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Site-selective aromatic C–H λ^3 -iodanation with cyclic iodine(III) electrophile in solution and solid phases

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An efficient and site-selective aromatic C–H λ^3 -iodanation reaction is achieved using benziodoxole triflate (BXT) as electrophile under room temperature conditions. The reaction tolerates a variety of electron-rich arenes and heteroarenes to afford the corresponding arylbenziodoxoles in moderate to good yields. The reaction can also be performed mechanochemically by grinding a mixture of solid arene and BXT under solvent-free conditions. The arylbenziodoxoles can be used for various C–C and C–heteroatom bond formations, and are also amenable to further modification by electrophilic halogenation. DFT calculations suggested that the present reaction proceeds via a concerted λ^3 -iodanation–deprotonation transition state, where the triflate anion acts as an internal base.

Introduction

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Direct and site-selective C–H functionalization of arenes and heteroarenes with a leaving group that can allow aryl–carbon and aryl–heteroatom bond formations offers a highly attractive strategy to access diverse (hetero)aromatic compounds. Transition metal-catalyzed arene C–H borylations, which install a boryl group as an electrofugal leaving group onto arenes, are among the most powerful C–H functionalization methods of this type.¹ The installation of a nucleofugal leaving group onto arenes can be equally attractive and complementary to the C– H borylation. However, traditional electrophilic halogenation reactions often suffer from drawbacks such as incomplete site selectivity and harsh reaction conditions.^{2,3} As such, methods for site-selective installation of synthetically versatile nucleofuges other than halogens are highly desirable.⁴

Trivalent iodine (λ^3 -iodane) moieties represent a class of useful nucleofuges in arene transformations. Thus, vast arrays of aryl–carbon and aryl–heteroatom bond forming reactions have been developed using diaryliodonium salts as electrophilic aryl-transfer agents.⁵ Particularly attractive among diaryliodonium salts are unsymmetrical ones that allow selective transfer of one of the aryl groups over the other, "dummy" aryl group (*e.g.*, mesityl).^{6,7} A direct C–H λ^3 iodanation approach has proved feasible for the synthesis of such compounds from electron-rich (hetero)arenes and bulky aryl- λ^3 -iodane reagent such as MesI(OH)OTs with acidic activator, or from (hetero)arenes, bulky aryl iodide, oxidant and acid.⁸ However, diaryliodonium salts are potentially unstable for isolation and prolonged storage, and are often used without isolation.^{8a-c} In this context, aryl- λ^3 -iodane compounds bearing a cyclic benziodoxol(on)e (BX) moiety could be a valuable alternative or complement to diaryliodonium salts, as their nonionic nature and rigid structure would endow them with enhanced stability for facile isolation and long-term storage as well as opportunity to tolerate a wider range of reaction conditions. The BX group has already had great success in the development of reagents for transferring groups such as trifluoromethyl, alkynyl, azido, and cyano groups.⁹ On the other hand, access to analogous (hetero)aryl-BX reagents remains relatively limited and their reactivity less explored. The direct preparation of aryl-BXs from arenes and 2-iodobenzoic acid was reported by Olofsson and Zhdankin (Scheme 1a).¹⁰ However, these compounds have not been utilized as aryl transfer agents. Instead, they were reported to produce 2functionalized benzoic acids in the reaction with nucleophiles.^{10b} More recently, Waser developed indole- and pyrrole-BX reagents via zinc-catalyzed BX transfer to indoles and pyrroles with acetoxy benziodoxolone and demonstrated their utility in C–H functionalization reactions (Scheme 1b),^{11,12} while the reaction required relatively high dilution and was not extended to arenes.

Herein, we report that Zhdankin's benziodoxole triflate (BXT; **1**) derived from α, α -bis(trifluoromethyl)-2-iodobenzyl alcohol¹³ undergoes C–H λ^3 -iodanation of (hetero)arenes with high site selectivity (Scheme 1c). This BX transfer reaction tolerates various electron-rich arenes and heteroarenes, allowing facile preparation of the corresponding aryl–BX derivatives in moderate to excellent yields under simple and mild conditions

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without any catalyst or promoter. Moreover, the reaction can also be performed mechanochemically using solid arene and BXT under solvent-free conditions. The aryl-BX compounds serve as aryl donors for a variety of C-C and C-heteroatom bond formations, and also tolerate further modification by electrophilic halogenation. Owing to the superior leaving group ability of the BX group, iodinated aryl-BX compounds can be used for chemoselective sequential cross-couplings.

(a) Aryl-benziodoxolones via in-situ oxidation/ λ^3 -iodanation

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Not utilized as Ar transfer agents

(b) Waser: Indole/pyrrole-benziodoxolones via Zn-catalyzed direct λ^3 -iodanation



High dilution, limited to indole/pyrrole derivatives

(c) This work: Aryl-benziodoxoles via catalyst-free direct λ^3 -iodanation



- Catalyst- and additive-free
- Low dilution or solvent-free mechanochemistry
- Ar-BX: Stable and synthetically versatile

Scheme 1 Synthetic approaches to (hetero)arylbenziodoxol(on)es via C–H λ^3 -iodanation.

Results and discussion

Pursuing our continuing interest in hypervalent iodine chemistry $^{\rm 14}$ and encouraged by our recent success in using ${\rm 1\!\!1}$ as a λ^3 -iodane electrophile,¹⁵ the present study commenced with the exploration of the reaction between anisole (2a, 1.5 equiv) and 1 (Table 1). The reaction proceeded smoothly in MeCN at room temperature, affording the aryl-BX product 3a with exclusive para-selectivity in 94% yield, which could be purified by routine chromatography and are stable to air and moisture (entry 1). No decomposition was observed upon storage at room temperature for at least one month. The reaction proved highly solvent-dependent. Aromatic and chlorinated solvents could be used albeit with a sizable decrease in the yield (entries 2-4). On the other hand, no product was observed in polar coordinating (DMF), ethereal (Et₂O), and protic (MeOH) solvents (entries 5-7). The yield slightly dropped by using equimolar mixture of 2a and 1 or using 1 as the excess reagent (entries 8 and 9). Note that an analogous BXT reagent derived from 2-iodobenzoic acid¹³ failed to promote the desired λ^{3} iodanation of 2a. While the above and the following experiments to explore the substrate scope were all set up in an Ar-filled glove box, the reaction actually proved to be unaffected by air and moisture. Thus, the model reaction

between 1 and 2a could be run under air to afford 3a in an DOI: 10.1039/D0SC02737E equally high yield (95%).



	•	
Entry	Solvent	Yield (%) ^b
1	MeCN	94
2	CH ₂ Cl ₂	83
3	toluene	65
4	chlorobenzene	69
5	DMF	0
6	Et ₂ O	0
7	MeOH	0
8 ^c	MeCN	84
9 ^d	MeCN	86

^a Unless otherwise noted, the reaction of 1 (0.10 mmol) and 2a (0.15 mmol) was carried out in the solvent (0.25 mL) at room temperature. ^b Determined by ¹⁹F NMR using 1,4-bis(trifluoromethyl)benzene as an internal standard. ^c 1 (0.10 mmol) and 2a (0.10 mmol) were used. ^d 1 (0.20 mmol) and 2a (0.10 mmol) were used.

With the optimized reaction conditions in hand, we explored the scope of the λ^3 -iodanation reaction (Table 2). A variety of monoalkoxyarenes took part in the reaction to afford the desired aryl–BX products **3a–3e** in high yields with exclusive para-selectivity. 1,3-Disubstituted arenes such as m-xylene, resorcinol dimethyl ether. and 3-methoxytoluene regioselectively afforded aryl-BX products 3f-3h with 1,2,4substitution pattern. The latter reacted exclusively at the paraposition of the methoxy group. 1-Alkoxy-2-substituted benzene including derivatives, dihydrobenzofuran and 9,9dimethylxanthene, were functionalized at the para-position of the alkoxy group, thus affording the products **3i-3o** in moderate to good yields, while elevated temperatures (60-80 °C) were necessary for 1-methoxy-2-halobenzenes. 3-Methylbenzoxazol-2(3H)-one reacted exclusively at the para-position of the nitrogen atom, as unambiguously supported by X-ray crystallographic analysis of the product **3p**.¹⁶ Electron-rich 1,3,5-trisubstituted arenes such as mesitylene, 1-bromo-3,5dimethoxybenzene, 3,5-dimethylanisole, and N-methyl metaxalone¹⁷ took part in the reaction to afford the products 3q-3t in good yields, where, for the latter three, the paraposition of the alkoxy group was selectively functionalized. Other trisubstituted methoxyarenes with different substitution patterns were also amenable to the present λ^3 -iodanation (see the products **3u-3w**). Electron-rich heteroarenes such as thiophene and indole derivatives could be employed as substrates for the present reaction, producing the products 3x-**3aa** in good yields. The scalability of the present λ^3 -iodanation reaction was demonstrated by gram-scale (3 mmol) synthesis of 3a and 3q, which could be achieved without a significant decrease in the yield (86% and 77% yields, respectively). It should be noted that the present method allows access to unique aryl-BX compounds such as 3m and 3z that contain

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^o The reaction was performed on a 0.2 mmol scale according to the standard conditions described in Table 1, entry 1. BX in the product formula refers to the benziodoxole moiety. ^b The yield for a 3 mmol-scale reaction is given in the parentheses. ^c The reaction was performed at 60 °C. ^d The reaction was performed at 80 °C. ^e The reaction was performed with **2ac** (0.2 mmol), **1** (0.3 mmol), and Na₂CO₃ (0.4 mmol) in chlorobenzene (1.0 mL).

Besides arenes and heteroarenes, 1,1-diphenylethene (**2ab**) and its *para*-fluoro-substituted derivative (**2ac**) reacted with BXT under the standard conditions to afford the corresponding

alkenyl–BXs **3ab** and **3ac** in good yields (Scheme 2a), $^{15c-e,18}_{MArticle}$ The reaction of 1,1-di(*p*-tolyl)ethene (**2ac**) did Not take place and the standard conditions but resulted in the decomposition of 1, while the addition of Na₂CO₃ and the use of chlorobenzene as the solvent allowed us to obtain the desired product **3ad** in a moderate yield (Scheme 2b). Other alkenes such as styrene, α -methylstyrene, and vinylcyclohexane failed to participate in the present C–H λ^3 -iodanation.



Recently, mechanochemistry has emerged as a powerful tool in synthetic chemistry for attractive merits such as solvent-free process, reduced reaction times, and ability to engage poorly soluble solid compounds, and unique reactivity and selectivity.¹⁹ Notably, mechanochemistry has proved to offer an ideal means to accelerate the present λ^3 -iodanation under solvent-free conditions. Thus, by simply subjecting a mixture of arene (0.3 mmol) and **1** (0.2 mmol) to ball milling (30 Hz for 2 h), aryl–BX derivatives **30**, **3q**, **3r**, and **3u** were obtained in good yields (Scheme 3a). Note that, except for **3q**, the starting arenes of these aryl–BXs are solid compounds. Additionally, the mechanochemical synthesis of **3r** could be performed on a gram scale using a slight excess of the arene **2r**, yielding analytically pure product without chromatographic purification (Scheme 3b).



Scheme 3 Mechanochemical $\lambda^3\mbox{-}iodanation$ of arenes

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Some important limitations of the present λ^3 -iodanation should be noted. Less electron-rich, electron-neutral or electron-poor arenes did not participate well in the reaction with 1 even at elevated temperatures (up to 80 °C), and were largely recovered. However, the reaction of moderately electron-rich o-xylene, which was sluggish under the original conditions (28% yield at 60 °C), could be promoted by the addition of Sc(OTf)₃ catalyst (20 mol%) and the use of CH₂Cl₂ as the solvent to afford the corresponding aryl-BX product **3ae** in 55% yield (Scheme 4a). Meanwhile, aryl-BXs bearing electronneutral phenyl (3af) or electron-deficient 4-bromophenyl (3ag) or 4-cyanophenyl (3ah) group could be synthesized in good yield via silicon-to-iodine(III) or boron-to-iodine(III) aryl transfer^{20,21} using the corresponding aryltrimethylsilane or aryltrifluoroborate (Scheme 4b-c). Highly electron-rich arenes, such as 1,2- and 1,4-dimethoxybenzenes and N,Ndimethylaniline, failed to give the desired aryl-BX products with **1** and decomposed to α, α -bis(trifluoromethyl)-2-iodobenzyl alcohol. This reduction of the I(III) reagent is likely caused by the ability of these electron-rich arenes to undergo single electron transfer.



Scheme 4 Preparation of aryl–BXs via Lewis acid-catalyzed C–H λ^3 -iodanation or aryl transfer from aryl silicon or boron reagents.

The functionalized aryl-BX products obtained by the present reaction could be used as versatile building blocks for further transformations via selective transfer of the arenederived aryl groups (Scheme 5). As illustrated in Scheme 5a, the benziodoxole moiety in 3a and 3g served as an excellent leaving group in Pd-catalyzed Suzuki-Miyaura, Sonogashira, Stille couplings, and Miyaura borylation,²² which afforded biaryl 4, aryl alkyne 5, styrene 6, and aryl boronate 7, respectively, in good yields. In addition, aryl-BX 3a was amenable to Cucatalyzed sulfonylation²³ and cyanation,²⁴ affording the corresponding aryl sulfone 8 and aryl nitrile 9, respectively. 3-Iodo-4-methoxyphenyl-BX 3m and 5-iodothien-2-yl-BX 3z underwent site-selective Sonogashira coupling with

trimethylsilylacetylene on the aryl–BX moiety over, the erylie iodide moiety to afford the monoalkynylated products **10** and **12**, respectively, which illustrated the superior leaving group ability of the BX group in oxidative addition to Pd(0) (Scheme 5b). Subsequent Sonogashira coupling of **10** and **12** with phenylacetylene provided unsymmetrically dialkynylated arenes **11** and **13**, respectively. Finally, the compounds **3g** and **3o** could be regioselectively brominated or chlorinated without affecting the BX group to afford the products **3v**, **14**, and **15** in good yields (Scheme 5c).^{3e} The sequential installation of BX and halogen may offer a means for chemoselective difunctionalization of aromatic compounds.





(b) Chemoselective sequential cross-couplings



 3z
 12, 61%
 13, 84%

(c) Halogenation of Ar-BX





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0 °C, 12 h; h) PdCl₂(PPh₃)₂, CuI, phenylacetylene, THF/Et₃N, rt, 12 h; i) NBS, HFIP, 40 °C, 24 h; j) NCS, HFIP, 80 °C, 24 h; k) NBS, HFIP, rt, 4 h.

To gain insight into the mechanism of the C–H λ^3 -iodanation, DFT calculations on the reaction between 1 and anisole (2a) were performed (Figure 1; see the Supporting Information for the computational detail). Prior to the iodanation event, the triflate on **1** is slipped to the *trans* position of the aryl group (**1** to 1' via TS1), which allows 2a to bind to the cis position of the aryl ligand (CP1).²⁵ This is followed by a six-centered TS for concerted λ^3 -iodanation/deprotonation of the *para*-position (**TS2***p*, ΔG^{\ddagger} = 19.3 kcal mol⁻¹) to give the product **3a** and TfOH, which is reminiscent of the concerted metalationdeprotonation mechanism in aromatic C-H activation by transition metal carboxylates.^{25,26} Note that λ^3 -iodanation without prior isomerization of 1 requires an unreasonably high activation energy (37.3 kcal mol⁻¹; Figure S4). The calculated endergonicity (2.1 kcal mol⁻¹) might be a reflection of computational artifact, which does not take the interaction between TfOH and MeCN (in the solution-phase reaction) or the intermolecular hydrogen bonding between TfOH molecules (in the solid-phase reaction) into account. Consistent with the experiment, analogous transition states for the λ^3 -iodanation of the ortho- and meta-positions were found to require higher activation energies (20.5 kcal mol⁻¹ and 27.5 kcal mol⁻¹, respectively; Figure S5).



Figure 1 Gibbs free energy diagram for the para C–H λ^3 -iodanation of anisole (2a) with BXT (1). The bond distances are in Å.

Conclusions

In summary, we have reported site-selective λ^3 -iodanation of aromatic compounds with benziodoxole triflate under simple and mild conditions. The reaction tolerates a variety of electronrich arenes and heteroarenes, affording arylbenziodoxole derivatives in moderate to excellent yields. Mechanochemistry has proved to offer further improvement, enabling expedient and solvent-free reaction between solid reactants. The scope of the arylbenziodoxole synthesis based on this metal-free C–H λ^{3} iodanation may be complemented by the Lewis acid-assisted λ^{3} iodanation or the aryl group transfer from the corresponding silicon and boron compounds. The thus-synthesized arylbenziodoxoles serve as versatile synthetic intermediates for C-C and C-heteroatom bond formations as well rices or for electrophilic aromatic substitution. Further studies / BAStheruse of benziodoxole triflate and related compounds as iodane transfer agents and the transformation of organo-BX compounds are currently underway.

Conflicts of interest

There are no conflicts to declare.

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Table of contents entry

A cyclic iodine(III) electrophile allows catalyst- and additive-free site-selective functionalization of arenes and heteroarenes in solution or mechanochemical settings.