

# Para-Selective Borylation of Monosubstituted Benzenes Using a Transient Mediator

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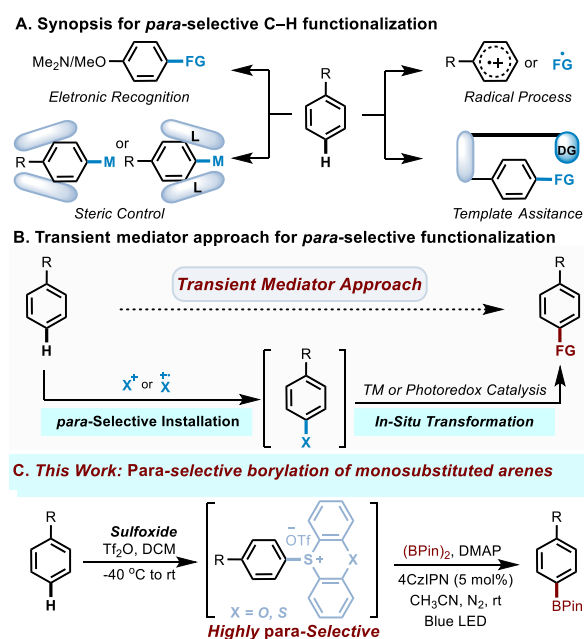
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Supporting Information Placeholder

**ABSTRACT:** Herein, we conceptualized a transient mediator approach that has the capability of *para*-selective C–H functionalization of monosubstituted aromatics. This approach is enabled by in situ generation of a versatile sulfonium salt via highly electrophilic phenoxathiine or thianthrene dication intermediate which can be readily generated from its sulfoxide with trifluoromethanesulfonic anhydride. Preliminary mechanistic study implied that the remarkable *para* selectivity might be related to the incredible electrophilicity of thianthrene dication intermediate. The versatility of this approach was demonstrated via *para*-borylation of various monosubstituted simple aromatics combining the sulfonium salt formation with further photocatalyzed transformation.

Tremendous efforts have been made in the field of precise control the site selectivity in C–H functionalization of aromatics during the past two decades.<sup>1–2</sup> However, achieving *para*-selectivity in direct C–H functionalization reactions remains a significant challenge, especially when the targeted arene owns multiple reactive sites with subtle steric and electronic discrepancy. Typically, *para*-selectivity control often dominated by steric and electronic factors of substrates, and high selectivity was observed mainly for electron-rich arenes, which have been represented in electrophilic aromatic substitution reaction of aromatics.<sup>3</sup> Recently, major progress to face this challenging *para*-C–H functionalization has been achieved through electronic recognition,<sup>4</sup> steric control,<sup>5</sup> template assistance,<sup>6</sup> and radical involved processes<sup>7</sup> (Scheme 1A). Despite undisputable advances, those methods are still lack of generality with insufficient regioselectivity, either requiring large excess of arenes or working with the assistance of directing group (template), and normally resulting in a mixture of *para*-substituted product with other isomers. The development of general and efficient approaches to achieve *para*-C–H functionalization without directing group assistance remains a significant task. Herein, we conceptualized a *transient mediator approach* that enables *para*-selective functionalization of monosubstituted benzene derivatives (Scheme 1B). We envisioned that a mediator could be selectively introduced to the *para* position of the substituents via a highly electrophilic cation or radical cation intermediate

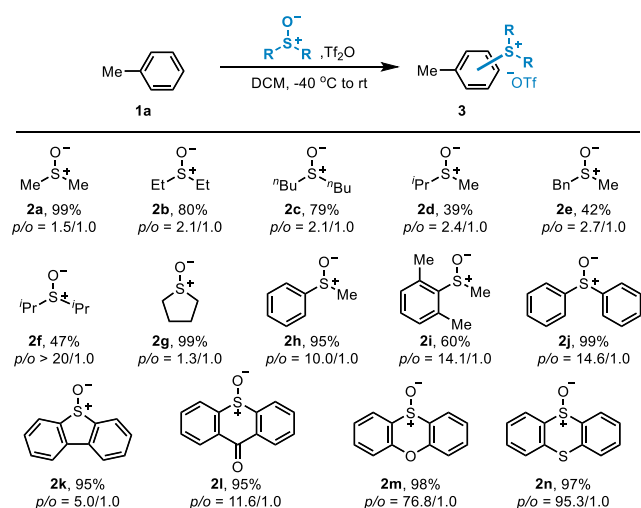
## Scheme 1. Background and Synopsis for *para*-C–H Functionalization of Monosubstituted Arenes



with electron or steric recognition. This resulted species could be readily converted to other functionalities with high efficiency providing the *para*-decorated aromatics. By carefully selecting the transient mediator and conditions, *para*-functionalization of monosubstituted benzene could be realized in a single synthetic operation. In this case, highly electrophilic phenoxathiine or thianthrene radical cation intermediate,<sup>8</sup> in situ initiated by its sulfoxide with trifluoromethanesulfonic anhydride, was capable of generating the corresponding sulfonium salt with a high *para*-selectivity. *Para*-borylation of monosubstituted benzene was realized by combining the sulfonium salt formation with further photocatalyzed borylation using phenoxathiine or thianthrene as the transient mediator.

We started our investigation by searching a suitable transient mediator, which has the capability of being installed at the *para*-position of the monosubstituted aromatics with high selectivity, and being readily converted to other functional groups. Be aware of the remarkable activity of sulfide dication, a highly active intermediate formed in situ by treating sulfide oxide with  $\text{Ti}_2\text{O}_3$ ,<sup>9</sup> we hypothesized that the electrophilic sulfide dication might be a potential handle for addressing this challenging problem by adjusting the steric effects. In situ generated dimethyl sulfide dication (DMSD) reacted with toluene providing the corresponding sulfonium salts in 99% yield with an insufficient selectivity ( $p/o = 1.5/1.0$ ). The selectivity was slightly improved with the increase of steric hindrances (**2b-e**). Diisopropyl sulfoxide (**2f**) gave a remarkable *para/ortho* ratio of  $>20/1.0$ , whereas the efficiency of sulfonium salt formation is unsatisfying and cannot be further improved probably due to bulky isopropyl substituent. It is noteworthy that methyl phenyl sulfoxide (**2h**) maintained the high efficiency and high selectivity simultaneously, giving 10.0/1.0 selectivity and 95% yield. Encouraged by this result, we decided to focus on evaluation of aryl sulfoxides (**2i-n**). Despite more steric hindrance sulfoxide **2i** led to lower reactivity, diphenyl sulfoxide **2j** provided its sulfonium salt in quantitative yield with similar selectivity. Compared to diphenyl sulfoxide, less steric hindrance dibenzothio-phenone sulfoxide (**2k**) and thioxanthone sulfoxide (**2l**) resulted in lower selectivities. Gratifyingly, phenoxathiine sulfoxide (**2m**) and thianthrene sulfoxide (**2n**) significantly improved the selectivity to  $>76/1$  (*para/ortho*) with high efficiency.

### Scheme 2. Evaluation of Sulfoxides.<sup>a,b</sup>

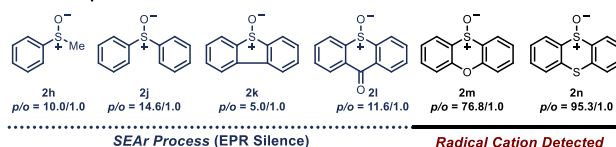


<sup>a</sup>Conditions: toluene (0.5 mmol), sulfoxide (0.6 mmol),  $\text{Ti}_2\text{O}_3$  (0.6 mmol), DCM (0.5 mL),  $\text{N}_2$ ;  $-40^\circ\text{C}$  for 30 min, then rt for 1 h. <sup>b</sup>The yield was determined by  $^1\text{H}$  NMR using  $\text{CH}_2\text{Br}_2$  as the internal standard. The selectivity was determined by the  $^1\text{H}$  NMR.

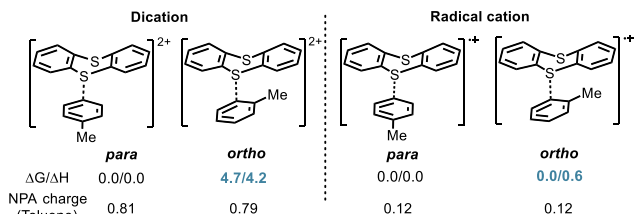
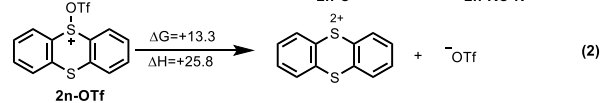
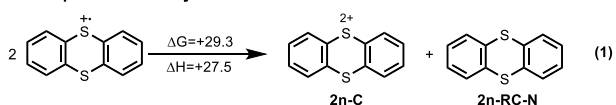
To shed light on the causation for remarkable *para* selectivity using phenoxathiine and thianthrene derived sulfoxide, detailed mechanistic studies were carried out. Although the sulfoxide screening confirmed that the regioselectivity can be partially controlled by the steric effects, the EPR experiment of the reaction system with various in situ generated sulfide dication indicated that the striking *para*-selectivity might also be related to the formation of phenoxathiine<sup>10a</sup> and thianthrene radical cation intermediates.<sup>10b-f,11</sup> In comparison, thioxanthone sulfoxide

### Figure 1. Mechanistic Study

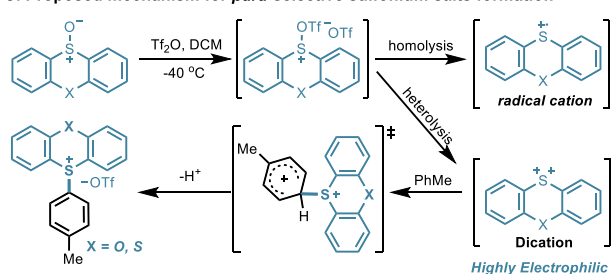
#### A. EPR response for various sulfate dicationates



#### B. Computational study

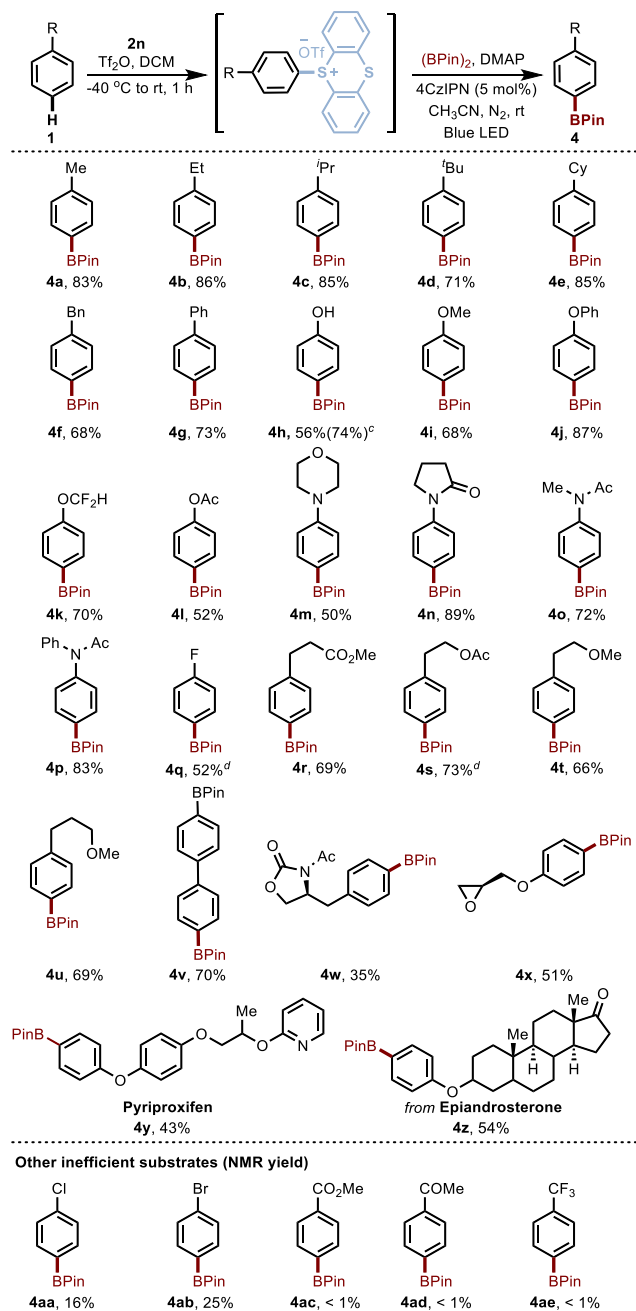


#### C. Proposed mechanism for *para*-selective sulfonium salts formation



(**2l**) with similar scaffold without EPR response resulted in a lower *para* selectivity (Figure 1A). However, the reaction didn't proceed at low concentration of sulfoxide and  $\text{Ti}_2\text{O}_3$ , despite the radical cation intermediate existed which confirmed by the EPR experiment. We hence doubted whether the radical cation intermediate is real reactive species for sulfonium salts formation, and were intrigued by the origin of the outstanding regioselectivity. To further understand this process, preliminary computational studies were performed at SMD-M062X/def2-TZVP level of theory, and three possible intermediates, radical cation, radical cation dimer and sulfide dication, were systematically investigated. The intermediates of C-S formation with toluene and thianthrene radical cation didn't show apparently energy difference ( $< 0.6$  kcal/mol) indicating the poor selectivity of *para/ortho* position by the calculated energy scanning of forming C-S distance (see Figure S8). Based on Dunsch's study (ref 10g), a dimer intermediate could be formed via a reversible dimerization of thianthrene radical cation, however, the dimer can't lead to stable adducts for the reasonable *para/ortho* selectivity in the electrophilic substitution of toluene through calculations (see Figure S9) We next turned our attention to the plausible thianthrene dication intermediate, and found the sulfide dication intermediate is facile from heterolysis of sulfide dication **2n-OTf** with slightly endothermic rather than disproportionation from thianthrene radical cation. The large free energy difference ( $> 4.0$  kcal/mol) between *para*- and *ortho*- intermediates imply that the sulfide dication would be the possible

### Scheme 3. Scope of Monosubstituted Arenes. <sup>a,b</sup>



<sup>a</sup>Reaction conditions: 1) **1** (0.2 mmol), **2n** (1.2 equiv), Tf<sub>2</sub>O (1.2 equiv), DCM (1.0 mL), -40 °C to rt, 1 h; 2) DMAP (2.0 + 2.0 equiv), 4-CzIPN (5 mol %), (BPin)<sub>2</sub> (4.0 equiv), Blue LED, 8 h. <sup>b</sup>Isolated yield; for all substrates, high *para* selectivities were obtained (*para*/*others* > 50/1). <sup>c</sup>TIPS-protected phenol was used. <sup>d</sup>Reaction conditions: **2n** (2.4 equiv), Tf<sub>2</sub>O (2 equiv) and DMAP (3 + 2 equiv.) were used rather than the standard conditions.

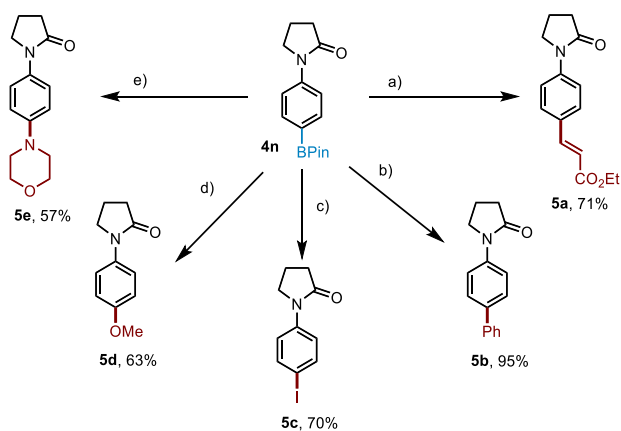
active species responsible for the high regioselectivity. And the dispersedly positive NPA charge (see Figure S11) on both thi-anthrene and toluene lead the *exo*-conformation in the favorable *para*-intermediate to minimize the electrostatic repulsions, which can rationalize the experimental observation of high *p/o* ration. Based on the DFT study, we therefore postulated that the *para*-selective sulfonium formation proceeded via electronic

substitution with the highly electrophilic sulfide dication intermediate, followed by deprotonation to form sulfonium salts (Figure 1C). Besides, the less efficiency with electron-deficient substrates, like PhCF<sub>3</sub>, PhCO<sub>2</sub>Me, also supported this reaction proceeded via cation intermediates.<sup>11a</sup>

Given the versatility of aryl boronic acid in organic synthesis,<sup>12</sup> we are curious if we can achieve the *para*-borylation of monosubstituted benzenes by in situ converting the resulted sulfonium salt<sup>13</sup> in a single synthetic operation. Several elegant examples towards the challenging *para*-C–H borylation of arenes have been witnessed in the last decade. For example, Itami and coworkers<sup>5a</sup> have reported an Ir-catalyzed *para*-C–H borylation by altering the steric hindrance on ligands, moderate to poor *para* selectivity was obtained using less congested monosubstituted arenes, such as cumene (*para*:*others* = 58:42) and ethylbenzene (*para*:*others* = 32:68). Recently, Nakao Group<sup>5d-f</sup> and Chattopadhyay group<sup>6c</sup> has achieved the Ir-catalyzed *para*-selective borylation of aromatic esters and amides in high selectivity by adopting the rational designed bimetallic or non-covalent interaction strategy. However, those strategies cannot be extended to undirected aromatics without polar functional group assistance. After scrupulously evaluated the reaction parameters for *para*-borylation, we found the *para*-borylated toluene can be obtained in 83% yield using DMAP as base and activator, 4CzIPN as photocatalyst in CH<sub>3</sub>CN (For detailed screening, see Supporting Information). With the optimized conditions in hand, the generality of this protocol was examined. As summarized in Scheme 3, alkylated benzene derivatives provided desired borylated products in high yields (**4a–e**), while diphenylmethane gave moderate yield (**4f**, 68% yield). Biphenyl also produced the corresponding boronic acid pinacol ester in 73% yield (**4g**). Electron rich phenol (**1h–l**) and aniline (**1m–p**) derivatives are also suitable substrates for this protocol, in which the tolerance with difluoromethoxybenzene, *N*-phenylmorpholine, 1-phenyl-2-pyrrolidinone are noteworthy. TIPS-protected phenol (**1h**) provided the unmasked *para* borylated phenol in 74% yield, whereas phenol also can be used in the reaction with slightly lower yield. Electron-deficient fluorobenzene (**1q**) was compatible with this procedure along with high *para* selectivity. Derivatives of hydrocinnamic acid (**1r**), 2-phenylethanol (**1s–t**), phenylpropanol (**1u**), borylated biphenyl (**1v**), *L*-phenylalaninol (**1w**), and (*S*)-2-oxiranylanisole (**1x**) underwent this protocol yielding the desired products in moderate to high yields. Some complex scaffolds (**1y**, **1z**) were also compatible, demonstrating this protocol is versatile for late-stage functionalization of drug molecules. Moreover, the electron deficient substrates provided low activities (**1aa–ae**) probably due to the electrophilic nature of dication intermediate in the sulfonium salts formation step.

The *para*-borylated products can be readily transformed to various *para*-decorated arenes efficiently as summarized in Scheme 4. Using **4n** as model scaffold, the boronic acid pinacol ester can be smoothly converted to alkenyl, aryl, iodide, methoxyl, and aminyl in high efficiency. This protocol opens a new avenue for synthesis of 1,4-disubstituted arenes, a scaffold frequently found in biologically active compounds.

## Scheme 4. Transformation of Aryl Boron



Conditions: a)  $\text{CH}=\text{CHCO}_2\text{Et}$ ,  $\text{Pd}(\text{OAc})_2$  (10 mol %),  $\text{Na}_2\text{CO}_3$  (2.0 equiv), DMF, 50 °C,  $\text{O}_2$ , 3 h; b)  $\text{PhBr}$  (1.0 equiv),  $\text{Pd}(\text{dppf})\text{Cl}_2$  (5 mol %),  $\text{K}_3\text{PO}_4$  (3.0 equiv),  $\text{H}_2\text{O}$  (5.0 equiv), THF, 70 °C, 3 h; c)  $\text{KI}$  (1.5 equiv),  $\text{CuI}$  (10 mol %), 1,10-phenanthroline (20 mol %),  $\text{MeOH}/\text{H}_2\text{O}$  (4:1), 80 °C, 20 h; d)  $\text{MeOH}$ ,  $\text{Cu}(\text{OAc})_2$  (1.0 equiv), DMAP (2.0 equiv), 4 Å MS, rt, air, 24 h; e) morpholine (2.0 equiv),  $\text{Cu}(\text{OAc})_2$  (1.0 equiv),  $\text{Et}_3\text{N}$  (2.0 equiv), 4 Å MS,  $\text{CH}_3\text{CN}$ , 80 °C, air, 24 h.

In summary, *para*-borylation of monosubstituted benzenes has been demonstrated using phenoxathiine or thianthrene as the transient mediator. Preliminary mechanistic study indicated that the key to the remarkable *para*-selectivity might be the use of highly electrophilic phenoxathiine or thianthrene dication species. Detailed mechanistic study and the application of this transient mediator approach for site-selective functionalization are ongoing projects in our laboratory.

## ASSOCIATED CONTENT

Experimental procedures, complete characterization data, copies of  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra. The Supporting Information is available free of charge via the Internet at <http://pubs.acs.org>.

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