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Palladium-Catalyzed Hydroxylation of Aryl Halides with Boric Acid

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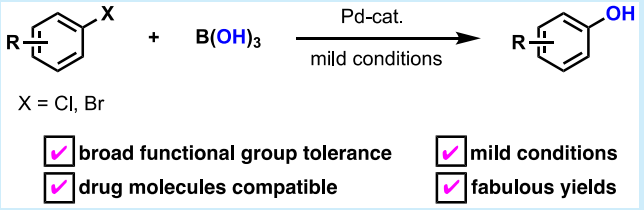
ABSTRACT: Boric acid, $B(OH)_3$, is proved to be an efficient hydroxide reagent in converting (hetero)aryl halides to the corresponding phenols with a Pd catalyst under mild conditions. Various phenol products were obtained in good to excellent yields. This transformation tolerates a broad range of functional groups and molecules, including base-sensitive substituents and complicated pharmaceutical (hetero)aryl halide molecules.

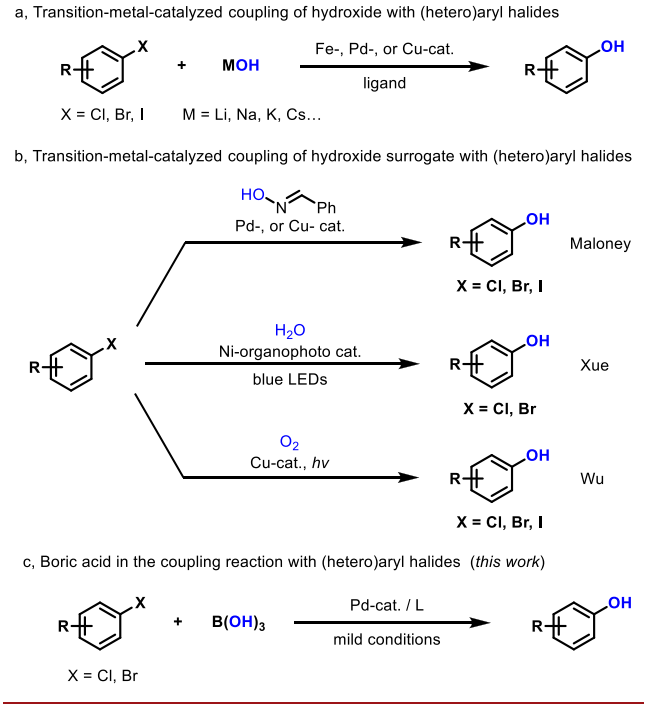


Phenol motifs are widely present in natural products, ligands, agrochemicals, medicines, and materials, they are also among the most critical building blocks in synthetic chemistry.[1] Historically, the preparation of phenols includes the hydrolysis of aryl sulfates or halides, Sandmeyer hydroxylation of anilines, oxidation of arylmetal derivatives, condensation or cyclization of unsaturated carbonyl derivatives, the cumene process, and a few other miscellaneous methods.[2]

In recent decades, with the development of transition-metal-catalyzed reactions, several new approaches to access phenols have been developed. Aryl halides can be coupled with alkali-metal hydroxides (MOH) under Cu,[3] Fe,[4] and Pd catalysis[5] in water-containing conditions (Scheme 1a). Obviously, these conditions do not tolerate base-sensitive functional groups, such as ester, cyano, carbonyls, and some types of heterocyclic compounds. Recently, Fier and Maloney strategically overcame this drawback by using benzaldehyde oximes as the hydroxide resource (Scheme 1b). However, a stoichiometric amount of harmful benzonitrile was generated as byproduct.[3s,5k] More recently, photoredox protocols have been employed in the synthesis of phenols. Xue reported a Ni-catalyzed organo-photoredox hydroxylation of aryl halides with H_2O,[6] and Wu reported a Cu-catalyzed photoredox-mediated hydroxylation of (hetero)aryl halides with O_2.[7] Though these photoredox procedures tolerate a wide range of functional groups, the reaction yields are generally not high. Nevertheless, a hydroxylation protocol that uses a readily available hydroxide reagent, tolerates a broad scope of functional groups, gives phenols in high yields, and proceeds under mild conditions is still highly demanded, especially for the synthesis of drug molecules and natural products and for late-stage diversification.[8]

Organoboron compounds, such as boronic acids, boronic esters, and trifluoroborates, have been widely used as nucleophilic coupling partners in the construction of C−C and C−N bonds under Pd, Ni, or Cu catalysis.[9,10] Boric acid, $B(OH)_3$, is a stable, inexpensive, and nontoxic compound that has been used as a mildly acidic catalyst in esterification and condensation reactions.[11] Herein we disclose that boric acid is a highly efficient hydroxide reagent in the Pd-catalyzed cross-coupling reaction between (hetero)aryl halides and $B(OH)_3$. This transformation provides various phenols in good to

Scheme 1. Synthesis of Phenols from Aryl Halides



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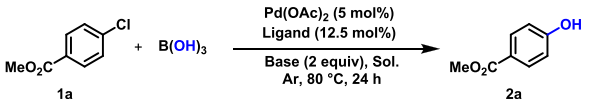
excellent yields under mild conditions and tolerates a wide range of functional groups as well as complicated drug molecules.

To start the discovery, the reaction between methyl 4-chlorobenzoate (**1a**) and boric acid was examined under various conditions. With $Pd(OAc)_2$ as the catalyst, Xphos as the ligand, and K_3PO_4 as the base in THF at 80 °C for 24 h, the reaction mixture provided the desired product, methyl paraben (**2a**), in 9% yield (Table 1, entry 1). Various ligands were screened, and Brettphos gave **2a** in 17% yield (entry 2). Bidentate XantPhos was inactive for the reaction (entry 3). While sterically hindered monodentate phosphine ligands were found to be effective for the transformation, *t*-BuXPhos afforded **2a** in 28% yield, and *t*-BuBrettPhos gave **2a** in 50% yield (entries 4 and 5). With *t*-BuBrettPhos as the ligand, the solvent for the reaction was screened. Toluene was inert for the transformation. CH_3CN and 1,4-dioxane gave **2a** in 37% and 39% yield, respectively. NMP was found to be the superior solvent for the reaction, giving **2a** in 87% yield (entries 6–9).[12] The effect of the base was determined with *t*-BuBrettPhos and NMP. NaO^{t}Bu afforded **2a** in 25% yield, and NaOEt and NaOAc provided **2a** in very low yield (entries 10–12). Finally, both K_2CO_3 and Cs_2CO_3 were found to be excellent bases for the transformation, giving paraben **2a** in >99% yield (entries 13 and 14).

Table 1. Optimization of the Reaction Conditions[a]



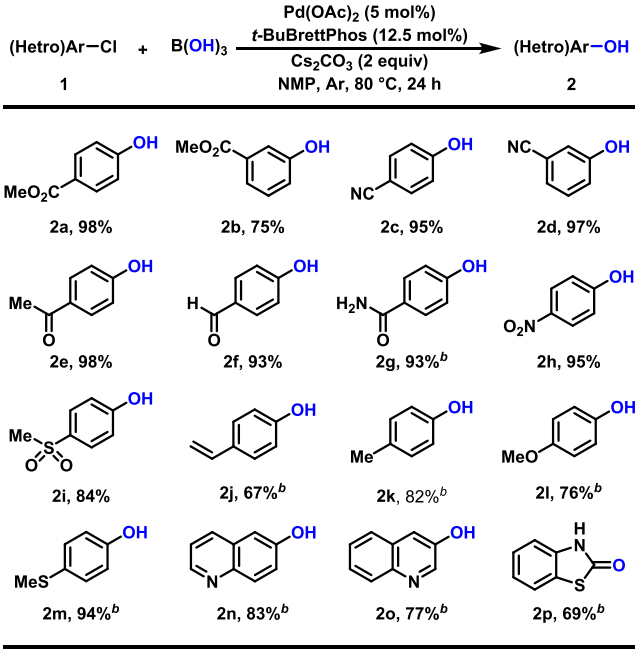
1a 2a

entry	ligand	base	solvent	yield (%)[b]
1	XPhos	K_3PO_4	THF	9
2	BrettPhos	K_3PO_4	THF	17
3	XantPhos	K_3PO_4	THF	0
4	*t*-BuXPhos	K_3PO_4	THF	28
5	*t*-BuBrettPhos	K_3PO_4	THF	50
6	*t*-BuBrettPhos	K_3PO_4	toluene	0
7	*t*-BuBrettPhos	K_3PO_4	MeCN	37
8	*t*-BuBrettPhos	K_3PO_4	1,4-dioxane	39
9	*t*-BuBrettPhos	K_3PO_4	NMP	87
10	*t*-BuBrettPhos	NaO*t*-Bu	NMP	25
11	*t*-BuBrettPhos	NaOEt	NMP	10
12	*t*-BuBrettPhos	NaOAc	NMP	4
13	*t*-BuBrettPhos	K_2CO_3	NMP	>99
14	*t*-BuBrettPhos	Cs_2CO_3	NMP	>99

[a]Reaction conditions: **1a** (0.2 mmol), $B(OH)_3$ (0.3 mmol), $Pd(OAc)_2$ (5 mol %), ligand (12.5 mol %), base (2 equiv), solvent (1 mL), Ar atmosphere, 80 °C, 24 h. [b]Yields were determined by ^{1}H NMR analysis of the crude reaction mixtures using 1,3,5-trimethoxybenzene as the internal standard.

The feasibility of using boric acid as a hydroxide reagent to prepare phenols was surveyed with various (hetero)aryl chlorides (Scheme 2). A variety of base-sensitive substituents on (hetero)aryl chlorides were well-tolerated under these conditions. For example, chlorobenzenes bearing an ester group at the *para* or *meta* position provided the corresponding phenols **2a** and **2b** in 98% and 75% yield, respectively. Chlorobenzenes with cyano substituents at the *para* or *meta* position afforded the desired phenols **2c** and **2d** in 95% and 97% yield, respectively. 4-Acetylchlorobenzene provided piceol (**2e**) in 98% yield. 4-Chlorobenzaldehyde gave 4-hydroxybenzaldehyde (**2f**) in 93% yield. *p*-Chlorobenzamide afforded 4-hydroxybenzamide (**2g**) in 93% yield. 4-Nitro- and 4-(methylsulfonyl)chlorobenzene gave the corresponding phenols **2h** and **2i** in 95% and 84% yield, respectively. *p*-Chlorostyrene provided the desired 4-vinylphenol (**2j**) in 67% yield. Besides these electron-withdrawing groups, electron-rich chlorobenzenes were also compatible with these conditions. For example, *p*-chlorotoluene gave *p*-cresol (**2k**) in 82% yield under these conditions. 4-Chloroanisole afforded the desired mequinol (**2l**) in 76% yield, and 4-(methylmercapto)-chlorobenzene provided 4-(methylmercapto)phenol (**2m**) in 94% yield. Moreover, heteroaryl chlorides successfully coupled with boric acid under these conditions, and the desired products were achieved in good yields. For example, 6-chloroquinoline and 3-chloroquinoline delivered the corresponding 6- and 3-hydroxyquinilines **2n** and **2o** in 83% and 77% yield, respectively. The coupling of 2-chlorobenzothiazole with boric acid provided the tautomerized hydroxylation product **2p** in 69% yield.

Scheme 2. Pd-Catalyzed Hydroxylation of Aryl Chlorides[a]



[a]Reaction conditions: **1** (1 mmol), $B(OH)_3$ (1.5 mmol), $Pd(OAc)_2$ (5 mol %), *t*-BuBrettPhos (12.5 mol %), Cs_2CO_3 (2 equiv), NMP (2 mL), 80 °C, Ar, 24 h. [b]100 °C, 14 h.

These conditions are also applicable for the coupling reaction between aryl bromides and boric acid, and the desired phenols were obtained in good to excellent yields (Scheme 3). Base-sensitive substituents on the bromobenzene were well-tolerated. For example, aryl bromides bearing an ester substituent at the *para* or *meta* position provided the desired phenols **2a** and **2b** in 94% and 86% yield, respectively. Cyano substituents on the bromoarene afforded the desired cyano-substituted phenols **2c** and **2d** in 97% and 94% yield, respectively, and 4-cyano-α-bromonaphthene gave the desired α-naphthol **4a** in 82% yield. Bromobenzenes bearing an acetal substituent at the *para* or *meta* position afforded the desired products **2e** and 3-acetylphenol (**4b**) in 98% and 72% yield, respectively. 4-Bromobenzaldehyde gave a 99% yield of **2f**. Besides, these conditions were also compatible strong electron-withdrawing groups. For example, 4-nitro- and 4-

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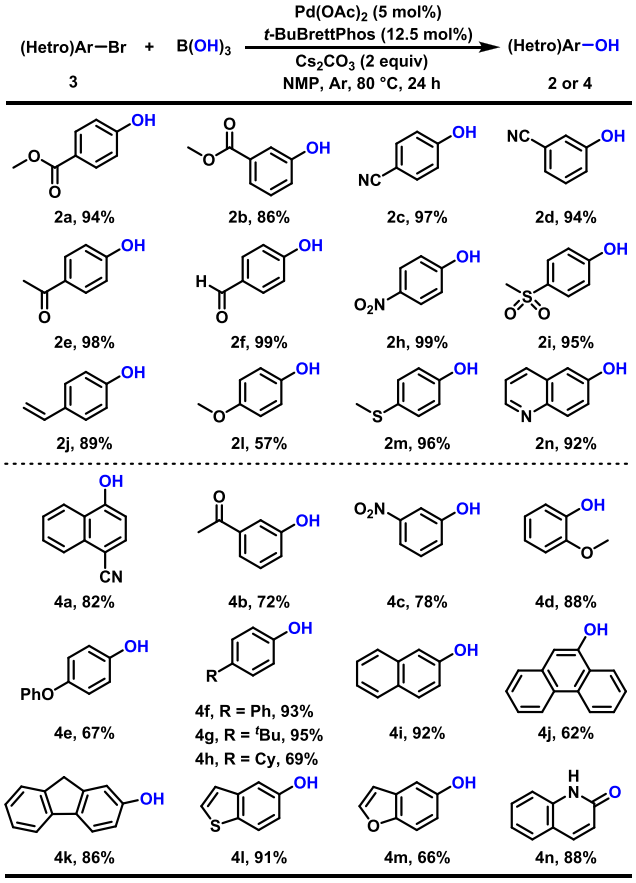
Scheme 3. Pd-Catalyzed Hydroxylation of Aryl Bromides[a]

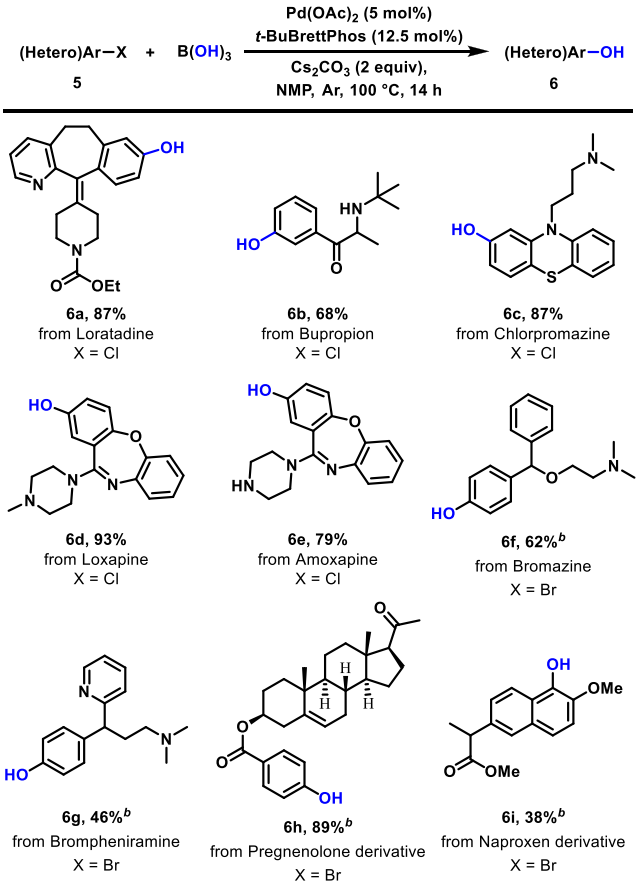


[a]Reaction conditions: aryl bromide **3** (1 mmol), $B(OH)_3$ (1.5 mmol), $Pd(OAc)_2$ (5 mol %), *t*-BuBrettPhos (12.5 mol %), Cs_2CO_3 (2 equiv), NMP (2 mL), 80 °C, Ar, 24 h.

(methylsulfonyl)bromobenzene afforded the desired phenols **2h** and **2i** in almost quantitative yields, and 3-bromonitrobenzene provided the desired phenol **4c** in 78% yield. In addition, 4-bromostyrene gave **2j** in 89% yield. These functional groups provide additional handles for further synthetic elaboration. Furthermore, electron-donating substituents were also compatible with the transformation, providing the desired electron-rich phenols in moderate to excellent yields. For example, *o*- and *p*-bromoanisole afforded the desired phenols **2l** and **4d** in 57% and 88% yield, respectively. 4-Phenoxybromobenzene provided the desired phenol **4e** in 67% yield. 4-(Methylmercapto)bromobenzene gave the desired phenol **2m** in 96% yield. Bromobenzenes bearing phenyl, *tert*-butyl, and cyclohexyl substituents at the *para* position provided the desired phenols **4f**, **4g**, and **4h** in 93%, 95%, and 69% yield, respectively. Moreover, polycyclic aromatic bromides coupled with boric acid smoothly under these mild conditions, providing the polycyclic phenols in good to excellent yields. For example, α- and β-bromonaphthalene offered the corresponding 1-naphthol derivative **4a** and 2-naphthol derivative **4i** in 82% and 92% yield, respectively. Similarly, 9-phenanthrol (**4j**) was obtained in 62% yield and 2-fluorenol (**4k**) in 86% yield from the corresponding bromoarenes. Additionally, heteroaryl bromides were also compatible with these mild reaction conditions, providing the medicinal-chemistry-attractive heteroaryl phenols in good to excellent yields. For example, electron-rich thiophenyl and benzofuranyl bromides gave the corresponding heterophenols **4l** and **4m** in 91% and 66% yield, respectively. Electron-deficient 6-bromoquinoline provided quinolin-6-ol (**2n**) in 92% yield, and 2-bromoquinoline gave quinolin-2(1*H*)-one (**4n**), the tautomer of quinolin-2-ol, in 88% yield.

On the basis of these excellent results, the hydroxylation of complicated aryl halides, such as bioactive and drug molecules, were examined under these optimal conditions (Scheme 4).

Scheme 4. Hydroxylation of Biorelevant Molecules[a]



[a]Reaction conditions: **5** (0.5 mmol), $B(OH)_3$ (0.75 mmol), $Pd(OAc)_2$ (5 mol %), *t*-BuBrettPhos (12.5 mol %), Cs_2CO_3 (2 equiv), NMP (1 mL), 100 °C, Ar, 14 h. [b]80 °C, 24 h.

This hydroxylation procedure abides aryl chloride-containing drug molecules well, regardless of the electronic properties or functional groups varieties. For example, the loratadine molecule (**5a**) gave the corresponding phenol **6a** in 87% yield without decomposing the carbamate component or the double bond. Bupropion (**5b**) was converted to the corresponding phenol **6b** in 68% yield. In this reaction, both free secondary amine and ketone carbonyl groups remain untouched. The chlorpromazine molecule (**5c**), an electron-rich and amine side chain-containing molecule, also provided the corresponding phenol **6c** in 87% yield. Loxapine (**5d**) and amoxapine (**5e**) share the same core structure. When treated with boric acid under these conditions, loxapine gave a 93% yield of the desired phenol **6d**, while amoxapine, which contains free NH, still provided the corresponding phenol **6e** in 79% yield. The couplings of aryl bromo-containing drug molecules with boric acid proceed smoothly under these

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optimal conditions, too. For example, bromazine (**5f**) was converted to the corresponding phenol **6f** in 62% yield, and brompheniramine (**5g**) gave the corresponding phenol **6g** in 46% yield, presumably because of coordination of the free pyridine ring with the Pd catalyst. Finally, aryl bromides derived from natural products or drug molecules were also feasible for the coupling with boric acid. For example, bromo-substituted pregnenolone (**5h**) provided the desired phenol **6h** in 89% yield, and 5-bromonaproxen (**5i**) gave the hydroxylated product **6i** in only 38% yield, presumably because of steric hindrance from both the −OMe group and the *peri* hydrogen.

In summary, we have demonstrated that boric acid is an efficient hydroxide reagent for the preparation of various phenols from the corresponding (hetero)aryl chlorides or bromides. The mild reaction conditions enable a wide functional group tolerance, including even base-sensitive functional groups. The transformation provides the desired phenols in good to excellent yields. This methodology is also feasible for the hydroxylation of complicated drug molecules and natural product derivatives.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03069.

Experimental procedures and ^{1}H NMR, ^{13}C NMR, ^{19}F NMR, and HRMS spectra (PDF)

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Notes

The authors declare no competing financial interest.

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