases such as Na$_3$PO$_4$, K$_2$CO$_3$, and Cs$_2$CO$_3$, which have a similar basicity to that of K$_3$PO$_4$, were not effective for the reaction (entries 1–3). Potassium acetates[5] and alkoxides such as potassium phenoxide[8] and potassium *tert*-butoxide[7a] are frequently used for the Pd- or Cu-catalyzed borylation of aryl halides and triflates.

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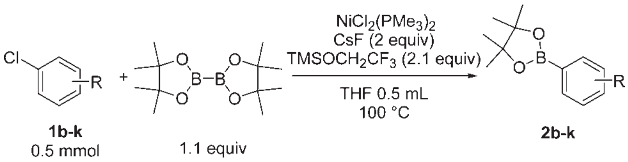
[5] (a) Tang, M.; Keshipeddy, S.; Zhang, Y.; Wei, X.; Savoie, J.; Patel, N. D.; Yee, N. K.; Senanayake, C. H. *Org. Lett.* **2011**, *13*, 1366. (b) Molander, G. A.; Trice, S. L. J.; Dreher, S. D. *J. Am. Chem. Soc.* **2010**, *132*, 17701. (c) Billingsley, K. L.; Buchwald, S. L. *J. Org. Chem.* **2008**, *73*, 5589. (d) Billingsley, K. L.; Barder, T. E.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2007**, *46*, 5359. (e) Murata, M.; Sambommatsu, T.; Watanabe, S.; Masuda, Y. *Synlett* **2006**, 1867. (f) Broutin, P. E.; Cerna, I.; Campaniello, M.; Leroux, F.; Colobert, F. *Org. Lett.* **2004**, *6*, 4419. (g) Ishiyama, T.; Ishida, K.; Miyaura, N. *Tetrahedron* **2001**, *57*, 9813. (h) Baudoin, O.; Guenard, D.; Gueritte, F. *J. Org. Chem.* **2000**, *65*, 9268. (i) Murata, M.; Oyama, T.; Watanabe, S.; Masuda, Y. *J. Org. Chem.* **2000**, *65*, 164. (j) Murata, M.; Watanabe, S.; Masuda, Y. *J. Org. Chem.* **1997**, *62*, 6458. (k) Ishiyama, T.; Itoh, Y.; Kitano, T.; Miyaura, N. *Tetrahedron Lett.* **1997**, *38*, 3447. (l) Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508. (m) Kawamorita, S.; Ohmiya, H.; Iwai, T.; Sawamura, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 8363.

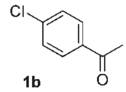
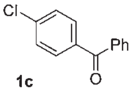
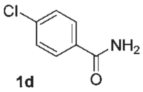
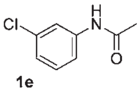
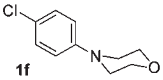
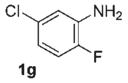
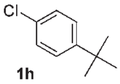
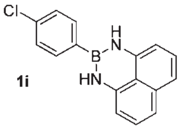
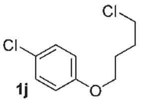
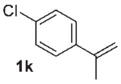
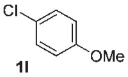
[6] (a) Huang, K.; Yu, D.-G.; Zheng, S.-F.; Wu, Z.-H.; Shi, Z.-J. *Chem.—Eur. J.* **2011**, *17*, 786. (b) Murata, M.; Sambommatsu, T.; Oda, T.; Watanabe, S.; Masuda, Y. *Heterocycles* **2010**, *80*, 213. (c) Leowanawat, P.; Resmerita, A.-M.; Moldoveanu, C.; Liu, C.; Zhang, N.; Wilson, D. A.; Hoang, L. M.; Rosen, B. M.; Percec, V. *J. Org. Chem.* **2010**, *75*, 7822. (d) Moldoveanu, C.; Wilson, D. A.; Wilson, C. J.; Leowanawat, P.; Resmerita, A.-M.; Liu, C.; Rosen, B. M.; Percec, V. *J. Org. Chem.* **2010**, *75*, 5438. (e) Wilson, D. A.; Wilson, C. J.; Moldoveanu, C.; Resmerita, A.-M.; Corcoran, P.; Hoang, L. M.; Rosen, B. M.; Percec, V. *J. Am. Chem. Soc.* **2010**, *132*, 1800. (f) Moldoveanu, C.; Wilson, D. A.; Wilson, C. J.; Corcoran, P.; Rosen, B. M.; Percec, V. *Org. Lett.* **2009**, *11*, 4974. (g) Wilson, D. A.; Wilson, C. J.; Rosen, B. M.; Percec, V. *Org. Lett.* **2008**, *10*, 4879. (h) Rosen, B. M.; Huang, C.; Percec, V. *Org. Lett.* **2008**, *10*, 2597. (i) Morgan, A. B.; Jurs, J. L.; Tour, J. M. *J. Appl. Polym. Sci.* **2000**, *76*, 1257.

[7] (a) Kleeberg, C.; Dang, L.; Lin, Z. Y.; Marder, T. B. *Angew. Chem., Int. Ed.* **2009**, *48*, 5350. (b) Zhu, W.; Ma, D. *Org. Lett.* **2006**, *8*, 261. (c) Fang, H.; Kaur, G.; Yan, J.; Wang, B. *Tetrahedron Lett.* **2005**, *46*, 671.

[8] Takagi, J.; Takahashi, K.; Ishiyama, T.; Miyaura, N. *J. Am. Chem. Soc.* **2002**, *124*, 8001.

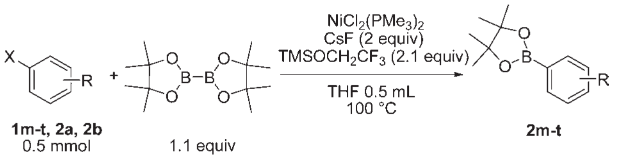
Table 3. Borylation of *Para*- and *Meta*-Substituted Aryl Chlorides

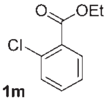
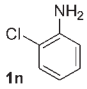
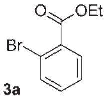
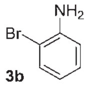
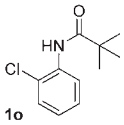
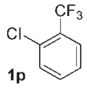
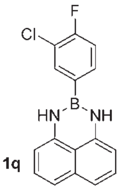
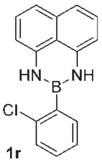
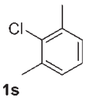


entry	substrate	product	Ni cat. (mol %)	reaction time (h)	yield[a] (%)
1	 **1b**	**2b**	2	12	81
2	 **1c**	**2c**	1	12	73
3[b]	 **1d**	**2d**	1	12	75
4[b]	 **1e**	**2e**	1	12	93
5	 **1f**	**2f**	3	12	86
6	 **1g**	**2g**	3	12	81
7	 **1h**	**2h**	3	12	72
8	 **1i**	**2i**	3	12	82
9	 **1j**	**2j**	3	12	78
10	 **1k**	**2k**	3	2	79
11	 **1l**	**2l**	5	2	93

[a] Isolated yield. [b] THF was replaced by 1,4-dioxane.

Table 4. Borylation of *Ortho*-Substituted Aryl Halides



entry	substrate	product	Ni cat. (mol %)	reaction time (h)	yield[a] (%)
1	 **1m**	**2m**	5	2	78
2	 **1n**	**2n**	3	12	80
3	 **3a**	**2m**	5	1	78
4[b]	 **3b**	**2n**	3	1	84
5[c]	 **1o**	**2o**	3	12	85
6	 **1p**	**2p**	2	12	88
7	 **1q**	**2q**	3	12	85
8[d]	 **1r**	**2r**	5	3	86
9[c, e]	 **1s**	**2s**	10	12	90

[a] Isolated yield. [b] THF was replaced by toluene. [c] THF was replaced by 1,4-dioxane. [d] Reaction temperature was 120 °C. [e] The reaction was carried out with bis(pinacolato)diboron (1.0 mmol, 2.0 equiv), CsF (1.5 mmol, 3.0 equiv), and $TMSCH_2CF_3$ (1.75 mmol, 3.5 equiv) at 135 °C.

However, these bases afforded a low yield for the present borylation (entries 4–6). We then attempted the addition of protic compounds, which are known to accelerate transition-metal-catalyzed borylation with diborons.[9] However, the addition of H_2O and ethanol in the borylation using K_3PO_4 afforded lower yields (entries 7 and 8). In contrast, 2,2,2-trifluoroethanol drastically improved the yield (entry 9), suggesting that potassium 2,2,2-trifluoroethoxide generated *in situ* worked effectively as a base. Then, we examined the addition of various metal 2,2,2-trifluoroethoxides on the reaction. Since metal 2,2,2-trifluoroethoxides are known to be explosive,[10] we performed the reactions using a mixture of an inorganic salt and

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[9] For selected papers, see: (a) Thorpe, S. B.; Guo, X.; Santos, W. L. *Chem. Commun.* **2011**, *47*, 424. (b) Tobisu, M.; Fujihara, H.; Koh, K.; Chatani, N. *J. Org. Chem.* **2010**, *75*, 4841. (c) Hirano, K.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2007**, *9*, 5031. (d) Mun, S.; Lee, J. E.; Yun, J. *Org. Lett.* **2006**, *8*, 4887.

trimethyl(2,2,2-trifluoroethoxy)silane. As a result, the yield reached 90% using CsF (entry 10). The use of THF instead of toluene further improved the yield to 99% (entry 11). Since the addition of only CsF or $TMSOCH_2CF_3$ afforded a poor yield, it can be concluded that cesium 2,2,2-trifluoroethoxide is required to obtain an excellent yield (entry 11 vs 12 and 13).

The scope of various aryl halides in this borylation is summarized in Tables 3 and 4. Table 3 shows the results using *para*- and *meta*-substituted aryl chlorides. The reactions proceeded smoothly with substrates having various functional groups, which included carbonyl, amide, unprotected amine, protected boryl,[12] and alkenyl groups (entries 1–4, 6, 8, and 10). For the borylation of amide-substituted aryl chlorides, 1,4-dioxane was a better solvent than THF in terms of yield (entries 3 and 4). The chloro moiety on the alkyl substituent remained intact under these reaction conditions (entry 9). Aryl chlorides with electron-withdrawing substituents such as **1b**, **1c**, and **1d** gave satisfactory yields with 1–2 mol % of catalyst (entries 1–3). In contrast, more catalyst (3–5 mol %) was required to obtain good yields in the borylation of electron-rich aryl chlorides, **1f**, **1g**, **1j**, and **1l** (entries 5, 6, 9, and 11).

Table 4 summarizes the results of the borylation of *ortho*-substituted aryl halides. Interestingly, the catalyst system of $NiCl_2(PMe_3)_2$, CsF, and $TMSOCH_2CF_3$ was revealed to borylate ethyl 2-chlorobenzoates and 2-chloroaniline in satisfactory yields (entries 1 and 2), indicating that this catalyst system is exceptionally suitable for *ortho*-substituted substrates. Additionally, bromo derivatives were borylated for a much shorter reaction time than chloro derivatives (entries 3 and 4). Satisfactory yields were obtained even when the substrates featured sterically bulky substituents such as **1s** and **1t**, although higher reaction temperatures and 5–10 mol % of catalyst were required (entries 9 and 10). It is known that the borylation of 2,6-substituted aryl halides is difficult due to steric hindrance and has only been achieved using a Pd catalyst for aryl chlorides.[5a,d,m] So far, no report on the Ni-catalyzed borylation of 2,6-substituted aryl chlorides has been published. Therefore, it is noteworthy that the result shown in entry 9 is the first example of Ni-catalyzed borylation of a 2,6-substituted aryl chloride.

In conclusion, we demonstrated that the combination of $NiCl_2(PMe_3)_2$, CsF, and $TMSOCH_2CF_3$ is an efficient catalyst system for the borylation of various aryl halides with bis(pinacolato)diboron. In particular, metal 2,2,2-trifluoroethoxides are rare bases for the coupling reaction. Further work is underway to expand the scope of substrates and clarify the effect of the metal fluorinated alkoxides.

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Supporting Information Available. Experimental procedures and spectral data for isolated products. This material is available free of charge via the Internet at http://pubs.acs.org.

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