

Carboiodanation of arynes: Organoiodine(III) compounds as nucleophilic organometalloids

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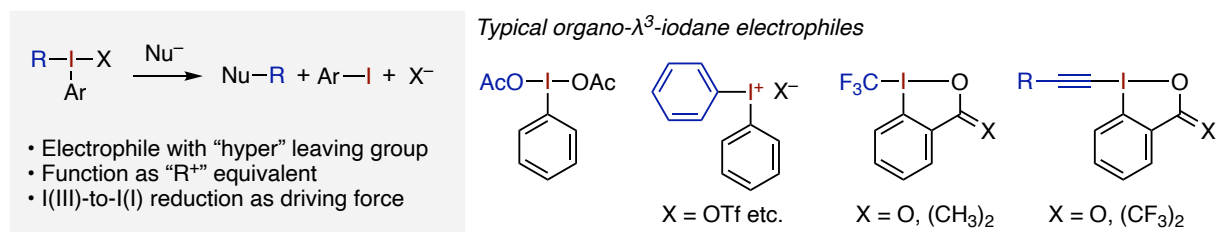
Abstract: Organic iodine(III) compounds represent the most widely used hypervalent halogen compounds in organic synthesis, where they usually perform the role of an oxidant or electrophile to functionalize electron-rich or nucleophilic organic compounds. In contrast to this typical reaction mode and the nature of organohalogen compounds in general, we discovered a novel reactivity of organoiodine(III) compounds that behave as organometallic-like nucleophiles toward arynes. Possessing diverse transferable ligands and being supported by a cyclic spectator ligand, the organoiodine(III) compounds undergo addition across the electrophilic C–C triple bond of arynes while retaining the trivalency of the iodine center. This carboiodanation reaction can forge a variety of aryl–alkynyl, aryl–alkenyl, and aryl–(hetero)aryl bonds along with the concurrent formation of an aryl–iodine(III) bond under mild conditions. The newly formed aryl–iodine(III) bond serves as a versatile linchpin for downstream transformations, particularly as an electrophilic reaction site. The amphoteric nature of the iodine(III) group as a metalloid and a leaving group in this synthetic sequence enables the flexible and expedient synthesis of extended π -conjugated molecules and privileged biarylphosphine ligands, where all the iodine(III)-containing compounds can be handled as air- and thermally stable materials.

Organoiodine(III) compounds (organo- λ^3 -iodanes), which contain three iodine-bound ligands arranged in a T-shaped geometry, have found a broad range of applications in synthetic chemistry as oxidants and electrophiles (1). Their most typical reaction pattern involves displacement by a nucleophile (Nu^-), in which the three ligands on iodine(III) play distinct roles as a transferable group (R), an electronegative leaving group (X), and a static aryl substituent (Ar) (Fig. 1A). Here, the formation of a Nu-R bond is accompanied by expulsion of iodoarene and X anion, with the thermodynamically favorable trivalency-to-monovalency conversion of iodine being the primary driving force. Within this general reactivity manifold, synthetically useful organo- λ^3 -iodanes such as iodobenzene diacetate, diaryliodonium salts (2, 3), trifluoromethylbenziodoxoles known as Togni reagents (4), and ethynylbenziodoxoles (EBXs) (5-7) have been extensively used to develop techniques to functionalize nucleophilic organic molecules. Besides the thermodynamic aspect, the high kinetic reactivity of organo- λ^3 -iodanes is understood as a consequence of three-center four-electron (3c-4e) bonding of the apical R-I-X array (Fig. 1B). With four electrons accommodated in bonding and nonbonding orbitals, the 3c-4e bonding gives rise to the weakness of the apical bonds, localization of positive charge on iodine(III), and distribution of negative charges over the apical ligands R and X. This analysis accounts for the prominent electrophilicity of organo- λ^3 -iodanes at the iodine(III) center, which usually accepts the initial attack of the nucleophile as a part of the overall displacement reaction.

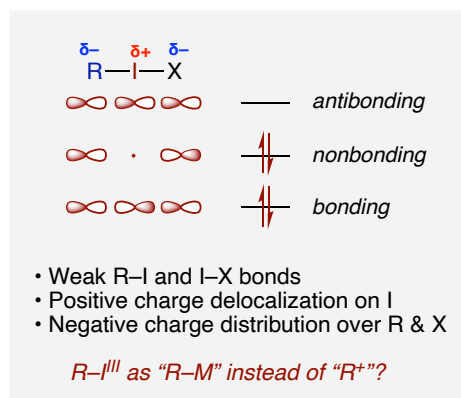
In the reaction mode discussed above, organo- λ^3 -iodanes formally function as “ R^+ ” equivalents toward the nucleophile. This well-established reaction mode notwithstanding, the uniquely polarized apical bond (i.e., $\text{R}(\delta^-)\text{-I}(\delta^+)\text{-X}(\delta^-)$), unlike the polarization of ordinary carbon-halogen bonds (i.e., $\text{R}(\delta^+)\text{-X}(\delta^-)$), poses a question as to whether organo- λ^3 -iodanes would behave as nucleophilic rather than electrophilic donors of the R ligand. In this respect, thermally unstable triaryliodanes have been demonstrated to serve as aryl anion equivalents toward Lewis and Brønsted acids (Fig. 1C). For example, the reaction between triphenyliodane and triphenylborane results in a transfer of one of the phenyl ligands from iodine to boron to give diphenyliodonium tetraphenylborate (8). A cyclic triaryliodane undergoes protonation of the phenyl ligand with various Brønsted acids, producing benzene along with diaryliodonium salt (9). These precedents, however, have little connection to practical organic synthesis. Addressing the above question in a synthetically relevant context, we report here that organo- λ^3 -iodanes can undergo addition across the highly electrophilic $\text{C}\equiv\text{C}$ triple bond of arynes (10-14) and related species to give new,

functionalized organo- λ^3 -iodanes (Fig. 1D). Reminiscent of the well-established carbometalation to arynes (15), this carbo- λ^3 -iodanation reaction has proved feasible using a broad range of organo-benziodoxole compounds bearing diverse electron-rich unsaturated ligands, including alkynyl, alkenyl, and (hetero)aryl groups. Unlike carbometalation, the iodine(III) group in these reaction products can now be leveraged as a versatile leaving group for cross-coupling reactions, thus offering a unique means to access functionalized aromatics.

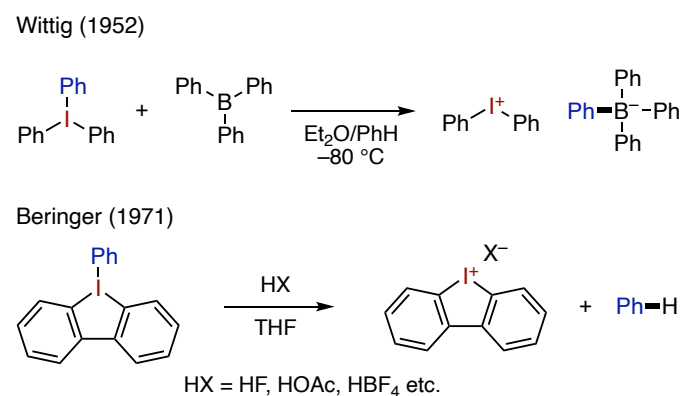
A Prototypical reactivity pattern of organo- λ^3 -iodanes as electrophiles



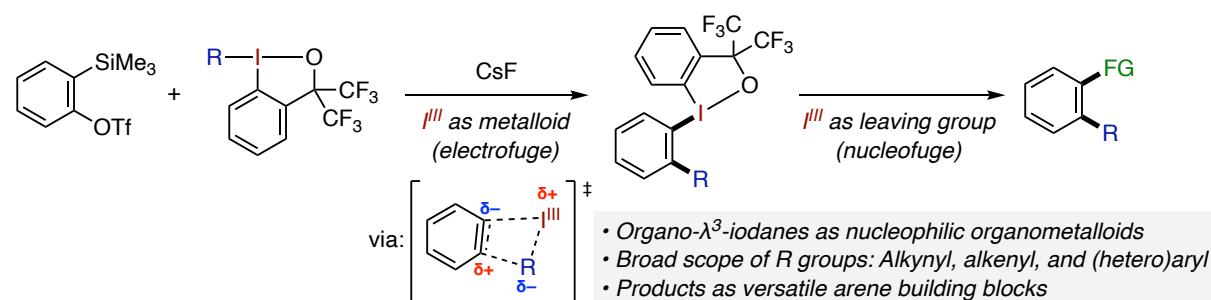
B Three-center four-electron (3c-4e) bond



C Triaryliodanes as aryl anion equivalents



D This work: Carbo- λ^3 -iodanation to arynes



E Potential nucleophilicity of EBX

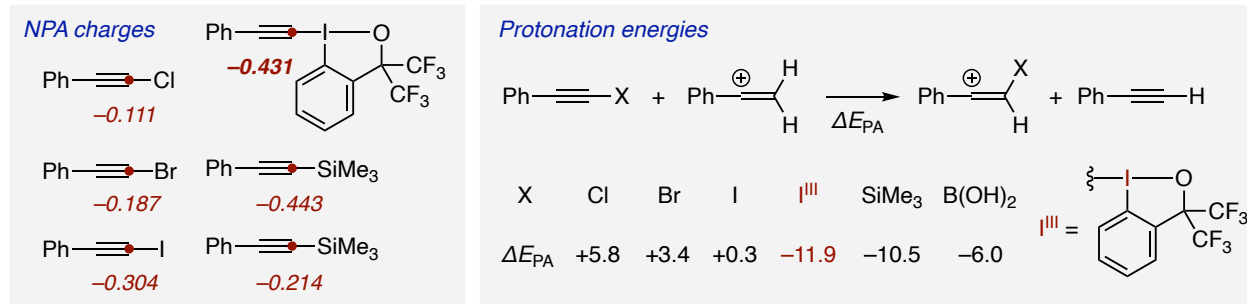


Fig. 1. Reaction modes of organoiodine(III) compounds. (A) Prototypical reaction mode of organo- λ^3 -iodanes as electrophilic group-transfer agents. (B) The molecular orbital diagram of the apical bond of organo- λ^3 -iodane explains its high reactivity as electrophile while implying its potential role as a nucleophilic organometalloid. (C) Literature precedents that demonstrate nucleophilicity of organo- λ^3 -iodanes. (D) This work: Organobenziodoxoles

behave as organometallic-like nucleophiles toward arynes to undergo addition across the C≡C triple bond. (E) Evaluation of the potential nucleophilicity of Ph-EBX by its NPA charge and protonation energy. The DFT calculation was performed at the M06-2X/def2TZVP-SDD(for I) level.

In search for a reaction that not only manifests the potential nucleophilicity of organo- λ^3 -iodanes but also enables a synthetically practicable and valuable transformation, the choice and design of both the transferable (R) and non-transferable (Ar and X) ligands on iodine(III) were considered crucial (16). For example, while deemed nucleophilic enough, triorganoiodanes having all three carbon ligands (cf. Fig. 1C) would be too unstable to be prepared, handled, and manipulated in a practical manner (8). On the other hand, diorganoiodonium salts, a typical class of organo- λ^3 -iodanes with weakly coordinating anions X (e.g., triflate, tetrafluoroborate), would lack nucleophilicity of the ligand R because the negative charge would be taken away by the counterion (3). In this context, organo- λ^3 -iodanes featuring a cyclic benziiodoxole (BX) skeleton appeared promising because its structural rigidity is known to render these compounds much more stable than analogous acyclic compounds (17) and thus allows for the accommodation of a variety of organic ligands, including alkynyl, vinyl, and (hetero)aryl groups, on the apical position (5-7, 18-20). The ability of the BX group to impart nucleophilicity to its apical carbon ligand was inferred by density functional theory (DFT) calculations on the nature of phenylethynylbenziiodoxole (Ph-EBX; Fig. 1E). The acetylenic carbon of Ph-EBX bears a much greater negative charge than that of parent phenylacetylene and analogous haloalkynes, which rivals the negative charge on phenyltrimethylsilylacetylene, a metalloid-substituted alkyne. Furthermore, the addition of a proton, the smallest electrophile, to Ph-EBX proves to be energetically much more favorable than the protonation of the parent phenylacetylene or haloalkynes, as demonstrated by a series of isodesmic reactions between substituted phenylacetylene and 1-phenylethen-1-ylum cation. The degree of stabilization is similar or even larger compared to the protonation of metalloid (SiMe₃ or B(OH)₂)-substituted alkynes. As for the electrophilic reaction partner, the C≡C triple bond of aryne was considered attractive because its addition reaction with organo- λ^3 -iodane would give rise to a new carbon–iodine(III) bond, which would then serve as an electrophilic reaction site for further synthetic elaborations.

The carboiodanation reaction of aryne was first discovered using Ph-EBX bearing a

bis(trifluoromethyl)benzyl alcohol moiety (**2a**; Fig. 2). When treated with *ortho*-trimethylsilyl phenyl triflate (**1a**, two equivalents), a well-established benzyne precursor, in the presence of CsF (4 equivalents) in acetonitrile at room temperature, this compound produced the *ortho*-alkynyl phenyl-BX **3a** in 83% yield. The reaction could be performed on a preparatively useful scale of 2 mmol, only with a slight decrease in the yield of **3a** (78%). Importantly, the reaction was specific to this particular type of alkynyl- λ^3 -iodane. The benzoic acid-based Ph-EBX **2a'**, another commonly used alkynyl- λ^3 -iodane, afforded an intractable reaction mixture, and so was the case with the alkynyliodonium tosylate **2a''**. A variety of aryl- and alkyl-substituted EBXs underwent addition to parent benzyne to produce the corresponding *ortho*-alkynyl phenyl-BXs **3b–3h** in moderate to good yields, displaying tolerance to both steric and electronic variations. The reactions of **2a** and **2b** with 3-methoxybenzyne, which prefers to accept the addition of a nucleophile at the C1 position (the carbon distal to the methoxy group) due to an inductive effect (21), regioselectively afforded the C1-alkynylated products **3i** and **3j**, respectively, each as a single regioisomer. This observation points to the nature of EBX as an alkynyl nucleophile. 1,2-Naphthalene was preferentially alkynylated at the C2 position to give the product **3k**, along with its C1-alkynylated isomer, in a ratio of 4:1 (22). Symmetrically substituted arynes reacted smoothly with **2a** to afford the corresponding products **3l–3n**. Furthermore, cyclohexyne,(23) a highly strained cyclic alkyne, also reacted with Ph-EBX to give the enyne derivative **3o** in good yield.

Searching for another class of organo- λ^3 -iodanes suitable for carboiodanation, we became interested in β -alkoxy vinylbenziodoxole (VBX) (19), which can be readily synthesized by *trans*-iodo(III)etherification of alkyne with benziodoxole triflate and alcohol (24) and has an electron-rich vinylic carbon due to the alkoxy group. To our delight, β -methoxy VBX derived from 1-phenyl-1-propyne underwent smooth addition to parent benzyne to produce the *ortho*-alkenyl phenyl-BX **3p** in good yield. Other β -methoxy VBXs derived from the corresponding internal or terminal alkynes also took part in the reaction to afford the corresponding products **3q–3v** in moderate to good yields. As demonstrated by the X-ray crystallographic structure of **3s**, the stereochemistry of the olefinic C=C bond was retained. Furthermore, β,β -diphenyl-substituted VBX, readily accessible by vinylic C–H iodination of 1,1-diphenylethylene (25), was found to undergo carboiodanation to benzyne to give the desired product **3w** in 75% yield. While much less reactive, *trans*- β -styryl VBX also exhibited reactivity toward benzyne to afford the iodane-

containing *trans*-stilbene **3x**. The reaction of β,β -diphenyl VBX with substituted arynes afforded the desired products **3y** and **3z**, albeit in moderate yields.

We finally explored the reactivity of electron-rich (hetero)aryl-BXs, which can be easily synthesized by C–H λ^3 -iodanation of the corresponding arenes (**25**), toward arynes. 2,4,6-Trimethoxyphenyl-BX underwent aryliodanation to parent benzyne to afford the *ortho*-aryl phenyl-BX **3aa** in 74% yield. This reaction was also scalable (2 mmol) albeit with a diminished yield (58%). Analogous 2,4,6-trimethoxyaryl-BXs with an additional bromo- or chloro-substituent also gave the corresponding adducts **3ab** and **3ac**. Successive replacement of the three methoxy groups of 2,4,6-trimethoxyphenyl-BX with less electron-donating methyl groups led to diminished reactivity (see **3ad–3af**), with mesityl-BX providing the product **3af** only in 19% yield. Despite increased steric hindrance, 2,4,6-triisopropylphenyl-BX also afforded the corresponding product **3ag**. Note that 2,4-dimethoxyphenyl-BX also afforded the corresponding benzyne adduct in 12% yield (not shown), whereas 4-methoxyphenyl-BX **2aj** was too unreactive to participate in the aryliodanation. Besides aryl-BXs, electron-rich 3-indolyl-BXs were viable reactants toward benzyne, producing the *ortho*-3-indolylphenyl-BXs **3ah** and **3ai** in good yields. The (hetero)aryl-BXs were also amenable to the reaction with substituted arynes (see **3aj–3am**), where the regioselective reaction outcomes with 3-methoxybenzyne and 1,2-naphthalene underlined the nature of these BX compounds as nucleophilic (hetero)aryl donors. X-ray crystallographic analysis also confirmed the structure of the product **3aj**. Note that benzoic acid-based indolyl- λ^3 -iodane **2ah'** (**26**) underwent addition to benzyne, albeit with a significantly diminished yield (21% by ^1H NMR analysis) of the desired product. Meanwhile, phenyl(2,4,6-trimethoxyphenyl)iodonium tosylate **2aa''** (**27**) failed to produce the adduct with benzyne, again highlighting the importance of the spectator ligand for the desired organometalloid-like reactivity.

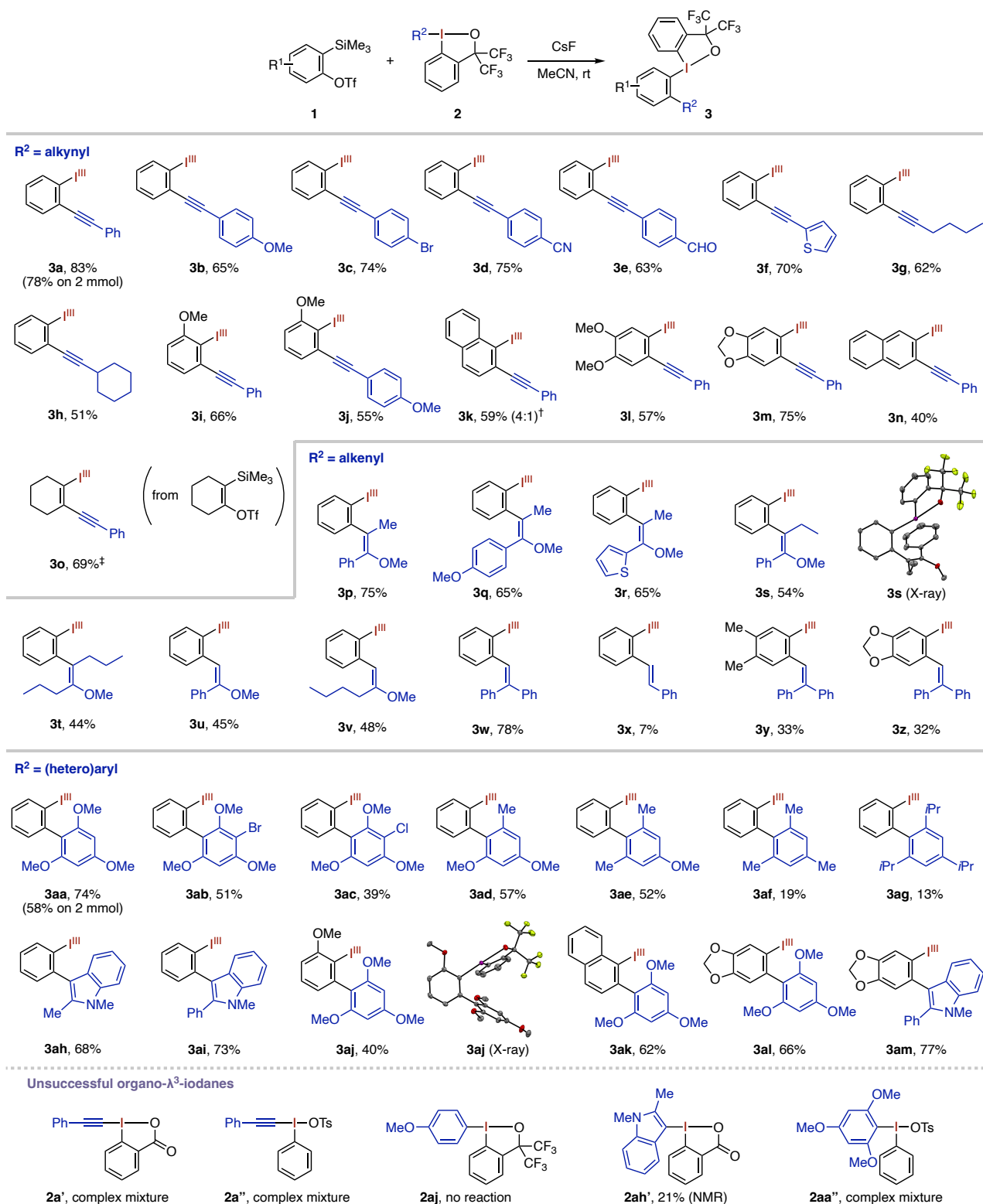


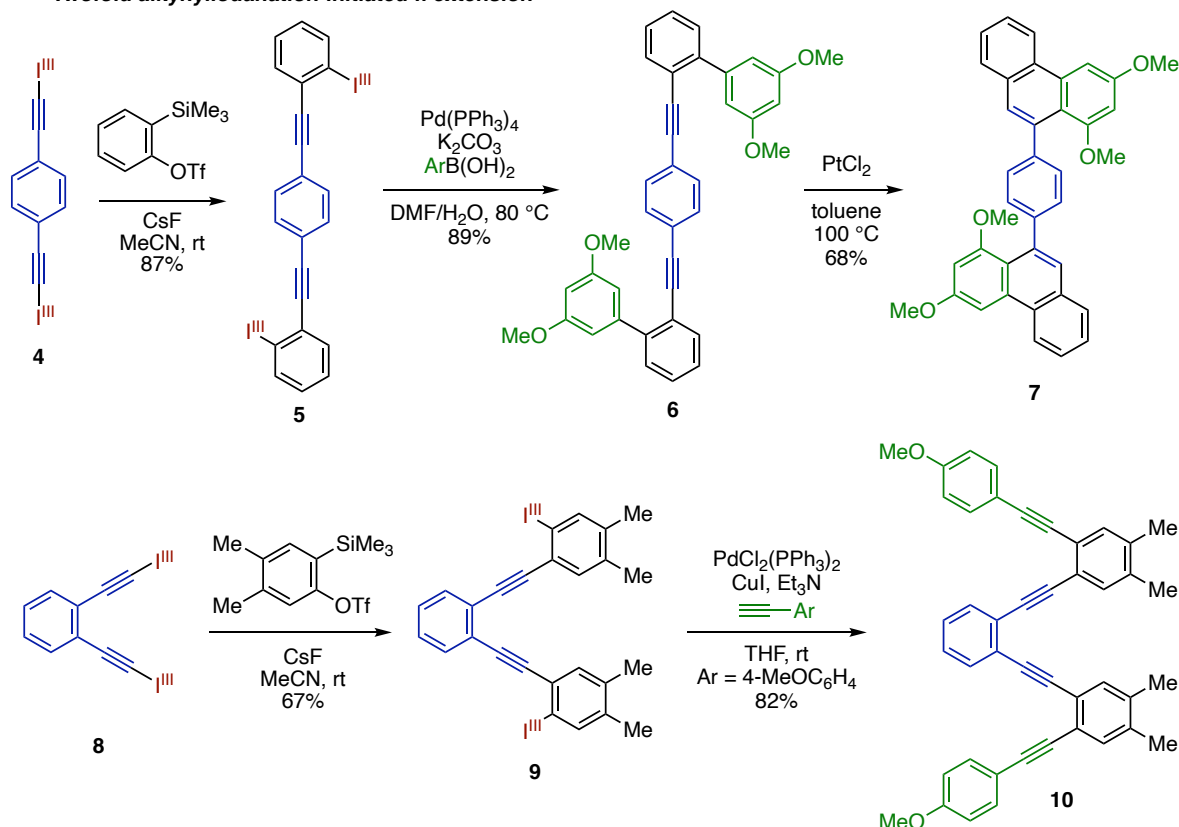
Fig. 2. Scope of carboiodanation of arynes with organobenziodoxoles. Typical reaction conditions: organobenziodoxole (0.1 mmol, 1 equiv), *ortho*-trimethylsilylaryl triflate (2 equiv), and CsF (4 equiv) in MeCN, rt, 12-18 h. The symbol I^{III} refers to the benziodoxole group. [†]The regioisomer ratio is shown in the parentheses. [‡]1 equiv of cyclohexyne precursor, 2 equiv of Ph-EBX, and 2 equiv of CsF.

The present carboiodanation technique enables the installation of various alkynyl, alkenyl, and (hetero)aryl groups, as well as an iodine(III) group that can serve as a versatile leaving group in palladium- and copper-mediated cross-coupling reactions, into the vicinal positions of a phenylene moiety. This characteristic of carboiodanation can be exploited in the synthesis of extended π -conjugated molecules and valuable ligands for catalysis, as illustrated in Fig. 3. *para*-Phenylene-linked bis-EBX **4** underwent twofold alkynyliodanation to benzyne to give the desired product **5** in an excellent yield of 87%. Subsequent twofold Suzuki–Miyaura coupling and PtCl₂-catalyzed cycloisomerization (28) furnished the *para*-phenylene-bridged bis(phenanthrene) derivative **7** in good yield (Fig. 3A). Twofold alkynyliodanation was also feasible between the *ortho*-phenylene-linked bis-EBX **8** and 4,5-dimethylbenzyne, resulting in the desired diyne **9** in 67% yield. Twofold Sonogashira coupling on **9** produced the *ortho*-phenylene-bridged tetrayne **10**, which would serve as a precursor for the synthesis of an *ortho*-(arylene ethynylene) oligomer (29). Bearing the vinyl ether moiety, the alkenyliodanation product **3n** could be used as a precursor for facile preparation of unsymmetrical phenanthrene **13** through Suzuki–Miyaura coupling and FeCl₃-mediated cyclization (30) (Fig. 3B).

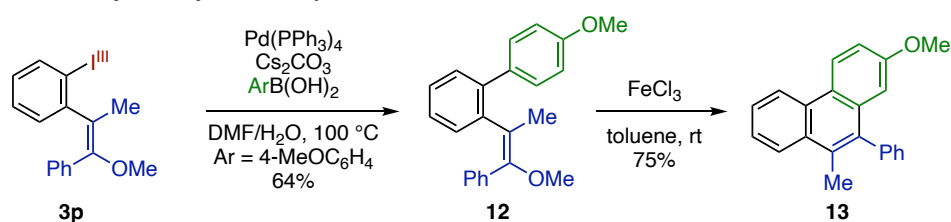
The present aryliodanation is limited to highly electron-rich aryl-BXs bearing alkoxy or alkyl substituents on the 2, 4, and 6-positions or 3-indolyl-BXs. Despite this limitation, we can proactively utilize the aryliodanation products for the synthesis of bulky and electron-rich biarylphosphines, which represent privileged ligands for transition metal catalysis, palladium-catalyzed cross-coupling in particular (Fig. 3C) (31). Starting from the indolyliodanation product **3ai**, CuI-mediated I(III)-to-I(I) conversion was followed by palladium-catalyzed P–C coupling between the resulting iodide **14** and dicyclohexylphosphine to afford the heterobiarylphosphine **15** featuring a brand-new backbone, in the form of the borane complex, in 85% overall yield. The biarylphosphine **16** could also be readily prepared in an analogous manner but using iodine-lithium exchange and trapping with chlorodicyclohexylphosphine. It is worth noting the parallelism between the present procedures and the established synthetic methods for biarylphosphines, which capitalize on the addition of aryl Grignard or lithium reagents to in situ-generated arynes (typically from *ortho*-bromochlorobenzene)(32, 33). Despite the robustness of the latter methods, we anticipate that the current approach would uniquely help expand the accessible chemical space of

(hetero)biarylphosphines, given that it could engage (hetero)aryl-BXs for which the corresponding Grignard and lithium reagents are not readily accessible (as in the case of **15**) and that the biaryl-BX intermediates can be handled and stored as air- and moisture-stable compounds.

A Twofold alkynyliodanation-initiated *n*-extension



B Assembly of unsymmetrical phenanthrene



C Aryliodanation products to bulky biarylphosphines

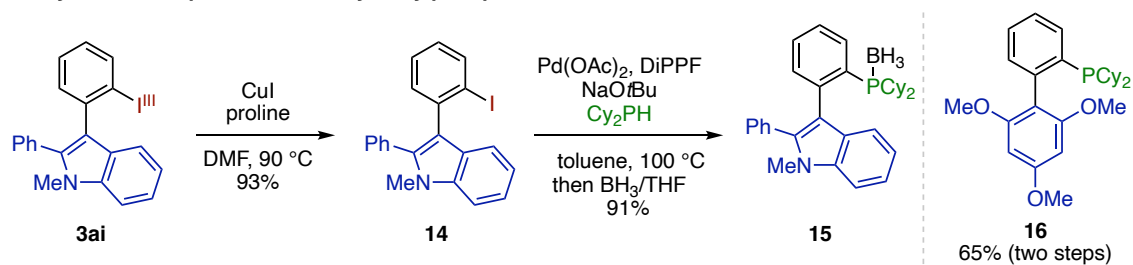


Fig. 3. Synthetic applications. (A) Twofold alkynyliodanation of aryne with *para*- or *ortho*-phenylene-linked bis-

EBX and subsequent extension of the π -conjugated system. **(B)** π -Extension of alkenyliodination products through cross-coupling and cyclization. **(C)** Conversion of aryliodination products into Buchwald-type bulky biarylphosphines. Experimental details are provided in the supplementary materials.

DFT calculations were performed to gain insight into the mechanism of the present carboiodination. A model reaction between parent benzyne and Ph-EBX was found to proceed via a four-centered transition state **TS1a** ($\Delta G^\ddagger = 13.1 \text{ kcal mol}^{-1}$), which led to the primary insertion product **INT1a** with large exergonicity of $-68.8 \text{ kcal mol}^{-1}$ (Fig. 4A). Reflecting the orientation of the ligands on iodine(III) and benzyne in **TS1a**, **INT1a** has a distorted trigonal pyramidal geometry around the iodine(III) center. This unfavorable intermediate readily undergoes a pseudorotation process (**TS2a**; $\Delta G^\ddagger = 2.1 \text{ kcal mol}^{-1}$) to give the final product (**PD1a**) with the favorable T-shaped geometry where the new aryl ligand and the alkoxy group occupy the apical positions. The reaction between benzyne and 2,4,6-trimethoxyphenyl-BX was also found to be initiated by a four-centered TS (**TS1b**; Fig. 4B). Unlike the case of Ph-EBX, however, **TS1b** led to only partial cleavage of the original aryl–iodine(III) bond while forming, to a significant degree, the new aryl–aryl and aryl–iodine(III) bonds. The resulting transient intermediate **INT1b** ($\Delta G = -4.1 \text{ kcal mol}^{-1}$) features a tetrahedral geometry around the incoming carbon and a distorted square-planar geometry around the iodine atom and can be regarded as an arenium/iodate(III) species. The arenium nature of the 2,4,6-trimethoxyphenyl moiety of **INT1b** is corroborated by the elongation of the C(*ipso*)–C(*ortho*) bonds and the contraction of the C–OMe bonds compared to the starting aryl–BX. **INT1b** collapses with very low activation energy (**TS2b**; $\Delta G^\ddagger = 0.2 \text{ kcal mol}^{-1}$), directly leading to the insertion product **PD1b**. β -Methoxy VBX was found to undergo an analogous two-step reaction pathway involving an oxocarbenium/iodate(III) intermediate (see Fig. S4). Both the four-centered TSs (**TS1a** and **TS1b**) commonly feature a distortion of benzyne from its original C_{2v} symmetry, where the benzyne carbon accepting the organic group has much a larger bond angle (133° – 135°) than that of the other (116° – 119°). This distortion is a signature of polarization of the aryne $C\equiv C$ bond (*2I*), where the more linear carbon is more positively charged and suited for nucleophilic addition. Indeed, the distribution of the natural population analysis (NPA) charges over the benzyne carbons corroborates this conjecture. Furthermore, consistent with the experiments, the reaction of intrinsically distorted 3-methoxybenzyne with Ph-EBX was

calculated to proceed much more favorably through the addition of the alkynyl group to the C1 position by 5.1 kcal mol⁻¹ (see Fig. S5).

To systematically evaluate the relative reactivity of organobenziodoxoles toward arynes, namely, arynophilicity (34), a series of competition reactions were performed using large excess mixture of two arynophiles (5 equivalents each) against benzyne as the limiting reactant (Fig. 4C). The CsF-mediated reaction of **1a** with a mixture of EBX **2b** and furan afforded the alkynyliodanation product **3b** and the cycloadduct of furan, 1,4-dihydro-1,4-epoxynaphthalene (**17**), in 7% and 74% yields, respectively (eq 1). EBX **2b** was also overwhelmed in a competition reaction with benzyl azide (eq 2). Given the modest reactivity of **2b** compared to these common arynophiles, in the following competition experiments, relative reactivities of organobenziodoxoles were assessed using 2,4,6-trimethoxyphenyl-BX **2aa** as a reference reactant (eq 3). Presented in a log scale, the thus-determined product ratios (which should be proportional to the ratio of the rate constants (k/k_{2aa})) revealed that the relative reactivity of organo-BXs used in the present study spans over two orders of magnitude. Aryl-substituted EBXs (**2a**, **2b**, and **2d**) are more reactive than **2aa** by up to ten times, while the reactivity of alkyl-substituted EBX **2g** is on par with **2aa**. β -Methoxy VBX **2p** and 2,2-diphenyl VBX **2w** are somewhat less reactive than **2aa**. The indolyl-BX **2ai** proves to be a superior arynophile to **2aa** yet inferior to aryl-substituted EBXs. Expectedly, the replacement of the methoxy group(s) of **2aa** with a methyl group(s) leads to a significant decrease in the arynophilicity, with mesityl-BX **2af** being less reactive than **2aa** by more than ten times.

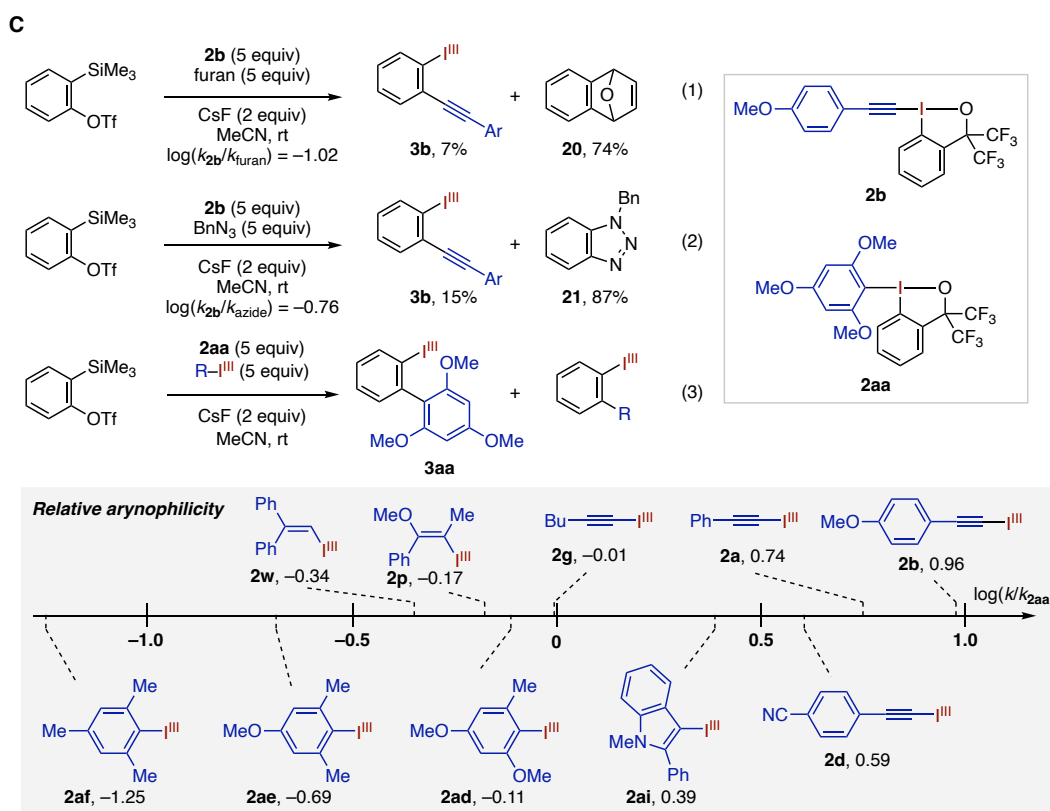
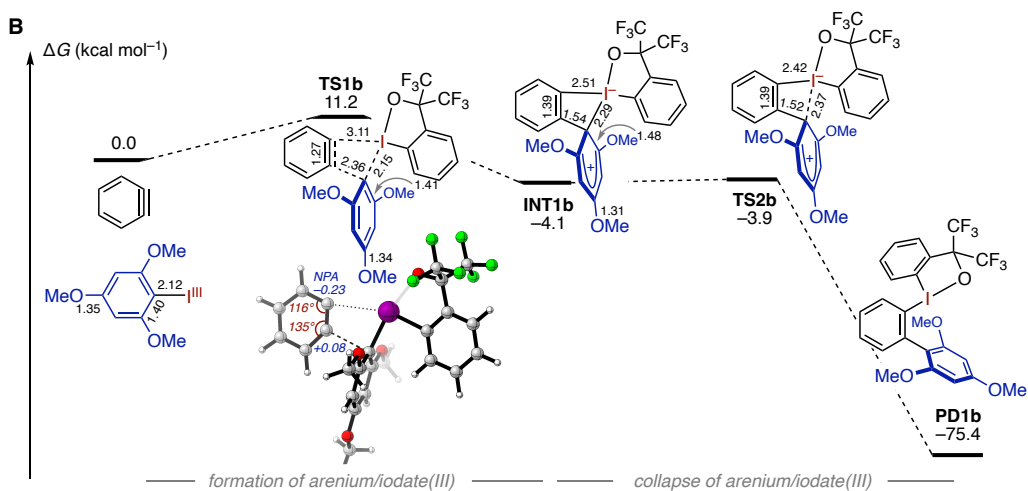
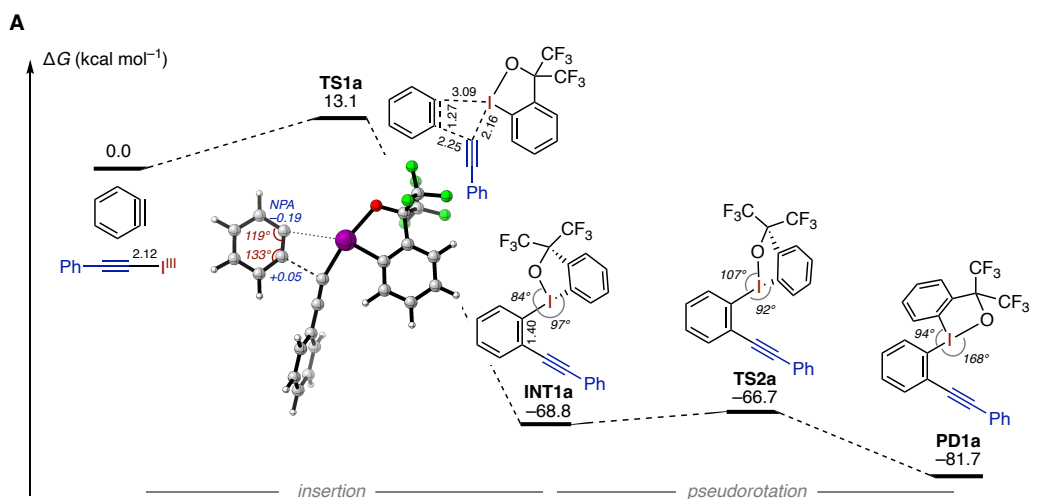


Fig. 4. Insights into the reaction mechanism and the relative reactivity of organo-BXs. (A) Free energy profile for benzyne insertion into Ph-EBX (level: M06-2X/6-311++G(2df,2p)-SDD(for I)/SMD(MeCN)//M06-2X/6-31G(d)-SDD(for I)/SMD(MeCN)). Bond lengths are indicated in Å. (B) Free energy profile for benzyne insertion into 2,4,6-trimethoxyphenyl-BX. (C) Competition experiments to determine the relative aryneophilicity of representative organobenzeniodoxoles.

The aryneophilic properties of electron-rich organobenzeniodoxoles, demonstrated in our study, enable the simultaneous creation of an aryl–alkynyl, an aryl–alkenyl, or an aryl–(hetero)aryl bond with an aryl–iodine bond on the vicinal positions of an aromatic scaffold without a need for air-sensitive catalysts and organometallic reagents. While formally mimicking carbometalation, the present transformation effectively achieves its conceptual counterpart, the carbohalogenation of arynes, owing to the capability of the thus-introduced iodine(III) group as a nucleofugal leaving group. Thus, with the breadth of the installable organic groups and the versatility of the iodine(III) group combined, the carboiodanation reaction offers a uniquely attractive method for synthesizing structurally diverse and densely functionalized aromatic molecules. We anticipate that the organometaloid-like reactivity of organobenzeniodoxoles would also kick in when exposed to highly electrophilic unsaturated species other than aryne and cycloalkyne (e.g., cyclic allene and 1,2,3-cyclohexatriene)(14, 35, 36) and that the scope of this reaction mode could further be expanded by judicious choice and tuning of the transferable ligands and the supporting ligands on iodine(III).

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