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Report

Borylation, Arene, Site-Selective, Palladium, Sulfonium salts

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Pd-Catalyzed Site-Selective Borylation of Simple Arenes via Thianthrenation

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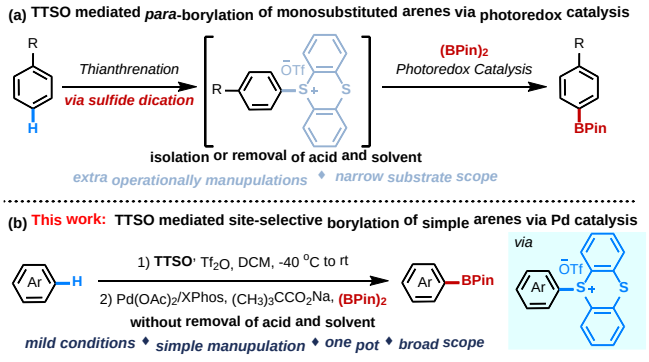
Site-selective borylation of simple arenes was realized in one pot via an electrophilic thianthrenation/Pd-catalyzed borylation sequence. The key to achieve this operatically simple process is the use of Pd catalysis which could tolerate the solvent and acidic conditions used in the thianthrenation step. This protocol features mild conditions, broad functional group tolerance, and simple manipulations, and is suitable for late-stage functionalization of a wide range of pharmaceuticals and complex bioactive molecules.

Background and Originality Content

Site-selective functionalization of undirected simple arenes remains a great challenge in synthetic community due to the subtle differences of several reactive sites regarding the electronic and steric properties in the same molecule.[1,2] Previously, site-selectivity has been obtained using electron rich anisole, aniline or heteroarenes in electrophilic aromatic substitution reaction[3]. By adopting sterically guided transition metal catalysts, excellent site-selectivity was realized when concerning 1,2- and 1,3-disubstituted simple arenes.[4] More recently, both covalent and noncovalent directing group approaches for transition metal catalysis allow the site-selective functionalization of aromatics with polar functional group assistance.[5,6] However, limited success on site-selective functionalization of simple arenes, especially monosubstituted electron-neutral and electron-deficient arenes, has been reported.

Recently, Ritter group has demonstrated a series of late-stage functionalization of arenes via the isolated aryl thianthrenium salts, in which remarkable site-selectivity was obtained.[7-9] Almost at the same timeline, we were developing a transient mediator approach for *para*-selective functionalization of monosubstituted simple arenes, and found thianthrene *S*-oxide (TTSO) and phenoxathiine 10-oxide could serve as the most selective and efficient mediators via sulfide dication intermediates (Scheme 1a).[10a] Ideally, this approach could provide a powerful alternative strategy providing a remarkable selectivity for a wide range of aromatics. However, this approach suffers from multiple manipulations requiring the isolation of sulfonium salts or removal of the solvent and acid in the first step. For example, our previous photoredox process cannot tolerate with the solvent, acidic conditions used in the first sulfonium salts formation step. Herein, we reported a simplified procedure for site-selective borylation of simple arene using this mediator approach (Scheme 1b), and the full scope of various monosubstituted and multisubstituted simple arenes were evaluated. The key to achieve this operatically simple process is the use of a Pd/phosphine catalyst which could tolerate the solvent and wastes in the thianthrenation step. In addition, a suitable base is also crucial to alter the pH value of the reaction system. This reaction features mild conditions, broader functional group tolerance, and simple manipulations in comparison to our previous photoredox process, thus makes it high value for late-stage functionalization of pharmaceuticals and bioactive complex molecules.

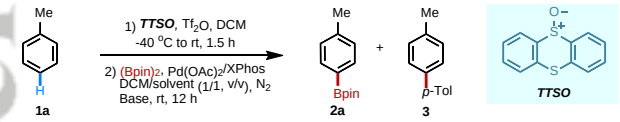
Scheme 1 Site-selective borylation via thianthrenation/Pd-catalyzed desulfurative borylation



Results and Discussion

Organoborons are appealing synthetic linchpin which are widely used in organic synthesis, and pharmaceutical industry.[11] As such, development of efficient site-selective borylation of undirected arenes are desired. Inspired by our recently TTSO mediated *para*-arylation and alkenylation reaction of monosubstituted arenes with Pd catalyst,[10b] we hypothesized that the TTSO-mediated site-selective borylation of simple arene could be realized with one synthetic operation via a thianthrenation/Pd-catalyzed desulfurative borylation sequence. We are glad to find that the Pd-catalyzed borylation reaction showed superior compatibility with the conditions used in the first sulfonium salts formation step. The desired *para*-borylated toluene could be obtained in 95% isolated yield in the presence of $Pd(OAc)_2$ (5.0 mol%), XPhos (5.0 mol%), sodium pivalate (3.0 equiv) in DCM/acetone (1/1, v/v) after systematically evaluation of the solvents and bases (entries 1-6). The use of sodium pivalate is crucial for this one-pot reaction, which could inhibit the formation of a dimerization byproduct. Based on our previous *para*-arylation with arylborons, we hypothesized that the biaryl byproduct derived from the coupling of the sulfonium salts intermediate with the arylboron product. A series of phosphine ligands (entries 7-12)

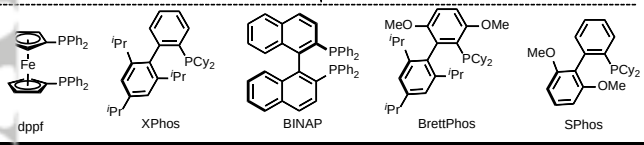
Table 1 Evaluation of reaction parameters.[a,b]



1a 2a 3

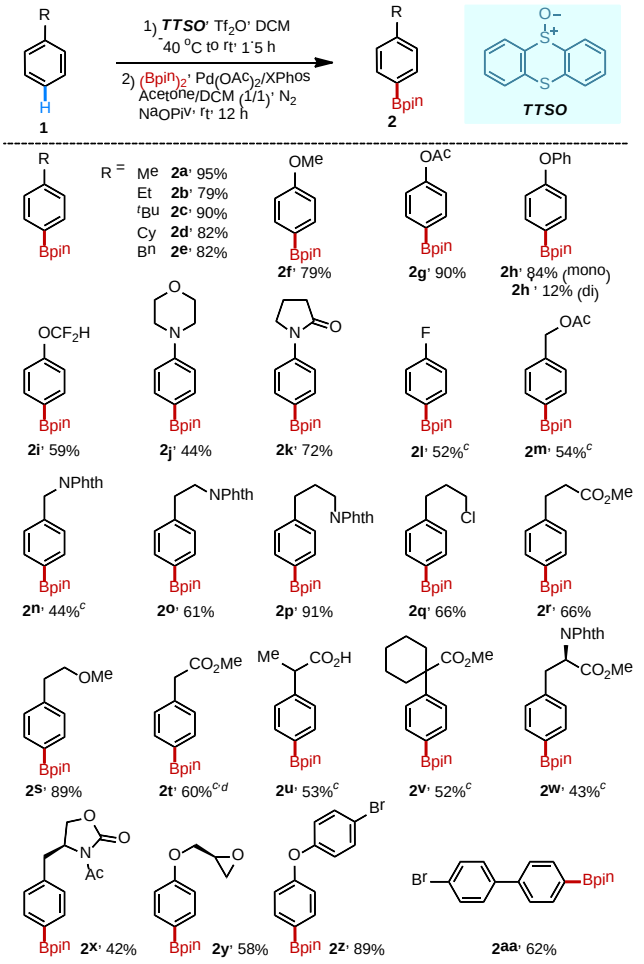
Entry	Solvent	Base	Yield (%) of 2a/3
1	MeOH	K_3PO_4	80/10
2	DMF	K_3PO_4	54/4
3	Acetone	K_3PO_4	92/4
4	Acetone	K_2CO_3	83/3
5	Acetone	KOPiv	93/3
6	**Acetone**	**NaOPiv**	**99 (95)**[c]/-

Entry	Pd sources	Yield (%)
7	$Pd(P^tBu_3)_2$ as catalysis	70
8	$Pd(dppf)Cl_2$ as catalysis	69
9	PPh_3 instead of XPhos	81
10	BINAP instead of XPhos	85
11	BrettPhos instead of XPhos	64
12	SPhos instead of XPhos	96



[a]Reaction conditions: 1) toluene (0.2 mmol), TTSO (0.24 mmol), Tf_2O (0.24 mmol), DCM (1.0 mL), N_2; -40 °C for 30 min, then rt for another 1 h; 2) [Pd] (5.0 mol %), Ligand (5.0 mol %), $(Bpin)_2$ (2.0 equiv), base (3.0 equiv), solvent (1.0 mL). [b]The yield was determined by ^1H NMR using CH_2Br_2 as the internal standard; only *para*-borylated product was observed. [c]Isolated yield.

Table 2 *Para*-borylation of monosubstituted arenes.[a,b]

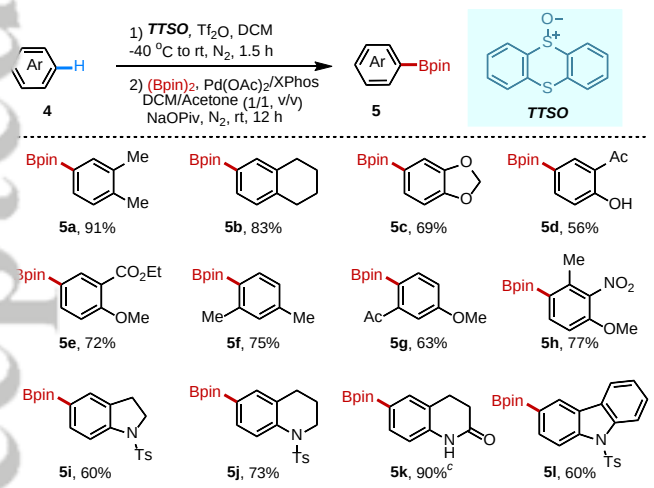


[a]Reaction conditions: 1) **1** (0.2 mmol), Thianthrene *S*-oxide (0.24 mmol), Tf_2O (0.24 mmol), DCM (1.0 mL), N_2; -40 °C for 30 min, then rt for 1 h; 2) $Pd(OAc)_2$ (5.0 mol %), XPhos (5.0 mol %), $(Bpin)_2$ (2.0 equiv), NaOPiv (3.0 equiv), Acetone (1.0 mL); Only *para*-borylation products were observed in crude ^1H NMR. [b]Isolated yield. [c]DCM (0.2 mL) was used. [d]$Pd(OAc)_2$ (10 mol %), XPhos (10 mol %) were used.

were also investigated, in which SPhos gave similar activity with XPhos albeit the others all led to inferior yields.

With the optimal conditions in hand, monosubstituted arenes were firstly evaluated. As summarized in Table 2, all substrates listed in the table gave excellent positional selectivities, and only *para*-borylated products were observed in crude ^{1}H NMR. Moreover, this newly developed protocol typically provided broader substrates scope in comparison with the photoredox catalysis. For instance, the Ac-protected benzyl alcohol (**1m**), Phth-protected benzyl amine (**1n**), Phth-protected phenethylamine (**1o**), Phth-protected 3-phenyl-1-propanamine (**1p**), native 2-phenylpropionic acid (**1u**) and amino acid derivative (**1w**) resulted in very low yields, and the dehalogenation happened for 1-chloro-3-phenylpropane (**1q**) under the previous photoredox conditions. Not surprisingly, alkylated benzene derivatives (**1a-e**), anisole (**1f**), Ac-protected phenol (**1g**), phenyl ether (**1h**), aniline derivatives (**1j-k**) were all compatible with this one-pot procedure, giving the desired arylborons in moderate to high yields. Fluorobenzene (**1l**) provided the *para*-borylated product in 52% yield. Other functional groups on alkyl chain did not significantly affect the efficiency of this process, like ester (**2r**, **2t**, **2v**), ether (**2s**), masked amino alcohol (**2x**), and epoxide (**2y**). Substituted phenyl ether (**1z**) and biphenyl (**1aa**) were also tolerated under current conditions, yielding the targeted products in 89% and 62% yields, respectively. Electron-deficient arenes and electron-deficient heterocycles are incompatible with this protocol probably due to the electrophilic properties of the sulfide dication intermediate in the thianthrenation step.

Table 3 Site-selective borylation of multi-substituted arenes.[a,b]

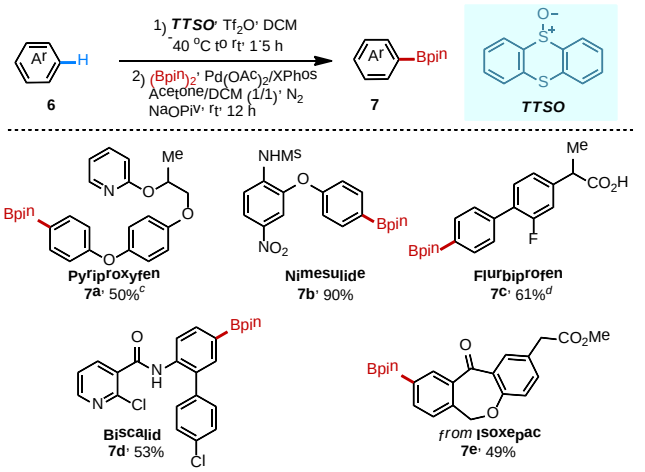


[a] Reaction conditions: 1) **2** (0.2 mmol), Thianthrene *S*-oxide (0.24 mmol), Tf_2O (0.24 mmol), DCM (1.0 mL), N_2; -40 °C for 30 min, then rt for 1 h; 2) $Pd(OAc)_2$ (5.0 mol %), XPhos (5.0 mol %), $(Bpin)_2$ (2.0 equiv), NaOPiv (3.0 equiv), Acetone (1.0 mL). [b]Isolated yield. [c]$Pd(OAc)_2$ (10 mol %), XPhos (10 mol %) were used.

Next, we turned our attention to explore the scope of the multisubstituted arenes. Typically, the boron group was installed to the most electron rich sites in the arenes due to the highly electrophilic properties of the thianthrenium dication intermediate. A wide range of disubstituted arenes (**4a-g**) and trisubstituted arene (**4h**) are suitable substrates for this TTSO-mediated borylation protocol. Notably, the electron-rich heterocycles including indoline (**4i**), 1,2,3,4-tetrahydroquinoline (**4j**), 1,2,3,4-tetrahydroquinolin-2-one (**4k**), and carbazole (**4l**) are also suitable substrates for this reaction, selectively delivering the boron group to the *para*-position to the nitrogen on those heterocycles.

Due to the remarkable site-selectivity and versatility of arylborons as a synthetic linchpin, the TTSO-mediated site-selective borylation represents a charming process for late-stage functionalization of drugs and complex bioactive molecules. With our newly developed one-pot process, site-selective borylation of pharmaceuticals, Pyriproxyfen (**6a**), Nimesulide (**6b**), Flurbiprofen (**6c**), Biscalid (**6d**), and Isoxepac methyl ester (**6e**) were demonstrated.

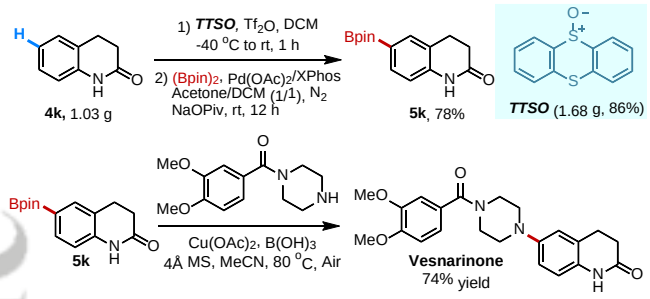
Table 4 Late-stage functionalization of bioactive scaffolds.[a,b]



[a]Reaction conditions: 1) **6** (0.2 mmol), Thianthrene *S*-oxide (0.24 mmol), Tf_2O (0.24 mmol), DCM (1.0 mL), N_2; -40 °C for 30 min, then rt for 1 h; 2) $Pd(OAc)_2$ (5.0 mol %), XPhos (5.0 mol %), $(Bpin)_2$ (2.0 equiv), NaOPiv (3.0 equiv), Acetone (1.0 mL). [b]Isolated yield. [c]$Pd(OAc)_2$ (10 mol %), XPhos (10 mol %) were used. [d]DCM (0.2 mL) was used.

The scalability of this process was demonstrated by the borylation of 3,4-dihydro-2(1*H*)-quinolinone (**4k**) on 7.0 mmol scale, and 78% yield of targeted arylboron was obtained. Most importantly, the mediator thianthrene *S*-oxide (TTSO) could be recycled in 86% total yield upon the oxidation of recovered thianthrene (Scheme 2). In addition, drug molecule Vesnarinone could be obtained in one step employing borylated 3,4-dihydro-2(1*H*)-quinolinone as starting material. .

Scheme 2 Gram-scale reaction and synthetic application



Conclusions

In summary, thianthrene S-oxide mediated selective C-H borylation of a wide range of arenes has been demonstrated via Pd catalyzed desulfurative borylation reaction. This synthetically simple one-pot process is highly useful for the late-stage functionalization of bioactive molecules and for the synthesis of bioactive compounds.

Experimental

General procedure for site-selective borylation: A 10 mL Schlenk tube was charged with thianthrene *S*-oxide (55.7 mg, 0.24 mmol, 1.2 equiv.), CH_2Cl_2 (1.0 mL) and **1a** (0.2 mmol, 1.0 equiv.) under a nitrogen atmosphere. The suspension was then cooled to -40 °C, followed by the dropwise addition of Tf_2O (44 µL, 0.24 mmol, 1.2 equiv.). The resulting blue mixture was stirred at -40 °C for 30 min, and was allowed to stir at room temperature for another 1 hour. Then, bis(pinacolato)diboron (0.4 mmol, 2.0 equiv), $Pd(OAc)_2$ (2.4 mg, 5.0 mol%), XPhos (4.8 mg, 5.0 mol%), sodium pivalate (74.5 mg, 0.6 mmol, 3.0 equiv) were added under a nitrogen atmosphere, followed by the addition of acetone (1.0 mL). The reaction mixture was stirred at room temperature for 12 hours. Subsequently, the mixture was passed through a pad of Celite with DCM as the eluent to remove the insoluble precipitate. The resulting solution was concentrated and purified by preparative thin-layer chromatography to afford the desired product **2a**.

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2018xxxxx.

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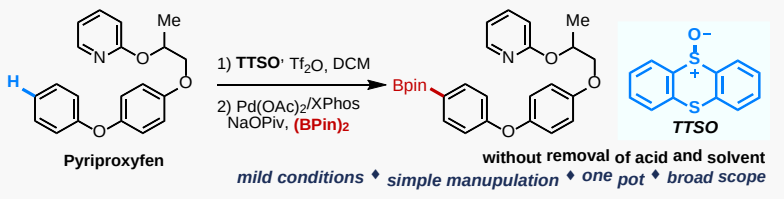
Pd-Catalyzed Site-Selective Borylation of Simple Arenes via Thianthrenation



Site-selective borylation of simple arenes was realized in one pot via an electrophilic thianthrenation/Pd-catalyzed borylation sequence. This protocol features mild conditions, broad functional group tolerance, and simple manipulations, and is suitable for late-stage functionalization of a wide range of pharmaceuticals and complex bioactive molecules.

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