

Aromatic Borylation/Amidation/ Oxidation: A Rapid Route to 5-Substituted 3-Amidophenols

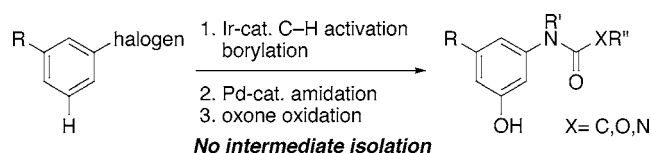
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ABSTRACT



5-Substituted 3-amidophenols are prepared by subjecting 3-substituted halobenzenes to an Ir-catalyzed aromatic borylation, followed by a Pd-catalyzed amidation, and finally an oxidation of the boronic ester intermediate. The entire C–H activation borylation/amidation/oxidation sequence can be accomplished without isolation of any intermediate arenes. Usefully, amide partners can include lactams, carbamates, and ureas.

5-Substituted 3-amidophenols, with the amido group including ureas and carbamates, represent a structure motif found in kinase inhibitors,¹ growth regulators,² and other biologically important compounds.³ Natural products containing 5-substituted 3-amidophenolic cores include the maytansinoids, herbimycins, trienomycins, and other ansamycin antibiotics,⁴ which are biosynthesized from 3-amino-5-hydroxybenzoic acid (AHBA),⁵ itself a 5-substituted 3-amidophenol (Figure 1).

The most common synthetic routes to 5-substituted 3-amidophenols involve an amidation of the functionalized aniline with carboxylic acid derivatives⁶ or an isocyanate.⁷ Such approaches can be straightforward, *if* the appropriate anilines

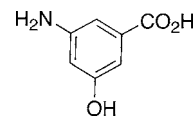


Figure 1. 3-Amino-5-hydroxybenzoic acid (AHBA).

are readily available. Unfortunately, this condition is rarely met because the vagaries of aromatic substitution make selective 1,3,5-trisubstitution of benzenes an onerous task. As a result, preparations of AHBA have typically been long and harsh.⁸ Likewise, many existing syntheses of 5-substituted 3-amidophenolic natural products use an inordinate number of steps to build the aromatic moiety.⁹

We had previously overcome similar electronic obstacles impeding the preparation of a variety of 3,5-disubstituted phenols. Specifically, we showed that sterically controlled regioselective catalytic aromatic borylation¹⁰ of 1,3-disubstituted arenes, followed by an in situ oxidation of the newly installed C–B bond constitutes an efficient one-pot synthesis of the desired phenols (Scheme 1).¹¹

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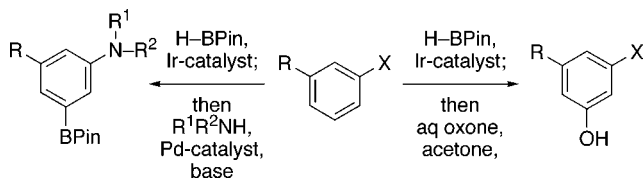
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(4) (a) Wrona, I. E.; Gabarda, A. E.; Evano, G.; Panek, J. S. *J. Am. Chem. Soc.* **2005**, *127*, 15026–15027. (b) Yu, T.-W.; Muller, R.; Muller, M.; Zhang, X.; Draeger, G.; Kim, C.-G.; Leistner, E.; Floss, H. G. *J. Biol. Chem.* **2001**, *276*, 12546–12555. (c) Floss, H. G. *Nat. Prod. Rep.* **1997**, *14*, 433–452 and references therein. (d) Larson, G. M.; Schaneberg, B. T.; Sneden, A. T. *J. Nat. Prod.* **1999**, *62*, 361–363. (e) Kibby, J. J.; Rickards, R. W. *J. Antibiot.* **1981**, *34*, 605–607.

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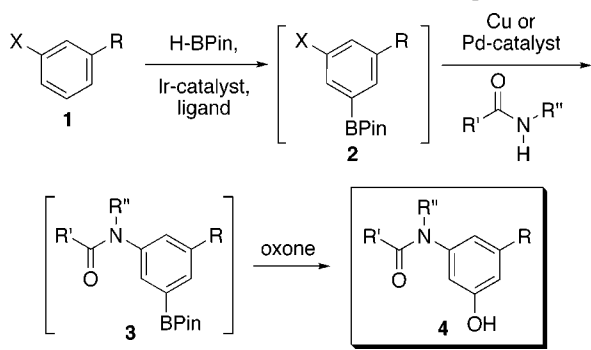
Scheme 1. One-Pot Aromatic Borylation/Oxidation¹¹ and Aromatic Borylation/Amidation¹³ Schemes



A hallmark of Ir-catalyzed aromatic borylation (the first step of our phenol synthesis) is its tolerance of halogen substituents.¹⁰ We have shown that these halogens can participate in Pd-catalyzed amination reactions¹² allowing for a one-pot aromatic borylation/amination route to a variety of amino-substituted arylboronic esters (Scheme 1).¹³

In the context of the one-pot protocols for aromatic borylation/amination and aromatic borylation/oxidation, the putative aromatic borylation/amidation/oxidation approach to 5-substituted 3-amidophenols in Scheme 2 piqued our

Scheme 2. Proposed One-Pot Aromatic Borylation/Amidation/Oxidation Route to 5-Substituted 3-Amidophenols



curiosity. Such a method would be uniquely efficient for preparing these types of functionalized arenes, especially if all reactions could be telescoped into a single reaction vessel.

For the key amidation step, we looked to follow the Ir-catalyzed aromatic borylation with an in situ C–N coupling between the halosubstituted arylboronic ester and an added amide. Over the past several years, Buchwald and co-workers have developed both Pd¹⁴ and Cu-mediated¹⁵ amidation

(9) Smith's synthesis of trienomyacin A is illustrative in this regard, as nearly 25% of their total synthetic steps were dedicated to building the aromatic region of the target molecule. See: Smith, A. B., III; Barbosa, J.; Wong, W.; Wood, J. L. *J. Am. Chem. Soc.* **1996**, *118*, 8316–8328.

(10) (a) Tse, M. K.; Cho, J.-Y.; Smith, M. R., III *Org. Lett.* **2001**, *3*, 2831–2833. (b) Cho, J.-Y.; Tse, M. K.; Holmes, D.; Maleczka, R. E., Jr.; Smith, M. R., III *Science* **2002**, *295*, 305–308. (c) Ishiyama, T.; Takagi, J.; Hartwig, J. F.; Miyauro, N. *Angew. Chem., Int. Ed.* **2002**, *41*, 3056–3058. (d) Ishiyama, T.; Takagi, J.; Ishida, K.; Miyauro, N.; Anastasi, N. R.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 390–391. (e) For a review see: Ishiyama, T.; Miyauro, N. *J. Organomet. Chem.* **2003**, *680*, 3–11.

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

(12) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046–2067.

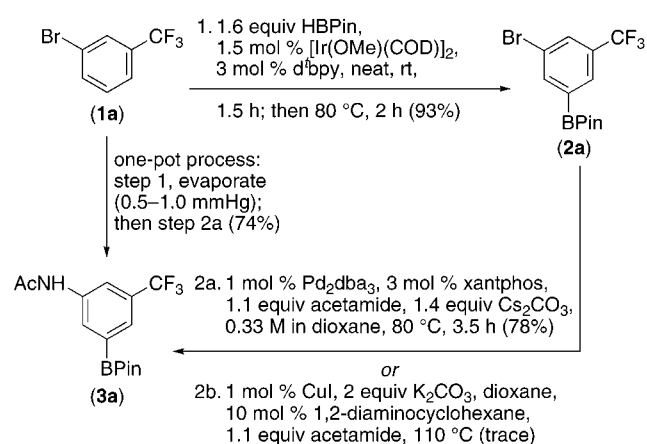
(13) Holmes, D.; Chotana, G. H.; Maleczka, R. E., Jr.; Smith, M. R., III *Org. Lett.* **2006**, *8*, 1407–1410.

protocols,¹⁶ both of which are quite mild and versatile. Carboxyamides, ureas, and carbamates have been coupled with a variety of aryl halides and triflates. Nonetheless, to the best of our knowledge there are no reported examples of amides coupling with aryl halides that bear a boronic ester group. As such, we were concerned that the C–N coupling conditions could also promote an undesired Suzuki reaction between the aryl halide and the boronic ester group. In fact, we had previously demonstrated that polyphenylenes could be efficiently generated by just such a process.^{10b}

In the aforementioned aromatic borylation/amination sequence, we found that Suzuki side reactions could be suppressed when the C–N couplings were run under dry conditions, which were achieved, in part, through the use of anhydrous K₃PO₄ as the base.¹³ For the proposed amidation protocol, we hoped that Suzuki rates could be similarly curbed despite the lower reactivity and elevated acidity of amides relative to amines.

Given these uncertainties, our initial efforts focused solely on the metal mediated amidation of boronic ester substituted aryl halides. We first tried the amidation of **2a** using acetamide and Cu-catalyzed conditions,¹⁵ but this met with little success (Scheme 3). Although control experiments

Scheme 3



proceeded as described by Buchwald, the couplings failed with aryl halides containing a boronic ester group. Copper loadings of 1–10 mol % were tested on amidations of both purified and crude **2a**, with both acetamide and benzamide. Unfortunately, throughout all experiments protodeborylation remained the major, if not exclusive, reaction during these amidation attempts.

In contrast, the amidation of **2a** with acetamide worked under Pd-catalysis,¹⁴ with no more than trace Suzuki coupling

(14) (a) Yin, J.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 1101–1104. (b) Yin, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 6043–6048. (c) Huang, X.; Anderson, K. W.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 6653–6655.

(15) (a) Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727–7729. (b) Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421–7428.

(16) Also see: Shakespeare, W. C. *Tetrahedron Lett.* **1999**, *40*, 2035–2038.

or protodeborylation occurring. Furthermore, slight modifications to the literature stoichiometries and other reaction conditions decreased amidation times of the halogenated arylboronic ester from overnight to a few hours (Scheme 3).¹⁷ Moreover, the amidation could be carried out on crude **2a** generated from the Ir-catalyzed aromatic borylation of **1a**, with pinacol borane (HBPin), catalytic [Ir(OMe)(COD)]₂, and d'bpy ligand.

With the one-pot borylation/amidation portion of the proposed sequence in hand and optimized, we undertook converting the amide-substituted arylboronic ester to the amido-phenol. Our previously developed one-pot catalytic aromatic borylation/oxidation used oxone as the oxidant.¹¹ In those oxidations, acetone was the standard solvent and the reactions were typically run in the absence of any base or buffer. Nonetheless, we had also shown ethereal solvents to be acceptable and Webb and Levy employed NaHCO₃ as buffer in their original report.¹⁸ Thus, we expected that neither the solvent nor the Cs₂CO₃ used in the amidation step would interfere with our plans to conclude the one-pot process with the oxone oxidation of the crude amidation intermediate (Scheme 2). This hypothesis proved incorrect as all attempts at a strictly one-pot catalytic aromatic borylation/amidation/oxidation failed to give any of the desired phenol.

We were able to determine that this failure stemmed from the catalytic milieu and not the amidation intermediates, as isolated **3a** (see Scheme 3) could be oxidized to the phenol with oxone in 95% yield. While a one-pot aromatic borylation/amidation followed by purification and then an oxidation would make for a fairly efficient route to 5-substituted 3-amidophenols, the poor resolution of amido-substituted boronic

esters on silica gel makes for a less than ideal protocol. Therefore we investigated if the crude aromatic borylation/amidation product could be adequately "cleaned-up" for the oxidation step without actually needing to isolate the amido-arylboronic ester. Toward this end we were gratified that passing the crude reaction mixture through a short plug of silica gel provided a mixture that once evaporated could be successfully subjected to the standard oxone conditions (Table 1).^{17,19}

Since the silica gel plug removed only insoluble solids and the most polar salts, pinacol originating from the borylation step remained in the final reaction mixture. Separating the pinacol from the similarly polar 5-substituted 3-amidophenols can be difficult. To avoid this problem, the final oxidation mixture was worked up with NaIO₄ to destroy the diol. In this way the pure phenols could readily be obtained in undiminished isolated yields.

With the 3-step protocol in place, we surveyed the scope of the sequence against a variety of haloarenes and amides (Table 1).¹⁷ For electron-deficient arylbromides reacting with primary amides (entries 1–7, 9, and 10), the process was clean and relatively high yielding. Suzuki byproducts and protodeborylation were minimal, if observed at all. A range of electron-withdrawing groups at the 5-position was tolerated, including esters and chloride. Benzonitriles could also be transformed into the desired products; however, [Ir(OMe)(COD)]₂ and d'bpy proved the C–H activation catalyst/ligand combination of choice for these substrates. For most other substrates tested, the substitution of [Ir(OMe)(COD)]₂ and d'bpy for (Ind)Ir(COD) and dmpe netted little difference in the overall process (Scheme 3 vs entry 1). That said, in the case of methyl 3-bromobenzoate the efficiency of the overall sequence was affected by incomplete borylation. Fortunately, simply reacting this substrate in an open flask (nitrogen atmosphere) under the [Ir(OMe)(COD)]₂ conditions allowed the borylation to run to full conversion (entries 5 and 6). Presumably, inhibition of catalysis is avoided when the hydrogen byproduct can escape.

In addition to carboxyamides, carbamates and ureas were also suitable amide partners. Several entries from this group of substrates merit additional comment. By employing Boc-NH₂ (entry 6) we could generate a carbamate protected AH-BA from commercially available starting materials in competitive overall yield. Additionally, entry 7 showed how a di-substituted urea could be formed without the need to prepare functionalized isocyanates.²⁰ Acrylamides could also be used in this process. However, with acrylamide itself the desired product could only be isolated in 37% yield (entry 9), whereas the more substituted tiglic amide was less prone to side reactions and afforded the final product in a synthetically useful 66% yield (entry 10).

Reactions of aryl bromides with electron-releasing or neutral groups and reactions that employ secondary amides (including lactams) tended to afford the products in lower

(17) (a) See the Supporting Information for details. (b) General procedure for one-pot C–H activation/borylation/amidation/oxidation: In a drybox, arene (2.0 mmol), HBPin (1.5–2.0 equiv), 2 mol % of (Ind)Ir(COD) (or 1.5 mol % of [Ir(OMe)(COD)]₂), and 2 mol % of dmpe (or 3 mol % of d'bpy for reactions run with [Ir(OMe)(COD)]₂) were transferred into an air-free flask equipped with a stirrer bar. (In reactions where solvent is needed, the reagents were dissolved in 1–6 mL of *n*-hexane and transferred to the air-free flask.) The flask was sealed (unless otherwise noted), brought out of the drybox, and placed in an oil bath preheated to 150 °C (or at room temperature for reactions run with [Ir(OMe)(COD)]₂). The reaction was run at this temperature until judged complete by GC-FID. At that time, the reaction was allowed to cool to room temperature. If solvent was used, it was removed by a gentle nitrogen flow. The crude borylation mixture was then pumped under high vacuum for several hours to remove the excessive HBPin. The flask was then returned to the drybox and charged with 1 mol % of Pd₂dba₃, 3 mol % of xantphos, amide (1.05–1.15 equiv), Cs₂CO₃ (1.4 equiv), and 6 mL of THF or DME. The flask was sealed, taken out of the box, and heated to the indicated temperature. The reaction was stirred at this temperature until judged complete by GC-FID. At this time, the reaction mixture (typically a yellow suspension) was then cooled to room temperature and filtered through a silica pad (1–2 cm thick × 4.5 cm diameter; ~12 g) eluting with acetone until the filtrate showed no UV activity on TLC (ca. 150–200 mL). The acetone was evaporated and the residue was dissolved back in 6 mL of acetone (or more if needed to obtain a homogeneous solution). To that stirred solution was added dropwise an aqueous solution of oxone (1.33 g (1.0 equiv) in 6 mL water) and the resulting reaction was stirred for 10 min at room temperature. At that time an aqueous suspension of NaIO₄ (430 mg (1.0 equiv per pinacol mol equiv) in 2 mL water) was added in a single portion followed by 2 mL of acetone. The mixture was further stirred for 1–2 h before being twice extracted with EtOAc. To the aqueous layer was then added solid NaHSO₃, and the mixture was swirled until color appeared and then diminished. The aqueous phase was then back extracted once or twice with EtOAc. The combined organics were washed with brine, dried over MgSO₄, and concentrated. The residue was purified on silica gel chromatography (3.5 cm wide, 25–30 cm long), using CH₂Cl₂/EtOAc or CH₂Cl₂/acetone eluent. Evaporation followed by drying under high vacuum afforded the final product.

(18) Webb, K. S.; Levy, D. *Tetrahedron Lett.* **1995**, *36*, 5117–5118.

(19) The composition of the offending species removed by the silica gel plug is uncertain at this time.

(20) Note: Reaction of the same substrate with PMBNH(CO)NH₂ afforded the corresponding urea substituted phenol in only 19% yield along with adventitious Suzuki products.

Table 1. Catalytic Aromatic Borylation/Amidation/Oxidation of 3-Substituted Halobenzenes^a

entry	arene	borylation conditions	amidation conditions	product (yield ^b)	entry	arene	borylation conditions	amidation conditions	product (yield ^b)
1	R = CF ₃ (1a)	HBPIn (1.8 equiv), conditions i, neat, 4 h	AcNH ₂ , THF, 80 °C, 4 h	 4a (63%)	8	R = CF ₃ (1a)	HBPIn (1.8 equiv), conditions i, neat, 4 h	δ-valerolactam, 100 °C, THF, 2 h	 4h (46%) ^d
2	R = CF ₃ (1a)	HBPIn (1.8 equiv), conditions i, neat, 4 h	BzNH ₂ , THF, 80 °C, 4 h	 4b (82%)	9	R = CF ₃ (1a)	HBPIn (1.8 equiv), conditions i, neat, 4 h	acrylamide, THF, 80 °C, 3.5 h	 4i (37%)
3	R = CN (1b)	HBPIn (1.6 equiv), conditions ii, hexane, 3 h	AcNH ₂ , THF, 80 °C, 3 h	 4c (68%)	10	R = Cl (1c)	HBPIn (1.7 equiv), conditions i, hexane, 3.5 h	tiglic amide, THF, 100 °C, 1.5 h	 4j (66%)
4	R = Cl (1c)	HBPIn (1.9 equiv), conditions i, neat, 4 h	AcNH ₂ , THF, 80 °C, 3 h	 4d (75%)	11	R = Me (1e)	HBPIn (2 equiv), conditions i, neat, 12 h	AcNH ₂ , DME, 120 °C, 3.5 h	 4k (43%) ^{e,f}
5	R = CO ₂ Me (1d)	HBPIn (2 equiv), conditions ii, hexane, 18 h ^c	AcNH ₂ , THF, 100 °C, 2 h	 4e (60%)	12	R = OMe (1f)	HBPIn (2 equiv), conditions i, neat, 10 h	AcNH ₂ , DME, 120 °C, 4 h	 4l (33%) ^{e,f}
6	R = CO ₂ Me (1d)	HBPIn (2 equiv), conditions ii, hexane, 18 h ^c	BocNH ₂ , THF, 100 °C, 2.5 h	 4f (46%) ^d	13	 (1g)	HBPIn (1.6 equiv), conditions i, hexane, 4 h	AcNH ₂ , THF, 100 °C, 27 h	 4a (40%) ^f
7	R = CF ₃ (1a)	HBPIn (1.8 equiv), conditions i, neat, 4 h	Bn ₂ NC(O)NH ₂ , THF, 100 °C, 1.5 h	 4g (55%)					

^a Reagents and conditions: (i) arene (2 mmol scale), H-Bpin, 2 mol % of (Ind)Ir(COD)-dmpe, 150 °C, neat or hexane, sealed tube under N₂; evaporate (0.5–1.0 mmHg); (ii) H-Bpin, 1.5 mol % of [Ir(OMe)(COD)]₂, 3 mol % of d'bpy, neat or hexane, rt; evaporate (0.5–1.0 mmHg); (iii) ~1.10 equiv of amide, 1 mol % of Pd₂dba₃, 3 mol % of xantphos, 1.4 equiv of Cs₂CO₃, 0.33 M in THF or DME, 80–120 °C; upon completion filter through a 4.5 cm diameter × 1–2 cm thick silica gel plug and evaporate; (iv) oxone, acetone, rt, 10 min; then 1 equiv of NaIO₄ 1–2 h. ^b Average isolated yield over three steps for two runs. ^c Run open to a nitrogen manifold vs a sealed flask. ^d Suzuki byproducts were also observed. ^e NaIO₄ workup was omitted. ^f Protodeborylation was also observed.

yields (entries 8, 11, and 12). In cases of secondary amides and lactams, Suzuki oligomerization becomes intrusive in the amidation step. Disappointingly, the Suzuki byproducts were not suppressed by using excess amide. With deactivated aryl bromides, side reactions increased. Suzuki oligomerization, phenyl transfer from the xantphos ligand, and protodeborylation were all observed. Moreover, the electron-rich aromatics did not respond well to the NaIO₄ workup. Thus for these products recrystallization or HPLC separation was required to eliminate pinacol contamination. Finally, a longer reaction time and higher temperature were required when an aryl chloride was the amidation partner (entry 13). This substrate also gave more protodeborylation; however, Suzuki oligomerization was largely suppressed, presumably due to the lower reactivity of the chloride.

In conclusion, the three-step sequence of aromatic borylation/amidation/oxidation on 3-substituted halobenzenes affords 5-substituted 3-amidophenols in good overall yields and without intermediate isolation. This chemistry further expands the utility of the catalytic aromatic C–H activation borylation reaction and provides an alternative route to these important compounds. We are presently applying this process in the theater of total synthesis.

Acknowledgment. We thank the Michigan Technology Tricorridor Fund and the Astellas USA Foundation for generous support and BASF for their kind gift of pinacolborane.

Supporting Information Available: Experimental details and product characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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