

C–H Activation/Borylation/Oxidation: A One-Pot Unified Route To Meta-Substituted Phenols Bearing Ortho-/Para-Directing Groups

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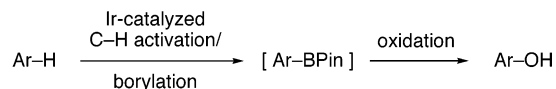
Phenols serve as synthetic building blocks for the construction of compounds ranging from polymers to pharmaceuticals.¹ Despite numerous phenol syntheses,^{2,3} straightforward routes to 3,5-disubstituted phenols bearing ortho-/para-directing groups are lacking.⁴ Traditional approaches to such phenols are obstructed by the fact that electronic effects typically govern regioselectivities in aromatic substitution chemistry. Thus, the 5-position in 1,3-disubstituted benzenes is notoriously inert when the substituents are ortho/para directors. Illustrative of this problem is 3-bromo-5-chlorophenol (**1**). To the best of our knowledge,⁵ the only two descriptions of this potentially useful⁶ and versatile molecule date back to 1926,⁷ including a synthesis by Hodgson and Wignall^{7a} that requires 10 steps starting from TNT!

Transition metal catalyzed C–H activations potentially offer general solutions to this dilemma since steric effects often dictate the regioselectivity of arene activation. Indeed, sterics dominate the regioselectivities for catalytic aromatic C–H activation/borylations,⁸ which effectively impart the chemical versatility of arylboronic acids and esters to aromatic C–H bonds. Moreover, we recently demonstrated that the functional group tolerance and selectivity of Ir catalysts enable the combination of such aromatic borylations with subsequent chemical events.^{8a} Since it is known that Oxone can oxidize arylboronic esters to phenols,⁹ we hypothesized that a one-pot aromatic C–H activation/borylation/oxidation protocol (Scheme 1) would constitute the most direct route to numerous structurally simple phenols whose practical use is currently limited by their accessibility.

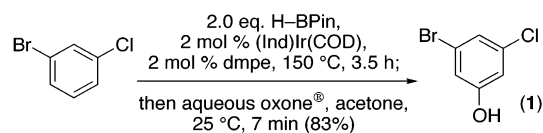
Iridium phosphine complexes catalyze the conversion of neat mixtures of arenes and pinacolborane (H–BPin) to arylboronic esters, where the arene is the limiting reagent.^{8a} Thus, we first attempted oxidation of arylboronic esters in crude reaction mixtures with Oxone using the literature protocol (Oxone, base, buffer, in 10–15% aqueous acetone at 2 °C).⁹ These attempts gave irreproducible yields. Surprisingly, a 1:1 acetone–water solution of Oxone, where the base and buffer were omitted, gave good to excellent yields at room temperature.¹⁰

Our typical protocol¹¹ (Scheme 2) consists of heating an H–BPin/arene mixture (H–BPin:arene ≈ 1.5–2.5:1) with (Ind)Ir(COD) (0.02 equiv vs arene) and 0.02 equiv 1,2-bis(dimethylphosphino)ethane (dmpe) at 150 °C (or 1,2-bis(diphenylphosphino)ethane (dppe) at 100 °C)^{8a} until the borylation is complete by GC-FID. After the reaction mixture has cooled to room temperature, acetone and an aqueous solution of Oxone are added sequentially. Within 10 minutes stirring at room temperature the oxidation is usually complete, typically affording the phenol as the only aromatic product. As shown in Scheme 2, 3-bromo-5-chlorophenol (**1**) was prepared in 83% yield from commercially available 3-bromochlorobenzene. In contrast to the arduous route from TNT, our sequence can be completed in a single flask over the course of an afternoon.

Scheme 1



Scheme 2



Scheme 3

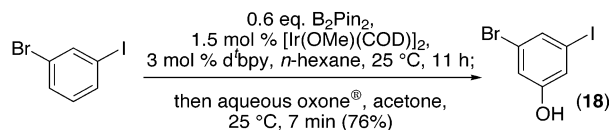


Table 1 summarizes syntheses of various other phenols using this protocol. As previously noted,⁸ electron-donating substituents retard aromatic borylations, but subsequent oxidations of the resulting arylboronic esters and the isolated yields of the corresponding phenols were not visibly perturbed by electronic effects. That said, for electron-poor phenols, complete removal of hydrogen-bond accepting solvents such as acetone or ether required distillation or sublimation.¹¹ Improvements over published routes were realized for most of the known phenols in Table 1.¹¹ Moreover, preparations of phenols **7** and **14–17** are described here for the first time.⁵ Perhaps most noteworthy, aromatic borylation/oxidation appears to be the first unified approach to **1–18**.

Over-oxidation¹² was not a problem, as quinones were not observed. Even for substrates bearing oxidizable nitrogens, such as the pyridine of entry 5 and the amino group of entry 16, no *N*-oxides were detected in the isolated products.¹³ Ethers and esters could survive the transformation (entries 3–4), but demethylation of 2,6-dichloroanisole (entry 8) accompanied borylation.¹⁴ The small van der Waals radius of fluoride makes possible the preparation of 5-bromo-2-fluorophenol (**13**). Furthermore, multiple hydroxyls can be installed by adjusting the amounts of H–BPin and Oxone (entries 13–14).

Borylations can also be performed in inert solvents such as cyclohexane (entries 5, 9–11, 13–15), which is then removed prior to the oxidation step. The oxidation step can be performed in other water-miscible solvents such as acetonitrile, DMF, dioxane, THF, or diglyme. Thus, while acetone remains our solvent of choice for the oxidation step, dimethyldioxirane is not a required intermediate.¹⁵ Oxidations in CHCl_3 or CH_2Cl_2 failed.¹⁶

While bromide and chloride tolerance was universal, partial deiodination of 1-bromo-3-iodobenzene occurred during borylation

Table 1. Phenols via One-Pot C–H Activation/Borylation/Oxidation^a

| entry | starting arene | H-BPin equiv. | borylation time (h) ^b | phenol | % yield ^c |
|---------------------|----------------|---------------|----------------------------------|--------|----------------------|
| 1 ^{d,e,f} | | 2.0 | 18 | (2) | 87 |
| 2 | | 1.5 | 12 | (3) | 81 |
| 3 | | 2.0 | 18 | (4) | 79 |
| 4 ^d | | 1.5 | 3 | (5) | 70 |
| 5 ^{d,g} | | 1.5 | 3 | (6) | 64 |
| 6 | | 2.0 | 12 | (7) | 85 |
| 7 | | 1.5 | 12 | (8) | 88 |
| 8 | | 2.5 | 16 | (9) | 68 |
| 9 ^{f,g} | | 2.5 | 50 | (10) | 72 |
| 10 ^g | | 2.0 | 3.5 | (11) | 80 |
| 11 ^g | | 1.8 | 3 | (12) | 89 |
| 12 | | 0.25 | 3.5 | (13) | 68 |
| 13 ^{e,g} | | 4.5 | 53 | (14) | 74 |
| 14 ^{d,e,g} | | 5.0 | 63 | (15) | 51 |
| 15 ^g | | 1.5 | 3.5 | (16) | 80 |
| 16 ^e | | 2.0 | 18 | (17) | 79 |

^a Typical conditions: Arene, H-BPin, 2 mol % (Ind)Ir(COD), 2 mol % dmpe, neat under N₂; then acetone, 1 equiv (per boron) aqueous Oxone, 25 °C, 7 min (see SI for details). ^b Borylation time can be H-BPin batch dependent. ^c Average isolated yields of two runs. ^d The borylation was described in ref 8a. ^e See SI for slight deviation from typical conditions. ^f Borylation run with dppe at 100 °C. ^g Borylation run in C₆H₁₂.

with (Ind)Ir(COD). This could be avoided by using Ishiyama and Miyaura's [Ir(OMe)(COD)]₂-d'bpy system to borylate with B₂Pin₂ at room temperature (Scheme 3).¹⁷

In summary, one-pot aromatic borylation/oxidation is an efficient protocol for preparing phenols. This method is particularly attractive for the generation of meta-substituted phenols bearing ortho-/para-directing groups, as such substrates are often difficult to access by other means.

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Supporting Information Available: Experimental procedures and spectral data for phenols 1–18 along with comparisons to previously described syntheses (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (10) Interestingly, Webb and Levy (ref 9) reported that oxidations above 15 °C gave lower yields.
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- (13) Preliminary spectroscopic studies suggest that transient amounts of *N*-oxides are being formed during these reactions. Further analyses of this process are ongoing and will be reported elsewhere.
- (14) Demethylation of 2,6-dichloroanisole is known to be facile. See Majetich, G.; Zhang, Y.; Wheless, K. *Tetrahedron Lett.* **1994**, 47, 8727–8730.
- (15) We have not ruled out in situ formation of DMDO when acetone is the solvent. However, our reactions are run in the *absence* of base or buffer, which are typically added to promote DMDO formation. See ref 9 and Murray, R. W. *Chem. Rev.* **1989**, 89, 1187–1201. Furthermore, a reaction using DMDO in place of aq Oxone only afforded a trace of the phenol.
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