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Site-selective aromatic C–H λ³-iodanation with a cyclic iodine(III) electrophile in solution and solid phases†

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An efficient and site-selective aromatic C–H λ³-iodanation reaction is achieved using benziodoxole triflate (BXT) as an 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 arenes 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 λ³-iodanation–deprotonation transition state, where the triflate anion acts as an internal base.

Introduction

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 on arenes, are among the most powerful C–H functionalization methods of this type.[1] The installation of a nucleofugal leaving group on arenes can be equally attractive and complementary to 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 (λ³-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 the 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 λ³-iodanation approach has proved feasible for the synthesis of such compounds from electron-rich (hetero)arenes and bulky aryl-λ³-iodane reagents such as MesI(OH)OTs with an acidic activator, or from (hetero)arenes, bulky aryl iodide, oxidants and acids.[8] However, diaryliodonium salts are potentially unstable for isolation and prolonged storage and are often used without isolation.[8a–c] In this context, aryl-λ³-iodane compounds bearing a cyclic benziodoxol(on)e (BX) moiety could be a valuable alternative or complement to diaryliodonium salts, as their non-ionic nature and rigid structure would endow them with enhanced stability for facile isolation and long-term storage as well as the ability to tolerate a wider range of reaction conditions. The BX group has already played an important role 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 2-functionalized 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 alcohol[13] facilitates C–H λ³-iodanation of (hetero)arenes with high site selectivity (Scheme 1c). This BX transfer reaction tolerates various electron-rich arenes and heteroarenes, allowing facile

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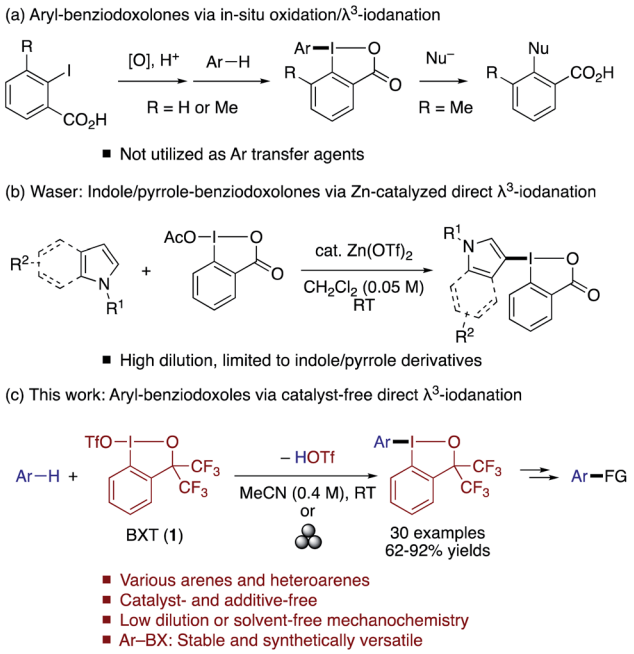
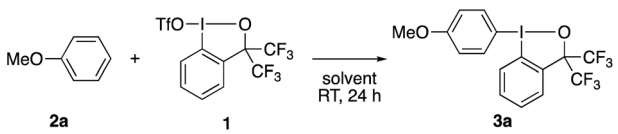


Scheme 1 Synthetic approaches to (hetero)arylbenziodoxol(on)es *via* C–H λ^3-iodanation.

preparation of the corresponding aryl–BX derivatives in moderate to excellent yields under simple and mild conditions without any catalyst or promoter. Moreover, the reaction can also be performed mechanochemically using solid arenes 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.

Table 1 Effect of the reaction conditions[a]



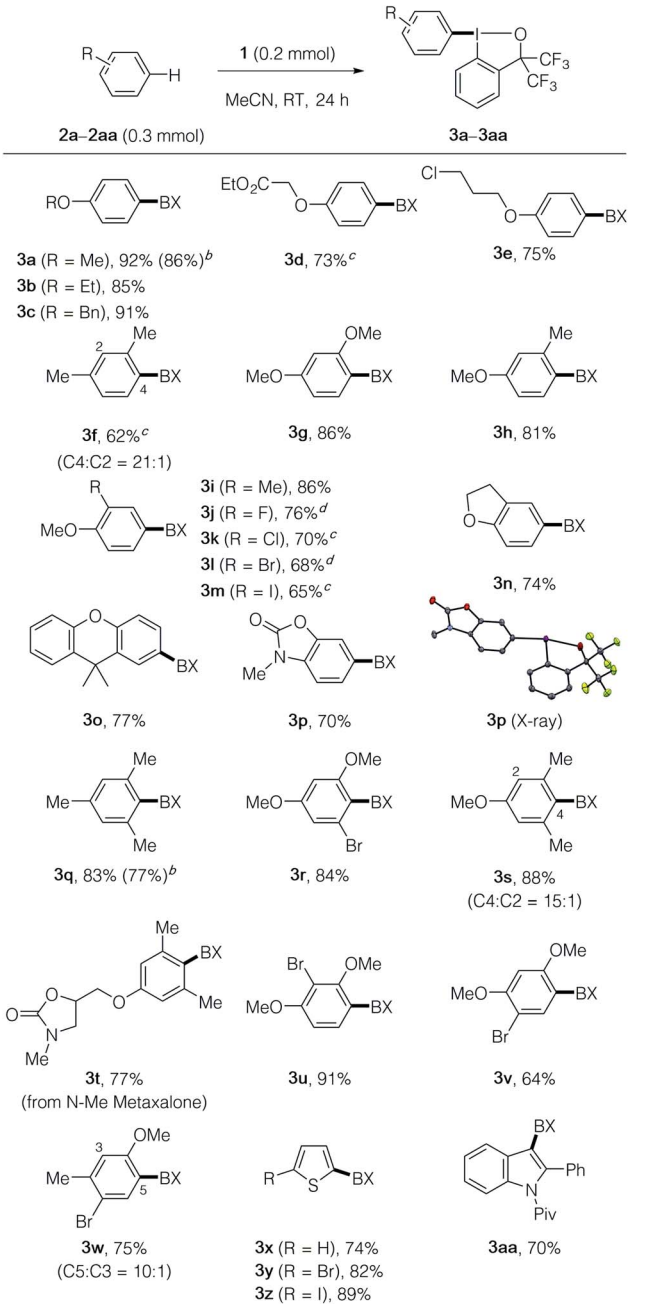
Entry	Solvent	Yield[b] (%)
1	MeCN	94
2	CH_2Cl_2	83
3	Toluene	65
4	Chlorobenzene	69
5	DMF	0
6	Et_2O	0
7	MeOH	0
8[c]	MeCN	84
9[d]	MeCN	86

[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 ^{19}F 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.

Results and discussion

Pursuing our continuing interest in hypervalent iodine chemistry[14] and encouraged by our recent success in using **1** as a λ^3-

Table 2 Aromatic C–H λ^3-iodanation with BXT[a]

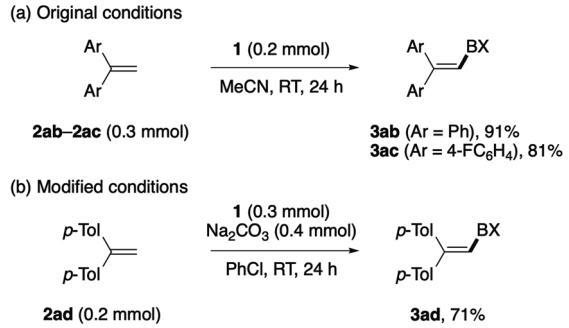


[a] The reaction was performed on a 0.2 mmol scale according to the standard conditions described in Table 1, entry 1. BX in the product formula refers to the benziodoxole moiety. [b] The yield for a 3 mmol-scale reaction is given in the parentheses. [c] The reaction was performed at 60 °C. [d] The reaction was performed at 80 °C.

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 is 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 (Et_2O), and protic (MeOH) solvents (entries 5–7). The yield slightly dropped upon using an 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 acid[13] 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 in air to afford **3a** in an equally high yield (95%).

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 a 1,2,4-substitution pattern. The latter reacted exclusively at the *para*-position of the methoxy group. 1-Alkoxy-2-substituted benzene derivatives, including dihydrobenzofuran and 9,9-dimethylxanthene, 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(3*H*)-one reacted exclusively at the *para*-position of the nitrogen atom, as unambiguously supported by X-ray crystallographic analysis of product **3p**.[16] Electron-rich 1,3,5-trisubstituted arenes such as mesitylene, 1-bromo-3,5-dimethoxybenzene, 3,5-dimethylanisole, and *N*-methyl metaxalone[17] took part in the reaction to afford the products **3q–3t** in good yields, where, for the latter three, the *para*-position 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 iodonium and iodide moieties, which would offer opportunities for selective and sequential functionalizations (*vide infra*).

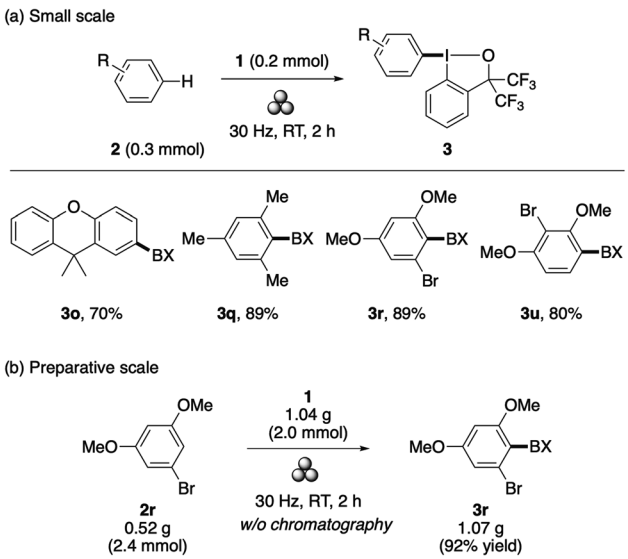
Besides arenes and heteroarenes, 1,1-diphenylethene (**2ab**) and its *para*-fluoro-substituted derivative (**2ac**) reacted with BXT under the standard conditions to afford the corresponding



Scheme 2 C–H λ^3-iodanation of 1,1-diarylethylenes.

alkenyl–BXs **3ab** and **3ac** in good yields (Scheme 2a).[14c–e,18] The reaction of 1,1-di(*p*-tolyl)ethene (**2ac**) did not take place under the standard conditions but resulted in the decomposition of **1**, while the addition of Na_2CO_3 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 due to its attractive merits such as a solvent-free process, reduced reaction times, 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 an arene (0.3 mmol) and **1** (0.2 mmol) to ball milling (30 Hz for 2 h), aryl–BX derivatives **3o**, **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 an

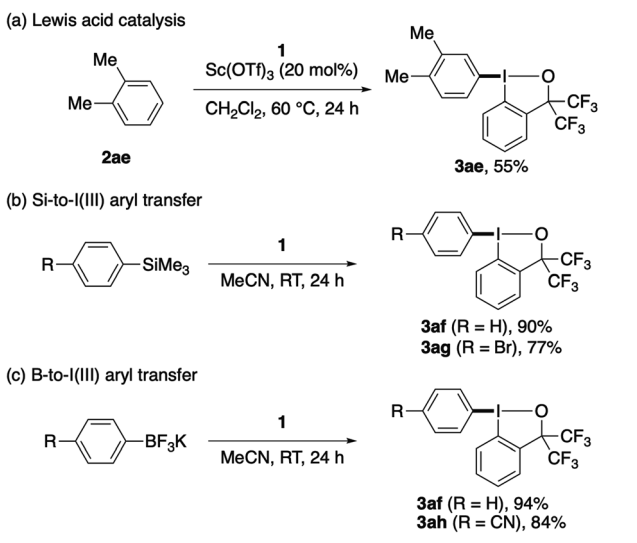


Scheme 3 Mechanochemical λ^3-iodanation of arenes.

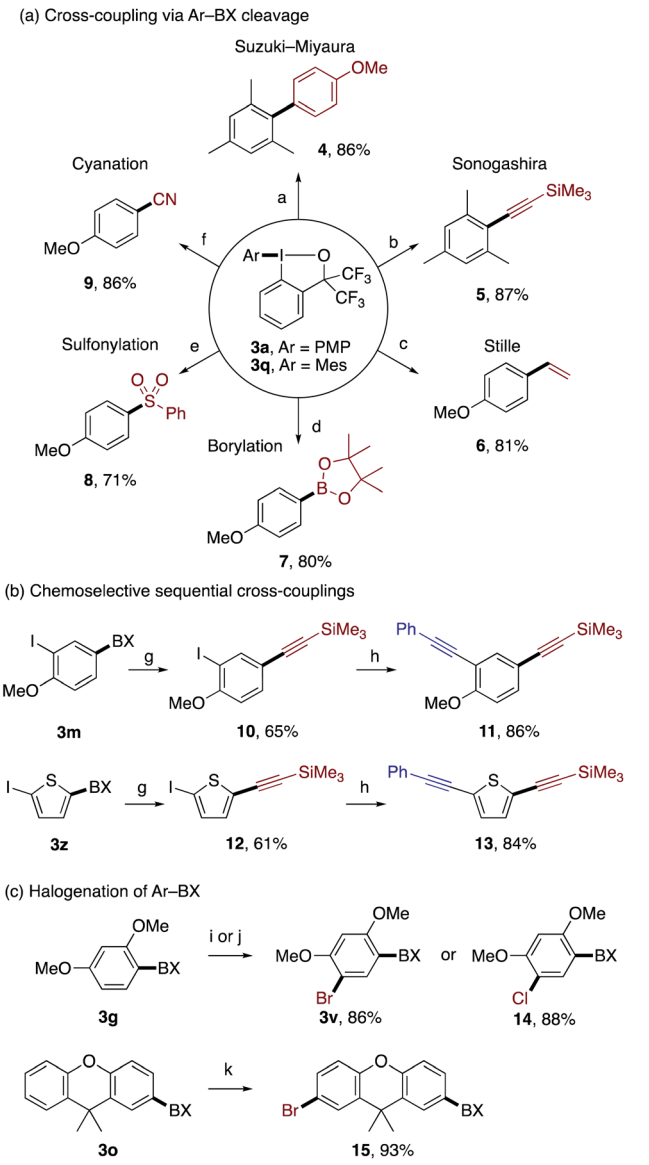
analytically pure product without chromatographic purification (Scheme 3b).

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 a $Sc(OTf)_3$ catalyst (20 mol%) and the use of CH_2Cl_2 as the solvent to afford the corresponding aryl–BX product **3ae** in 55% yield (Scheme 4a). Meanwhile, aryl–BXs bearing an electron-neutral 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 and c). Highly electron-rich arenes, such as 1,2- and 1,4-dimethoxybenzenes and *N*,*N*-dimethylaniline, 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.

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 arene-derived aryl groups (Scheme 5). As illustrated in Scheme 5a, the benziodoxole moiety in **3a** and **3q** served as an excellent leaving group in Pd-catalyzed Suzuki–Miyaura, Sonogashira, and 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 Cu-catalyzed sulfonylation[23] 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 aryl–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



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



Scheme 5 Product transformations. Reaction conditions: (a) $Pd(PPh_3)_4$, 4-$MeOC_6H_4B(OH)_2$, K_2CO_3, DMF/H_2O, 100 °C, 8 h; (b) $PdCl_2(PPh_3)_2$, CuI, trimethylsilylacetylene, Et_3N, DMF, rt, 12 h; (c) $PdCl_2(PPh_3)_2$, $(CH_2{=}CH)SnBu_3$, DMF, 60 °C, 12 h; (d) $Pd(OAc)_2$, PPh_3, CuI, B_2Pin_2, Cs_2CO_3, MeCN, rt, 24 h; (e) CuI, L-proline sodium salt, $PhSO_2Na$, DMSO, 90 °C, 24 h; (f) CuCN, L-proline, DMF, 90 °C, 24 h; (g) $PdCl_2(PPh_3)_2$, CuI, trimethylsilylacetylene, Et_3N, DMF, 0 °C, 12 h; (h) $PdCl_2(PPh_3)_2$, CuI, phenylacetylene, THF/Et_3N, rt, 12 h; (i) NBS, HFIP, 40 °C, 24 h; (j) NCS, HFIP, 80 °C, 24 h; and (k) NBS, HFIP, rt, 4 h.

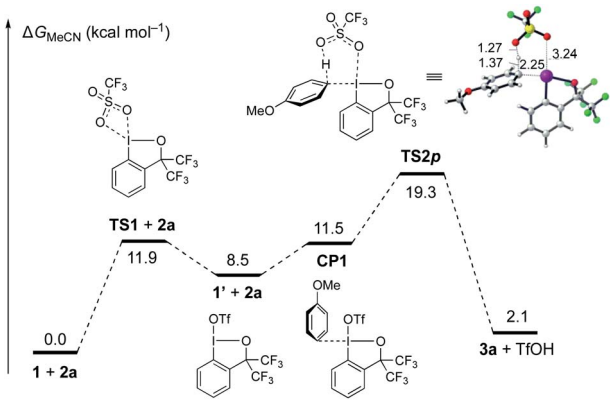


Fig. 1 Gibbs free energy diagram for the *para* C–H λ^3-iodanation of anisole (**2a**) with BXT (**1**). The bond distances are in Å.

and halogens may offer a means for chemoselective difunctionalization of aromatic compounds.

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 (Fig. 1; see the ESI† for the computational details). Prior to the iodanation event, the triflate in **1** 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***, $\Delta G^{\ddagger}$ = 19.3 kcal mol^{-1}) to give the product **3a** and TfOH, which is reminiscent of the concerted metalation–deprotonation 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}; Fig. S4†). The calculated endergonicity (2.1 kcal mol^{-1}) might be a reflection of a 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; Fig. S5†).

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 electron-rich arenes and heteroarenes, affording arylbenziodoxole derivatives in moderate to excellent yields. Mechanochemistry has proved to offer further improvement, enabling an 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 and for electrophilic aromatic substitution. Further studies on the use 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.

Acknowledgements

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