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One-Pot Borylation/Amination Reactions: Syntheses of Arylamine Boronate Esters from Halogenated Arenes

Daniel Holmes, Ghayoor A. Chotana, Robert E. Maleczka, Jr.,* and Milton R. Smith, III*

Department of Chemistry, Michigan State University, East Lansing, Michigan 48824 USA

smithmil@msu.edu

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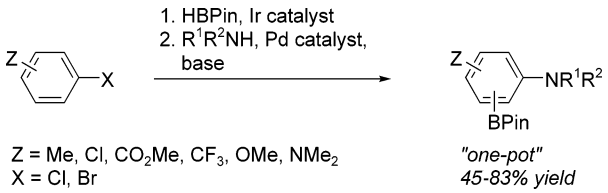
ABSTRACT



A one-pot protocol for converting 1,3- and 1,4-substituted aryl halides to arylamine boronate esters is described. This is achieved by sequential Ir-catalyzed aromatic borylation at the least hindered C–H bond of the aryl halide and subsequent Pd-catalyzed C–N coupling at the halide position of the crude arylboronic ester.

Metal-catalyzed halide substitution reactions have enhanced the synthetic utility of halogenated aromatic compounds. Noteworthy examples include C−C,[1] C−N, and C−O[2] bond-forming reactions, which are predominantly Pd-mediated processes.[3] Because the scope of these transformations is tied to commercial availability of halogenated compounds, processes that enable functionalization at nonhalogen sites can augment the substrate pool. In this regard, Ir-catalyzed borylation reactions are particularly intriguing because C−H bonds in halogenated aromatic systems can be converted selectively to C−B bonds.[4,5] We, and others, have shown that this selectivity enables one-pot elaborations of aryl halides to phenols, when the boronic ester is oxidized,[6] or to biaryls and polyaromatics when the nascent arylboronate ester is subjected to subsequent Pd-mediated C−C coupling.[4,5c,7]

These results suggest that other metal-catalyzed transformations of crude arylboronate esters produced from Ir-catalyzed aromatic borylations might be possible. In this Letter we describe a one-pot borylation/amination protocol where aryl halides can be converted to C-borylated anilines. In addition to requiring that the Pd-catalyzed reaction operates without interference from Ir species that remain after borylation, realization of the tandem catalytic process hinges on the successful differentiation between C−N and C−C

(1) (a) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147−168. (b) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483.

(2) (a) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131−209. (b) Wolfe, J. P.; Wagaw, S.; Marcoux, J. F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805−818. (c) Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852−860.

(3) For recent advances in Cu-catalyzed carbon−heteroatom bond-forming reactions, see: Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400−5449.

(4) Cho, J. Y.; Tse, M. K.; Holmes, D.; Maleczka, R. E., Jr.; Smith, M. R., III *Science* **2002**, *295*, 305−308.

(5) For related Ir-catalyzed borylations, see: (a) Ishiyama, T.; Takagi, J.; Ishida, K.; Miyaura, N.; Anastasi, N. R.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 390−391. (b) Ishiyama, T.; Takagi, J.; Yonekawa, Y.; Hartwig, J. F.; Miyaura, N. *Adv. Synth. Catal.* **2003**, *345*, 1103−1106 (c) Ishiyama, T.; Nobuta, Y.; Hartwig, J. F.; Miyaura, N. *Chem. Commun.* **2003**, 2924−2925.

(6) Maleczka, R. E., Jr.; Shi, F.; Holmes, D.; Smith, M. R., III *J. Am. Chem. Soc.* **2003**, *125*, 7792−7793.

(7) For a recent review on tandem catalsyis, see: Santos, E. N. D.; Fogg, D. E. *Coord. Chem. Rev.* **2004**, *248*, 2365−2379.

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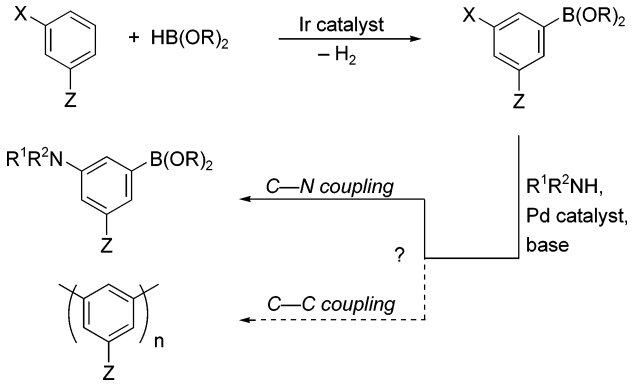
couplings with an aryl halide when amines and boronic esters are present in the reaction milieu.

Cross-couplings of aryl boron reagents or amines with aryl halides constitute two of the most important reactions for aryl halides. These reactions are typically facilitated by Pd catalysts in the presence of stoichiometric quantities of base. Given the similar reaction conditions for C−C and C−N couplings, attempted catalytic amination of the halogenated arylboronate ester in Scheme 1 could produce an arylamine

Scheme 1. Possible Outcomes for a One-Pot Borylation/Amination Sequence



if C−N coupling is favored, polyaromatic products if C−C coupling dominates, or a mixture of these products if C−N and C−C formation is competitive.

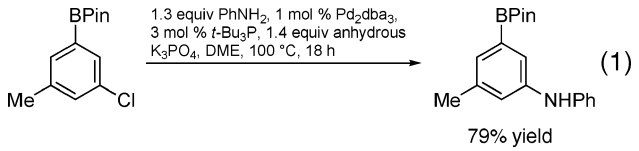
In terms of literature precedent, the prospects for selective amination according to Scheme 1 were bleak. As well as we are aware, there are no examples where C−B bonds survive during Pd-catalyzed amination conditions. Moreover, there are numerous examples where cross couplings of arylboronic acids[8] and esters[9] are accomplished in the presence of primary and secondary amines. However, our examinations of one-pot aromatic borylation/C−C coupling of arenes offered a ray of hope for the amination pathway in Scheme 1. Specifically, we found that Suzuki−Miyaura cross-couplings of pinacolate esters of arylboronic acids were typically slower than reactions of the arylboronic acids themselves.[10] Moreover, the rates of C−C couplings for pinacol boronate esters further diminish when the reactions are carried out under anhydrous conditions. Since virtually all examples of B−C/C−X cross-couplings of substrates with amine functionality involve boronic acids or boronate esters in the presence of either water or hydroxide, we reasoned that the combination of an aprotic base and an anhydrous, aprotic solvent offered the best chance for realizing C−N in lieu of C−C coupling.

(8) For selected examples, see: (a) Miura, Y.; Oka, H.; Momoki, M. *Synthesis* **1995**, *11*, 1419−1422. (b) Miura, Y.; Mamoki, M.; Nakatsuji, M. *J. Org. Chem.* **1998**, *63*, 1555−1565. (c) Miura, Y.; Nishi, T.; Teki, Y. *J. Org. Chem.* **2003**, *68*, 10158−10161. (d) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685−4696.

(9) Read, M. W.; Escobedo, J. O.; Willis, D. M.; Beck, P. A.; Strongin, R. M. *Org. Lett.* **2000**, *2*, 3201−3204.

(10) Chotana, A. G.; Holmes, D.; Maleczka, R. E., Jr.; Smith, M. R., III. Manuscript in preparation.

After an initial attempt of the one-pot reaction sequence failed, we explored aminations of the purified borylation product of 3-chlorotoluene. To our delight, selective C−N coupling was found by using anhydrous K_3PO_4 as the base according to eq 1. Returning to the one-pot sequence, we



examined the effects of the Ir and Pd precatalysts, base, and solvent on yields for the "one-pot" sequence in Scheme 2. The results are tabulated in Table 1.

Entries 1−4 examine the effects of the Ir source and the Ir ligand. While room temperature borylations are prohibitively slow for 3-chlorotoluene, the borylations could be carried out at 80 °C when the Ir ligand was 4,4′-di-*tert*-butyl-2,2′-bipyridyl (dtbpy). The best yields of the borylated arylamine were obtained when borylations were carried out with the (Ind)Ir(COD)/1,2-bis(dimethylphosphino)ethane (dmpe) Ir precatalyst/ligand formulation. In all cases, conversion of 3-chlorotoluene to the intermediate boronate ester was complete. Hence, the variations in yields for entries 1−4 likely arise from the efficiencies of the amination step.

Entries 1 and 5−8 illustrate the effects of the base on the amination step. K_3PO_4 and Cs_2CO_3 are both effective, whereas NaO^{t}Bu and KO^{t}Bu gave very low yields of the amino boronate ester. Entry 5 shows the deleterious effects of water as the amino boronate ester is not detected when $K_3PO_4 \cdot nH_2O$ is the base. In contrast to NaO^{t}Bu and KO^{t}Bu, where predominance of the intermediate boronate ester indicates that conversion to the amino boronate is simply slow, with $K_3PO_4 \cdot nH_2O$ the intermediate boronate ester is completely consumed. Entries 1, 9, and 10 show that the amination step is moderately sensitive to variations in the solvent, with DME giving superior results. Last, entries 1 and 11 illustrate the effect of the Pd precatalyst with Pd_2dba_3 being superior to $Pd(OAc)_2$, the principle difference being significant generation of the deborylated arylamine for the latter Pd precatalyst.

Armed with the results from Table 1, we examined the scope of the borylation/amination sequence for various 3-substituted halobenzenes for which borylation at the 5-position predominates. The general conditions in Scheme 3 were used and the results are listed in Table 2.

The isolated yields for the reactions in Table 2, based on the starting aryl halide, range from 47% to 83% with an average yield of 64%. This average corresponds to an 80% yield for the individual steps, assuming that the borylation and amination yields are identical. When the pure aryl boronate ester derived from borylation of 3-chlorotolene was isolated and subsequently aminated with aniline, the product in entry 1 was isolated in 60% overall yield based on 3-chlorotoluene, compared to the 75% yield obtained for the one-pot reaction. Thus, higher isolated yields are realized in the one-pot tandem reactions where isolation and purification

Scheme 2. One-Pot Borylation/Amination of 3-Chlorotoluene

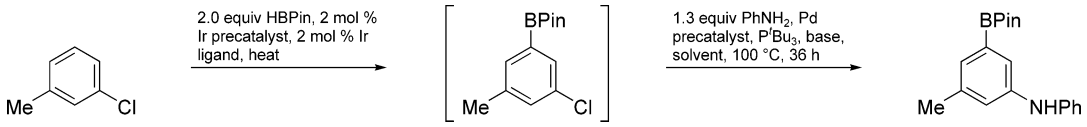
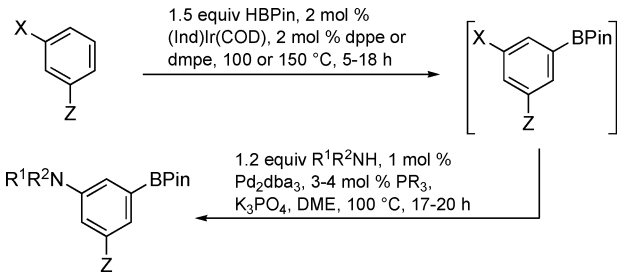


Table 1. Effects of Ir and Pd Precatalyst, Base, and Solvent on One-Pot Borylation/Amination of 3-chlorotoluene

entry	Ir precatalyst	Ir ligand	borylation conditions	Pd precatalyst	base	solvent	GC yield[a]
1	(Ind)Ir(COD)	dmpe	150 °C, 18 h	Pd_2dba_3	K_3PO_4	DME	93
2	(Ind)Ir(COD)	dppe	150 °C, 18 h	Pd_2dba_3	K_3PO_4	DME	89
3	(Ind)Ir(COD)	dtbpy	150 °C, 18 h	Pd_2dba_3	K_3PO_4	DME	87
4	$[Ir(\mu\text{-OMe})(COD)]_2$	dtbpy	80 °C, 24 h	Pd_2dba_3	K_3PO_4	DME	87
5	(Ind)Ir(COD)	dmpe	150 °C, 18 h	Pd_2dba_3	$K_3PO_4 \cdot nH_2O$	DME	0
6	(Ind)Ir(COD)	dmpe	150 °C, 18 h	Pd_2dba_3	Cs_2CO_3	DME	88
7	(Ind)Ir(COD)	dmpe	150 °C, 18 h	Pd_2dba_3	NaO^{t}Bu	DME	18
8	(Ind)Ir(COD)	dmpe	150 °C, 18 h	Pd_2dba_3	KO^{t}Bu	DME	10
9	(Ind)Ir(COD)	dmpe	150 °C, 18 h	Pd_2dba_3	K_3PO_4	dioxane	85
10	(Ind)Ir(COD)	dmpe	150 °C, 18 h	Pd_2dba_3	K_3PO_4	toluene	84
11	(Ind)Ir(COD)	dmpe	150 °C, 18 h	$Pd(OAc)_2$	K_3PO_4	DME	56

[a] GC yields based upon starting arene as an average of three runs.

Scheme 3



of the intermediate aryl halide boronate esters are avoided.[11] Entries 1−4 examine the effect of varying the amine on aminations of the borylation product of 3-chlorotoluene. The yields for aniline, morpholine, and *N*-methylaniline are excellent, while amination with dibutylamine gave a significantly lower yield of the 3-amino boronate ester. Entries 1, 6, 7, 10, and 11 show the effect of varying the Z substituent in Scheme 3. Electron-withdrawing substituents give lower yields of the 3-amino boronate esters. Since electron-withdrawing substituents on aryl boronic acids accelerate Suzuki−Miyaura cross-couplings, competition from this side reaction may contribute to the lower yields for electron-deficient aryl chlorides. Consistent with this notion, small quantities of aminated biaryls that arise from Suzuki−Miyaura coupling can be detected in the crude reaction mixture for entry 8.

Examples of 2- and 4-substituted halogenated benzenes that react with a high degree of regioselectivity are more limited. Nevertheless, the results from one-pot borylation/amination reactions using these substrates suggest that extensions beyond the regiochemistries in Table 2 are possible. Because unsymmetrical ortho-disubstituted benzenes typically exhibit poor borylation regioselectivities, the only 2-substituted halogenated benzene examined is *o*-dichlorobenzene. Regioselective borylation at the 4-position affords an intermediate boronate ester where the chloride positions are chemically distinct. Thus, synthetic utility depends on high regioselectivity in the amination step. Fortunately, the BPin group exerts a directing effect that, regardless of its origins (i.e., steric or electronic), responds to variations in the Pd phosphine ligand. While good regioselectivity is found for P*t*Bu$_3$ (2:1) and 2-dicyclohexylphosphino-2′-(dimethylamino)-1,1′-biphenyl (6:1), 2-(dicyclohexylphosphino)biphenyl gave superior results affording a 19:1 ratio of isomers in the isolated product favoring amination at the chloride position para to the BPin group. With the exception of regioselective amination at the 2-position of 2,3-dichloropyridine,[12] regioselectivities of this type have not been previously reported.

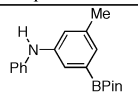
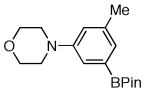
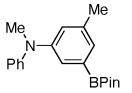
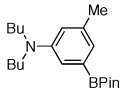
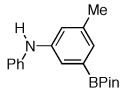
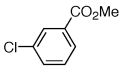
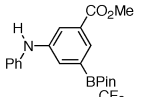
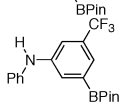
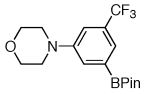
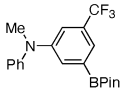
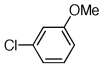
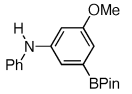
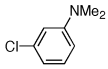
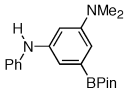
p-Dichlorobenzene similarly affords a single monoborylated product where the chloride positions are also chemically distinct. For this substrate, a 2-fold excess of arene is required to minimize diborylation. Consequently, the intermediate boronate ester was isolated. In contrast to the one-pot reaction for *o*-dichlorobenzene, subsequent amination of this boronate ester with aniline was less efficient and less regioselective, and deborylation was also observed. Attempts to isolate the pure amino boronate esters were unsuccessful.

When the 4-subtituent in 4-substituted chlorobenzenes is sufficiently large, borylation at the 2-position predominates. For example, 4-(trifluoromethyl)chlorobenzene affords a 95:5

(11) For a discussion of costs involved in product isolation, see: Anderson, N. G. *Org. Process Res. Dev.* **2004**, *8*, 260−265.

(12) Jonckers, T. H. M.; Maes, B. U. W.; Lemiere, G. L. F.; Dommisse, R. *Tetrahedron* **2001**, *57*, 7027−7034.

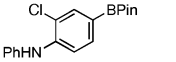
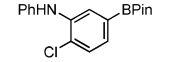
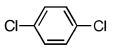
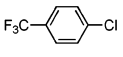
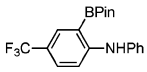
Table 2. Preparation of 1,3,5-Arylamino Boronate Esters by One-Pot Aromatic Borylation/Amination of aryl halides[a]

entry	aryl halide	amine	product	% yield[b]
1		$PhNH_2$		75
2		morpholine		73
3		PhN(H)Me		83
4		Bu_2NH		50
5		$PhNH_2$		63
6[c]		$PhNH_2$		47
7[c]		$PhNH_2$		71
8[c,d]		morpholine		49
9		PhN(H)Me		65
10		$PhNH_2$		61
11		$PhNH_2$		73

[a] General synthetic procedure: In a drybox, aryl halide (2.0 mmol), HBPin (4.0 mmol), (Ind)Ir (COD) (0.04 mmol), and dmpe (0.04 mmol) were transferred to a thick-walled, air-free flask equipped with a magnetic stirbar. The flask was sealed and the mixture stirred at 150 °C until the arene was consumed (GC-FID). The cooled reaction mixture was placed under vacuum for 1−2 h, after which anhydrous K_3PO_4 (2.8 mmol), Pd_2dba_3 (0.02 mmol), P(*t*-Bu)$_3$ (0.06 mmol), amine (2.4−2.6 mmol), and DME (3 mL) were added. The mixture was stirred at 100 °C until the boronate ester was consumed (GC-FID). See the Supporting Information for specific reaction conditions. [b] Isolated yields based upon an average of two runs. [c] Dppe was used in the borylation step. [d] Small amounts of aminated biphenyls were detected.

ratio of 2- and 3-monoborylated products. Subsequent amination of the crude reaction mixture with aniline and isolation gives isomerically pure 2-borylated amine. As was the case for *p*-dichlorobenzene, approximately 20% of the intermediate boronate ester suffers deborylation, suggesting that this may be a general problem for aminations of chlorides ortho to BPin groups.

Table 3. One-Pot Borylation/Amination of Ortho- and Para-Substituted Chlorobenzenes[a]

entry	aryl halide	product	% yield[b]
1		 19 :  1	46
2[c]		~ 10% GC-yield (7:1 isomer mixture) 3% 4-(N-phenylamino)chlorobenzene[d]	0
3			45

[a] See Supporting Information for specific reaction conditions. [b] Isolated yield based upon an average of two runs. [c] The intermediate boronate ester was isolated. [d] Upon consumption of the boron pinacolate ester, substantial aniline remained. Approximately 87% of the arene starting material is unaccounted for in the GC analysis of volatile products.

In summary, one-pot borylation/amination provides an efficient protocol for preparing the 1,3,5-arylamino boronate esters from 3-substituted aryl halides. The one-pot sequence can be extended to ortho- and para-substituted chlorobenzenes. In the case of dichlorobenzenes, a highly regioselective substitution has been observed para to the BPin group in the boronate ester derived from the borylation of *o*-dichlorobenzene. The key feature that enables the one-pot sequence is preference of C−N over C−C coupling when a primary or secondary amine, a pinacolate boron ester, and an aryl halide are subjected to Pd coupling conditions where anhydrous K_3PO_4 is the requisite base.[13,14] We are presently evaluating the generality and pursuing applications of this selectivity.[15]

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Supporting Information Available: Spectral data for all new compounds pictured, as well as general experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Although K_3PO_4 has been previously used in Suzuki−Miyaura cross-couplings[1b,13a] and Buchwald−Hartwig aminations,[13b] preservation of an arylboronate ester under amination conditions has not been reported to our knowledge: (a) Miyaura, N.; Ishiyama, T.; Sasaki, H.; Ishikawa, M.; Satoh, M.; Suzuki, A. *J. Am. Chem. Soc.* **1989**, *111*, 314−321. (b) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722−9733.

(14) Compatability of pinacolate ester with uncatalyzed aminations of aryl fluorides[14a] and chloropyrimidines[14b] has been noted: (a) Holland, R.; Spencer, J.; Deadman, J. J. *Synthesis* **2002**, 2379−2382 (b) Gong, B. Q.; Hong, F.; Kohm, C.; Jenkins, S.; Tulinsky, J.; Bhatt, R.; de Vries, P.; Singer, J. W.; Klein, P. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2303−2308.

(15) Shi, F.; Smith, M. R., III; Maleczka, R. E., Jr. *Org. Lett.* **2006**, *8*, 1411−1414.