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Cyclic Diaryl λ^3 -Chloranes: Reagents and Their C–C and C–O Couplings with Phenols *via* Aryne Intermediates

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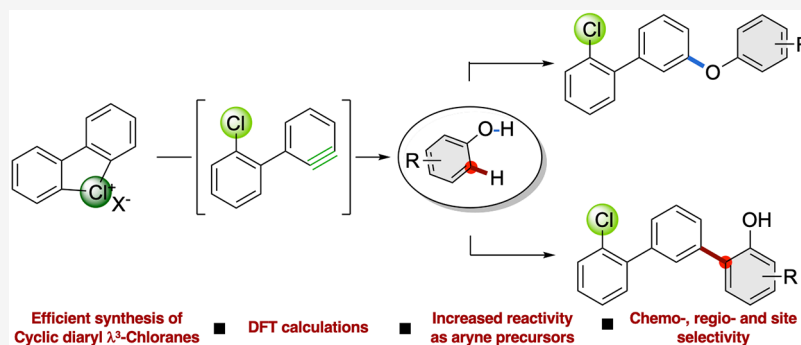
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ABSTRACT: Hypervalent chloranes are a class of rare and poorly explored reagents. Their unique electronic properties confer reactivity that is complementary to that of the common iodanes and emerging bromanes. Highly chemo- and regioselective, metal-free, and mild C–C and C–O couplings are reported here. Experimental and computational mechanistic studies elucidate the unprecedented reactivities and selectivities of these systems and the intermediacy of aryne intermediates. The synthetic potential of these transformations is further demonstrated *via* the post-functionalization of C–C and C–O coupling products obtained from reactions of chloranes with phenols under different conditions.

INTRODUCTION

Hypervalent compounds are nowadays fundamental tools in organic chemistry,^{1,2} both in academia and industry, serving as oxidants, electrophiles, and radical initiators.^{3–7} Widely investigated, the λ^3 -iodanes represent the most common hypervalent reagents. On the contrary, their isoelectronic bromine^{8–11} and chlorine^{12–14} congeners have remained unexplored for decades as a consequence of a lack of a general and efficient synthesis.¹⁵ We recently reported a safe and practical method for the preparation of cyclic diaryl λ^3 -bromanes.¹⁶ The enhanced nucleofugality and the strong electron-withdrawing property of λ^3 -bromanes arising from the higher ionization potential of Br confer to these compounds a unique reactivity (Figure 1a). Therefore, cyclic diaryl bromanes serve as original aryne precursors (Figure 1b)^{16,17} and halogen-bond organo-catalysts.^{18,19} In clear contrast, cyclic diaryl iodines undergo transition metal-catalyzed *ortho*-functionalizations,²⁰ clearly illustrating the differences between the cyclic diaryl λ^3 -bromanes and the corresponding iodanes.

Considering the higher ionization potential and electro-negativity of Cl, translating into a decreased positive charge in hypervalent λ^3 -chloranes, an amplified reactivity of diaryl λ^3 -chloranes as aryne precursors could be anticipated.^{12,21} Such a superior reactivity of Cl(III)-compounds, in comparison with Br(III)-species, is expected to translate into unprecedented

reactivity under metal-free conditions. The challenging synthesis of such compounds remains, however, a major impediment in uncovering this reactivity. A general synthetic route furnishing such compounds followed by a demonstration of their chemical behavior would thus open new vistas in the chemistry of emerging hypervalent compounds.

Due to the prevalence of the phenol motif in medicinal chemistry, agrochemistry, and natural products,^{22–24} the development of site-selective and transition metal-free methodologies for their late-stage functionalization is highly desirable.²⁵ In particular, cross-dehydrogenative coupling (CDC)-type reactions, rapidly expanding molecular complexity on the phenol scaffolds, have attracted considerable attention over the last years (Figure 1c).^{26,27} Various approaches toward O-arylation *via* cross-couplings of phenols²⁸ have been disclosed, including C–O coupling between phenols and arynes,^{29–31} and direct arylation with diaryl iodonium salts.⁵ In clear contrast, *ortho*-C-functionalization of phenols *via* cross-

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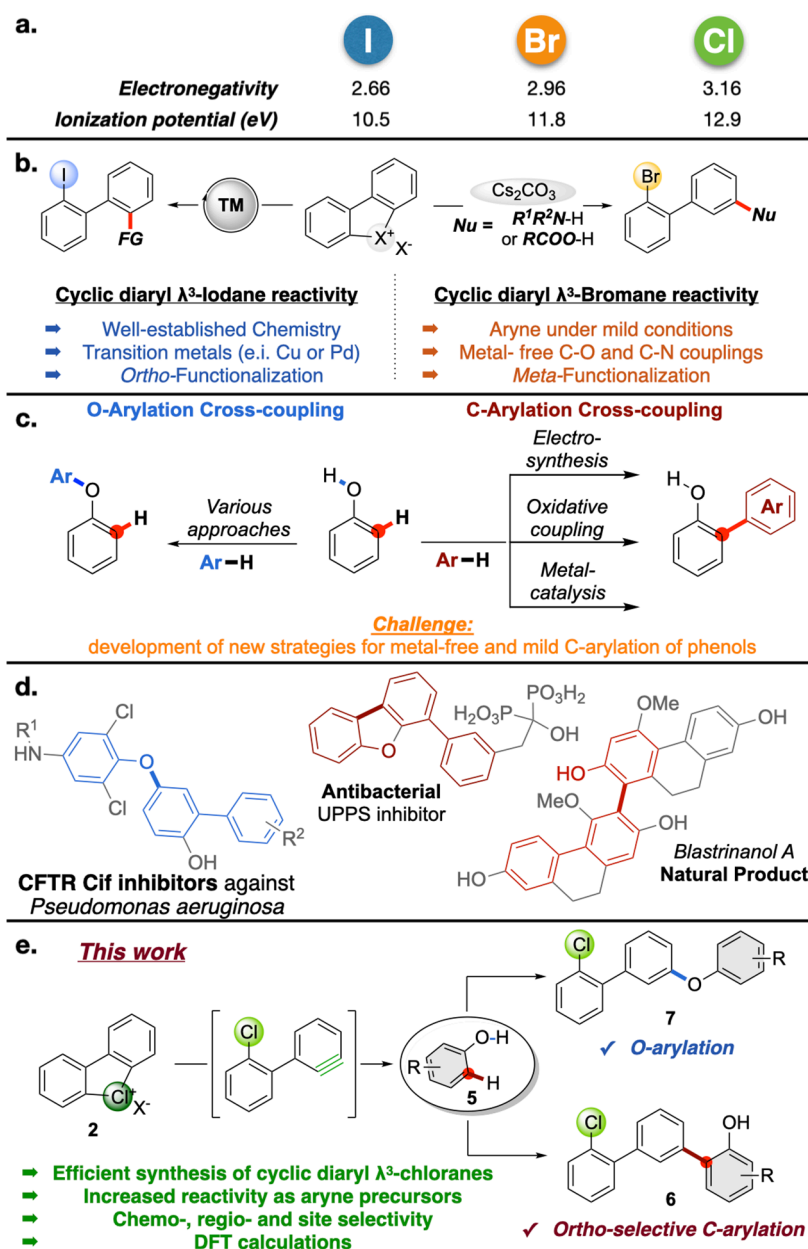


Figure 1. (a) Electronic properties of iodine, bromine, and chlorine; (b) reactivity of cyclic diaryl λ^3 -iodonium and bromonium salts; (c) common C–O and C–C couplings of phenols; (d) selected examples of biologically active terphenyls; (e) this work.

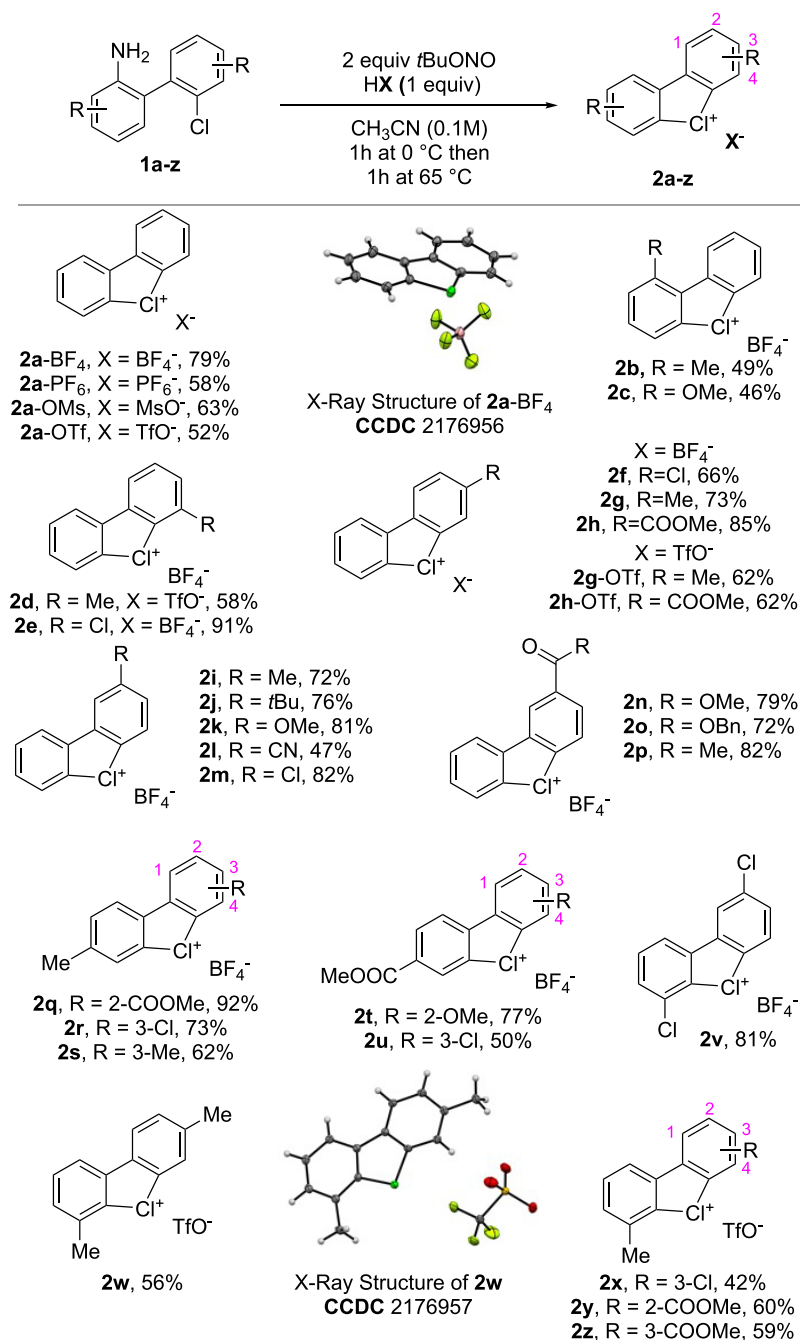
couplings is less developed and mainly limited to electrochemical transformations,³² oxidative couplings, and metal-catalyzed reactions.²⁷ On the contrary, the direct C-arylation of phenols with arynes under transition metal-free and mild conditions remains unprecedented.^{33,34} Consequently, considering the expected unusual reactivity of λ^3 -chloranes, combined with the interest in designing chemoselective C–O vs C–C cross-couplings of phenols and the broad diversity of terphenyl compounds in natural and biologically active products (Figure 1d),³⁵ we have embarked on exploring the reactivity of chloranes with phenols.

We report herein: (1) the synthesis and characterization of a large panel of cyclic diaryl λ^3 -chloranes; (2) their amplified reactivity as aryne precursors as illustrated in metal-free chemoselective C–O couplings; (3) previously unachievable site-selective, metal-free C–C couplings (Figure 1e). Noteworthy, the selectivity issues associated with this trans-

formation are multifaceted and go far beyond the C–O vs C–C chemoselectivity. Aiming at the development of synthetically useful protocols, control of *ortho*-/*meta*-functionalization should be reached together with a high site-selectivity, relating to the selective decoration of only one aromatic ring in case of unsymmetrical hypervalent chlorines. Moreover, mechanistic investigations and density functional theory (DFT) calculations rationalized the superior reactivity of chloranes, the solvent-dependent chemoselectivity of C–O vs C–C couplings, and the preferential *meta*-functionalization.

RESULTS AND DISCUSSION

Synthesis of Cyclic Diaryl λ^3 -Chloranes. We began our investigation by developing a simple and efficient approach for the preparation of cyclic diaryl λ^3 -chloranes **2**. Encouraged by our previously described synthetic route to cyclic diaryl λ^3 -bromanes, we hypothesized that similar mild reaction

Scheme 1. Scope of Cyclic Diaryl λ^3 -Chloranes

conditions, involving *t*BuONO as an organic oxidant and a Brønsted acid, could enable the preparation of **2** starting from a simple 1,1'-chloro(amino)biphenyl **1**³⁶ (Scheme 1). Remarkably, an aqueous solution of HBF₄ assented to isolate **2a-BF₄** in 79% yield through simple precipitation with diethyl ether. In analogy, the HPF₆, MsOH, and TfOH acids enabled the preparation of **2a** in moderate to good yields (52–63%). Subsequently, the generality of this method was evidenced while engaging various 1,1'-chloro(amino)biphenyls **1a-z**. A large variety of cyclic diaryl λ^3 -chloranes **2a-z** was thus furnished in excellent to moderate yields. Electron-donating groups, such as methyl, *tert*-butyl, and methoxy, were well tolerated at the 1-, 2-, 3-, and 4-positions, respectively, delivering the desired products **2b-k** in good to excellent yields (46–91%). Substrates bearing various electron-with-

drawing substituents, including chlorine, methyl and benzyl esters, as well as methyl ketone, were also compatible, further illustrating an interesting functional group tolerance. Notably, even a radical sensitive –CN moiety could be installed (**1l**), furnishing **2l** in synthetically useful 47% yield. Selected unsymmetric substrates (**1q–1z**) were successfully submitted to the standard reaction conditions, furnishing highly decorated cyclic diaryl λ^3 -chloranes. Particularly interesting are the “push–pull” λ^3 -chloranes, **2q**, **2t**, and **2x**, bearing electron-donating (Me- and MeO-) and electron-withdrawing groups (MeOOC- and Cl-), which were obtained in excellent yields. The robustness and usefulness of the procedure were furthermore demonstrated by performing the synthesis of **2d**, **2w**, **2x**, and **2z** at a gram-scale level (1.2 or 2.2 mmol scale).

Single crystal X-ray analysis of **2a**-BF₄ and **2w** confirmed the tricyclic structure of the hypervalent cyclic diaryl λ^3 -chloranes. Considering the scarcity of the hypervalent chlorine-type compounds and targeting their comparison with the corresponding bromanes and iodanes congeners, the crystallographic structures of these hypervalent compounds have been examined (Figure 2). The crystallographic data for the

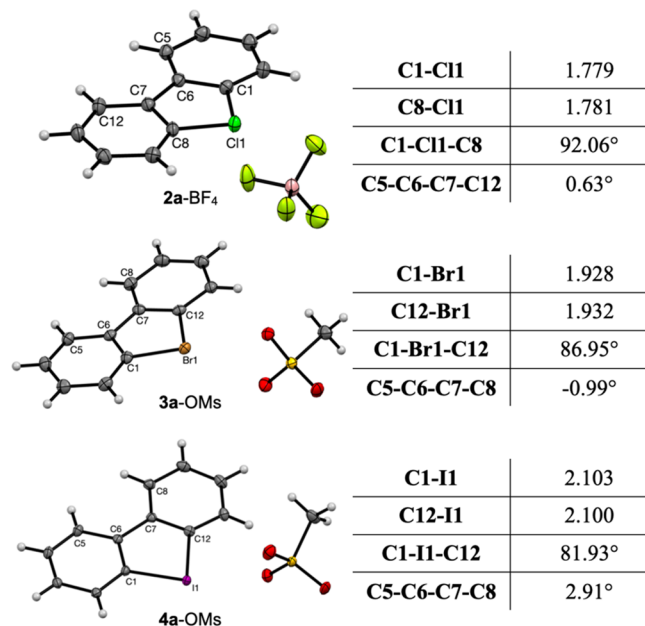


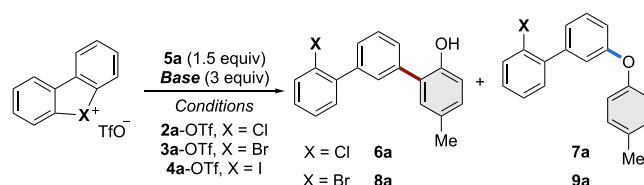
Figure 2. X-ray structure analysis of **2a**-BF₄ (CCDC 2176956), **3a**-OMs (CCDC 2063898) and **4a**-OMs (CCDC 2063903).

compounds **2a**-BF₄, **3a**-OMs, and **4a**-OMs revealed a peculiar structural trend. The bond length between the carbon and the hypervalent halogen atom increases in the order Cl(III) < Br(III) < I(III). Accordingly, a significant enlargement of the C–X–C angle is observed, translating into an almost perfect T-shaped structure for the chlorine compound (**4a**-OMs, 81.9°; **3a**, 86.9°; **2a**-BF₄, 92.0°), establishing the λ^3 -hypervalent compounds' three-center-four-electron bond (**3c**–**4e**) feature.

Reactivity. With the simple and scalable protocol delivering a large family of cyclic diaryl λ^3 -chloranes **2** in hand, we embarked on exploring their reactivity in sustainable, transition metal-free couplings. Aiming at the development of straightforward and site-selective diversification strategies of phenols, we began our study by investigating the reaction of hypervalent λ^3 -iodane (**4a**-OTf), λ^3 -bromane (**3a**-OTf), and λ^3 -chlorane (**2a**-OTf) with 4-methylphenol **5a** in the presence of a weak base, such as cesium or potassium carbonate (Table 1).

While no reaction occurred using the hypervalent λ^3 -iodine compounds (Table 1, entries 1, 4 and 7), the λ^3 -bromane and the λ^3 -chlorane substrates reacted smoothly. Encouragingly, in addition to the expected *meta*-selective C–O coupling, metal-free dehydrogenative *meta*-selective C–C bond formation was also observed, delivering product **6a** in a significant amount while using **2a**-OTf. Remarkably, the nature of the base and the solvent appeared to have a crucial impact on the C–O *vs* C–C chemoselectivity. Indeed, the hypervalent bromide **3a**-OTf in the presence of cesium carbonate provided the C–O coupling product **9a** in 70% yield (Table 1, entry 2). In clear contrast, under the same reaction conditions, **2a**-OTf showed a

Table 1. Reactivity of Cyclic Diaryl Hypervalent λ^3 -Reagents

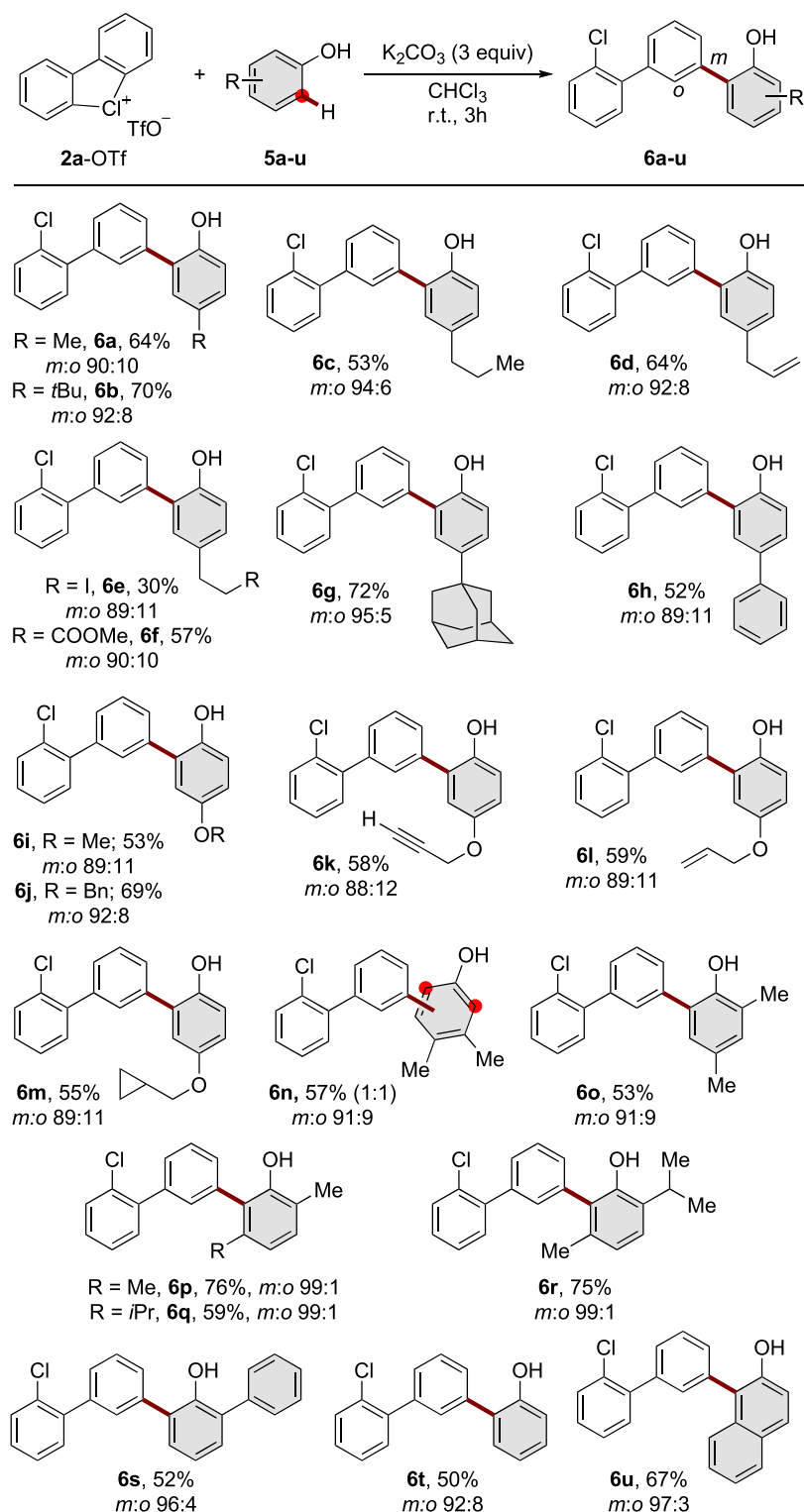


entry	X(III)-OTf	conditions ^a	yields ^b	
			C–C	C–O
1	4a-OTf	Cs ₂ CO ₃ ; CHCl ₃	no conversion	
2	3a-OTf		15%	70%
3	2a-OTf		35%	35%
4	4a-OTf	K ₂ CO ₃ ; CHCl ₃	no conversion	
5	3a-OTf		26%	9%
6	2a-OTf		49%	traces
7	4a-OTf	K ₂ CO ₃ ; H ₂ O	no conversion	
8	3a-OTf		no conversion	
9	2a-OTf		13%	60%

^aConditions: 0.1 mmol of X(III)-OTf reagent (**4a**-OTf, **3a**-Tf, **2a**-OTf), 0.15 mmol of **5a**, and 0.3 mmol of Cs₂CO₃ or K₂CO₃ in 1 mL of CHCl₃ or H₂O at room temperature for 16h. ^bIsolated yields.

complementary reactivity, favoring the formation of the challenging C–C coupling product (**6**), together with the C–O product (**7**) (Table 1, entry 3). The simple replacement of the Cs₂CO₃ base by the potassium salt almost completely inhibited the formation of the ether-derived product, furnishing selectively the direct arylation product, **6a**, in 49% yield (Table 1, entry 6). The use of water turned out to be an additional handle to control the reaction outcome. As in the aqueous medium, the reaction between **2a**-OTf and **5a** provided **7a** in 60% isolated yield (Table 1, entry 9), while no coupling occurred when using the hypervalent iodine **4a**-OTf and bromane **3a**-OTf (Table 1, entries 7 and 8), further highlighting the complementary and potent reactivity of these reagents. Additional control experiments were carried out to elucidate the nature and the role of the base and the solvent (see the SI, Table S-3) identifying potassium carbonate as crucial to avoid the concomitant production of both C–C and C–O coupling products, whereas the choice of the solvent gives a unique handle to reach high chemoselectivity. Noteworthy, in the case of both transformations, the generation of the *meta*-substituted products is largely favored, and only a trace amount of the *ortho*-coupling product is observed (see the SI, Table S-2).

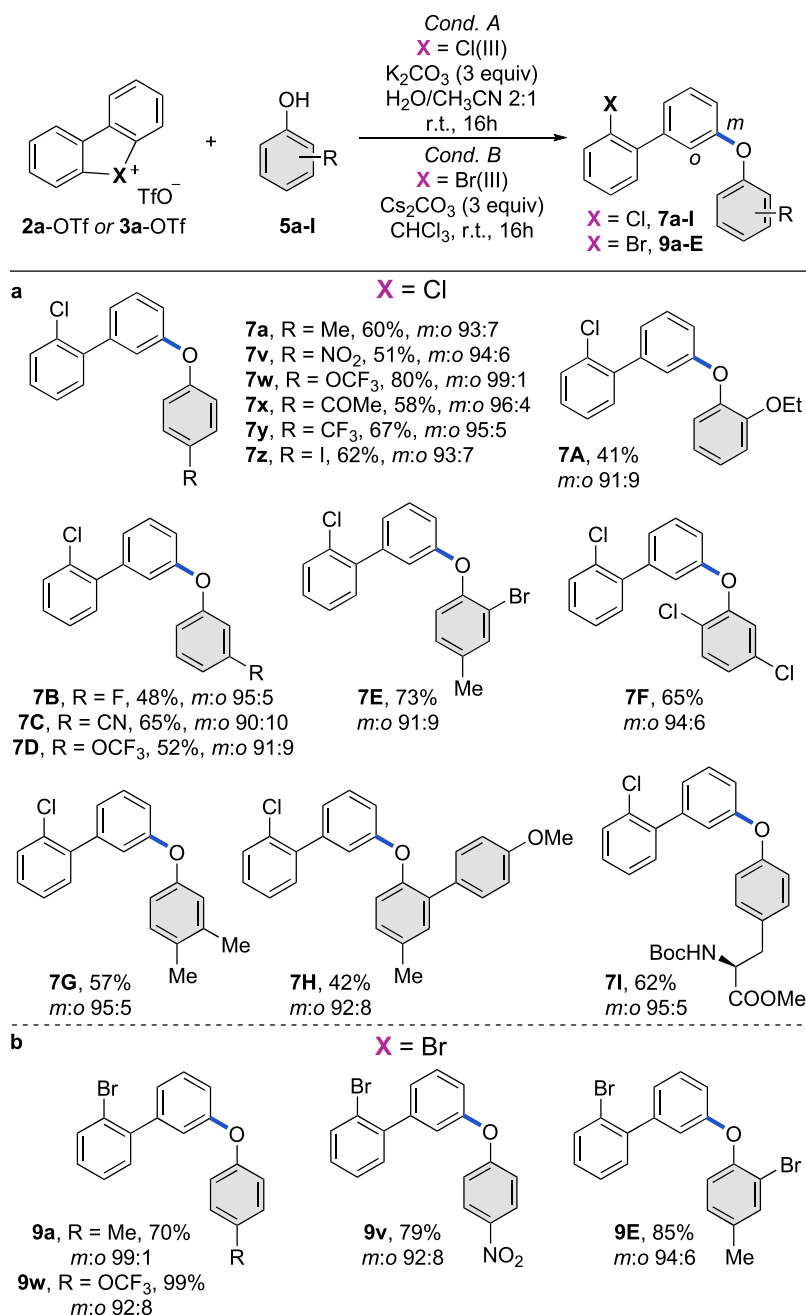
Scope of C–C and C–O Couplings. With the optimal reaction conditions in hand, we first investigated the generality of the metal-free dehydrogenative *ortho*-arylation of phenols (Scheme 2). In all cases, very high *meta*-selectivity has been observed with regard to the biaryl unit of the hypervalent chlorine precursor. Alkyl substituents (Me, *t*Bu, and Et) at the *para*-positions were well tolerated, providing **6a**, **6b**, and **6c** in moderate to good yields. Functionalization of the natural product chavicol (**5d**) afforded **6d** in 64% yield, illustrating compatibility with a synthetically useful allyl moiety. Functional groups, such as iodo (**5e**) and methyl ester (**5f**) derivatives, were tolerated under these mild reaction conditions, albeit **6e** was obtained only in 30% yield. Considering the special role of bioisosteres in medicinal chemistry,³⁷ the 4-adamantyl phenol **5g** was also investigated, providing the desired **6g** in 72% yield, whereas **5h** leads to **6h**

Scheme 2. Scope of Metal-Free C–C Bond Formation with Cyclic Diaryl λ^3 -Chloranes

in moderate amount. Protected 1,4-dihydroxyquinones **5i** and **5j** conveyed, respectively, **6i** and **6j** in synthetically useful yields. Couplings with sensitive moieties, such as propargyl **5k**, allyl **5l**, and cyclopropyl **5m** derivatives, occurred smoothly, yielding highly valuable products. Disubstituted phenol **5n** furnished a 1:1 mixture of regioisomers of **6n**. Interestingly, the introduction of an *ortho*-substituent on the phenol (**5o**) does not affect the reaction yield. Furthermore, a remarkable *ortho*-

regioselectivity (with respect to the OH group of the phenol) has been achieved while investigating unsymmetric and sterically hindered substrates, such as **5p**, **5q**, **5r**, and **5s**, delivering the desired products as single regioisomers in high yields (up to 76% yield). Finally, the arylation of phenol **5t** and 2-naphthol **5u** supplied regioisomerically pure **6t** and **6u**.

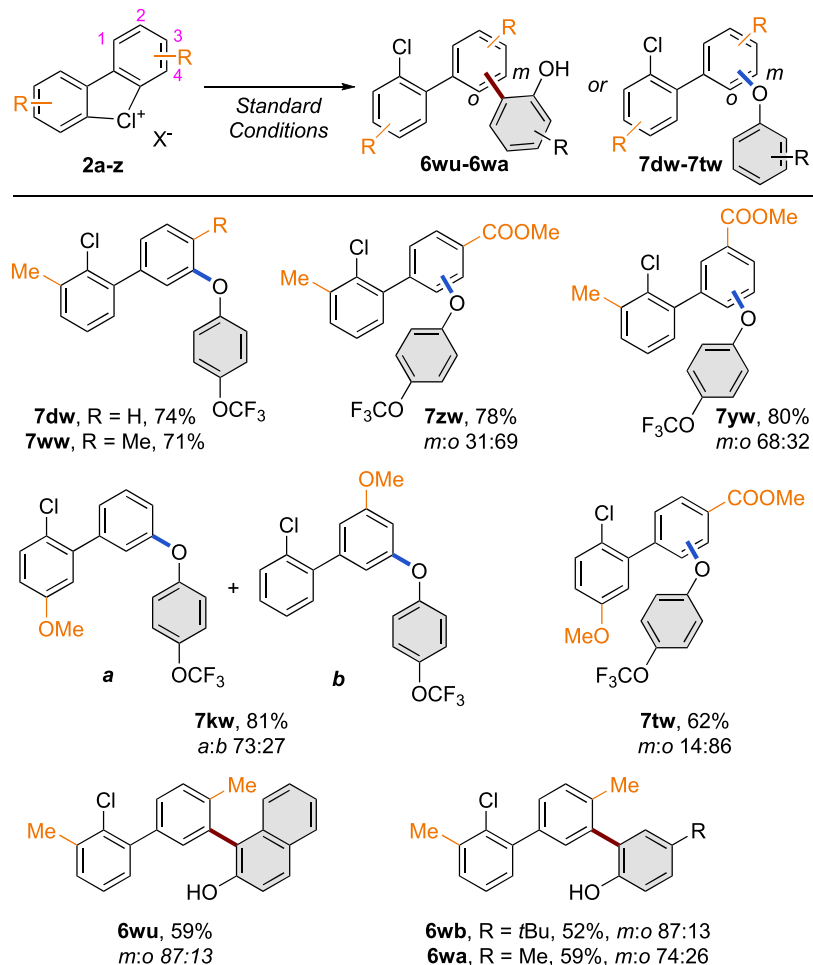
Intrigued by the discovery of a solvent-dependent chemo-selectivity, we then focused our attention on the development

Scheme 3. Scope of Metal-Free C–O Coupling; (a) with Cyclic Diaryl λ^3 -Chloranes; (b) with Cyclic Diaryl λ^3 -Bromanes

of a water-mediated metal-free C–O coupling (Scheme 3a). The versatility and the robustness of this approach were validated regarding the compatibility of this reaction with a large diversity of *ortho*-, *meta*-, and *para*-functionalized substrates **5**. Synthetically useful functional groups, including nitro **5v**, iodo **5z**, methyl ketone **5x** as well as cyanide **5c**, were well tolerated, furnishing the corresponding products in good yields. Phenols bearing electron-withdrawing groups, such as **5w** and **5y**, outcompeted the electron-rich coupling partners, due to the increased acidity. Remarkably, the C–O arylation of the challenging sterically hindered phenol **5h** was still possible, albeit **7h** was isolated in moderate yield. Moreover, L-tyrosine derivative **5i** was submitted to the standard reaction conditions and a good yield of the arylated product **7i** was obtained, further illustrating the high versatility of the method.

Cyclic diaryl hypervalent λ^3 -bromane **3a-OTf** was also briefly tested for the metal-free carbon–oxygen bond formation (Scheme 3b). Due to the lower reactivity of Br(III)-species under the standard procedure, an alternative protocol involving CHCl₃ as solvent and cesium carbonate as base was identified as suitable for various electron-rich and electron-poor phenols affording products **9** in good to excellent yields.

The complexity of the coupling between diaryl λ^3 -chloranes and phenols does not only rely on the chemoselectivity between C–O and C–C coupling, but an additional degree of selectivity arises from (1) a possible functionalization of the biaryl unit of the λ^3 -chloranes either in *ortho*- or *meta*-positions and (2) selective functionalization of one ring over the other in case of unsymmetrical hypervalent substrates. While using the simple **2a-OTf** substrate, *meta*-selective coupling is highly

Scheme 4. Unsymmetric Cyclic Diaryl λ^3 -Chloranes in C–O and C–C Bond Formations

avored (*m/o* selectivity from 99:1 to 88:12). To further investigate the *meta*-/*ortho*-regioselectivity trends, the reactivity of unsymmetric cyclic diaryl λ^3 -chloranes was tested (Scheme 4). Under the C–O coupling protocol, the 2-methyl substituted chloranes **2d** and **2w** were efficiently reacted with the phenol **5w**, delivering selectively *meta*-substituted products **7dw** and **7ww**, respectively, in 74 and 71% isolated yields. The presence of an electron-withdrawing group at the 3-position, such as methyl ester group (**2z**), provided **7zw** in good yield, but a regioselectivity-switch occurred, translating into formation of the *ortho*-regioisomer as the major product (*m/o* 31:69). On the other hand, the impact of the ester substituent, when introduced at the 2-position, is less pronounced, thus generating the *meta*-product **7yw** as the major regioisomer (*m/o* 68:32). In addition, the unsymmetric λ^3 -chloranes prone to undergo the functionalization at both, different biaryl aromatic units, tend to be functionalized at the less electron-rich aryl motif.^{38,39} Indeed, OMe-substituted chlorane **2k** delivered **7kw** as a mixture of two products in *a/b* regioselectivity ratio of 73:27. Impressively, a perfect regioselectivity was reached by designing a “push–pull”-type substrate. In case of **2t** bearing one electron-rich and one electron-withdrawing substituent, a complete regioselective control was achieved while reacting with **5w**. Finally, we extended the regioselectivity studies taking into consideration the effect of different phenols on the transformation with **2w** and **2b** into the C–C bond formation. Sterically hindered phenols **5u** and **5b** provided **6wu** and **6wb**

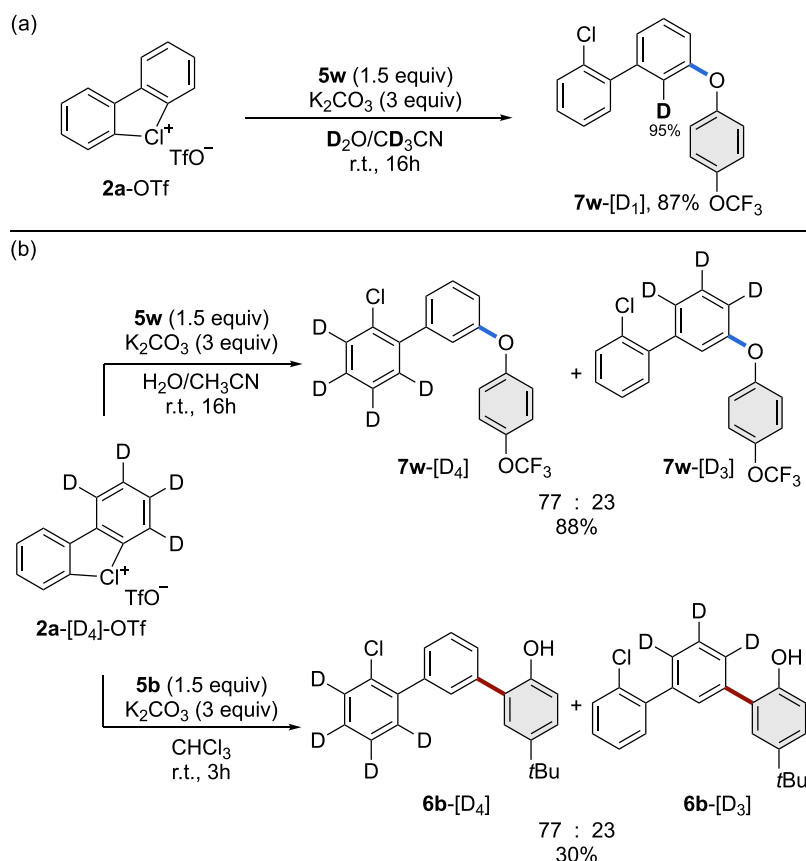
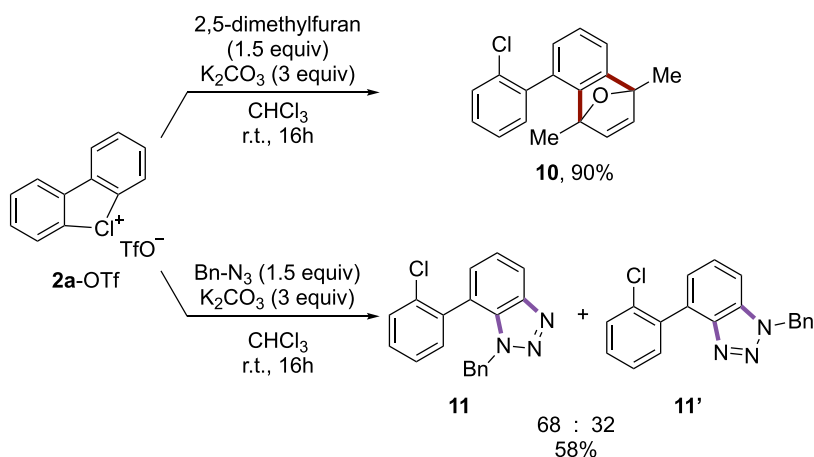
with a similar regioselectivity ratio of 87:13 *m/o*, while a methyl group (**5a**) furnished **6wa** in 59% yield, albeit with a marginally reduced regioselectivity.

To demonstrate even further the sustainability of this methodology, the C–O coupling was performed under flow protocol. Reaction of **2a-OTf** and the phenol **5a** delivered the desired product **7a** in 72% isolated yield after a simple liquid–liquid extraction and filtration through silica gel. Remarkably, a drastic reduction of the reaction time (13.3 min of residence time *vs* 16 h) and an improved chemoselectivity were reached under flow chemistry conditions (see the SI, Scheme S-12).

Mechanistic Studies. Captivated by the singular reactivity of this class of cyclic diaryl λ^3 -chloranes, mechanistic studies were undertaken, combining both experimental and DFT approaches.

Experimental Studies: Generation of Aryne Intermediate. First, competition tests between λ^3 -chloranes and λ^3 -bromanes, in both C–C and C–O coupling, were performed (see the SI, Scheme S-14 and Scheme S-15). Remarkably, C–C coupling is twice as efficient for λ^3 -chlorane **2a** than for λ^3 -bromane **3a**. Even more impressive is the almost 5 times increased reactivity observed for **2a** in the C–O coupling reaction. Following this trend, in case of the parallel reactions conducted with **2a-OTf** and **3a-OTf**, the bromine substrate provided the desired products **8b** and **9w** in only low yields, with 2-bromo-biphenyl being a major decomposition product. On the contrary, **2a-OTf** furnished the desired

Scheme 5. Mechanistic Studies

Scheme 6. Cyclic Diaryl λ^3 -Chloranes in Cycloaddition Reactions

product in good yields, proving the higher and complementary reactivity of the latter.

Subsequently, deuteration studies were conducted (Scheme 5a). C–O coupling between 2a-OTf and 5w, conducted in deuterated solvents, furnished 7w-[D₁] in good yield with high deuterium incorporation (up to 95%) at the *ortho*-position. This result perfectly validates the expected formation of the aryne intermediate and the *meta*-functionalization. Upon a nucleophilic attack, a carbanion intermediate is formed which can be easily trapped in the presence of [D⁺]-sources.⁴⁰

Afterwards, aiming at the determination of the kinetic isotope effect characterizing these metal-free C–C and C–O couplings, deuterated substrate 2a-[D₄]-OTf was reacted with

5w and 5b, respectively (Scheme 5b). Both reactions delivered 6a-[D] and 7w-[D] as a mixture of -[D₄] and -[D₃] adducts with an identical [D₄]/[D₃] ratio of 77:23, suggesting that the aryne generation features a KIE of 3.3 and might be expected to be the rate-determining step of these transformations.

Generation of the aryne intermediate was also proven by trapping such a highly reactive species (Scheme 6). Taking advantage of highly versatile cycloaddition reactions for the construction of new carbon–carbon and carbon–nitrogen bonds, 2a-OTf was reacted with 2,5-dimethylfuran and benzyl azide, thus delivering 10 in excellent yield and 11 as a separable mixture of products in 58% yield.

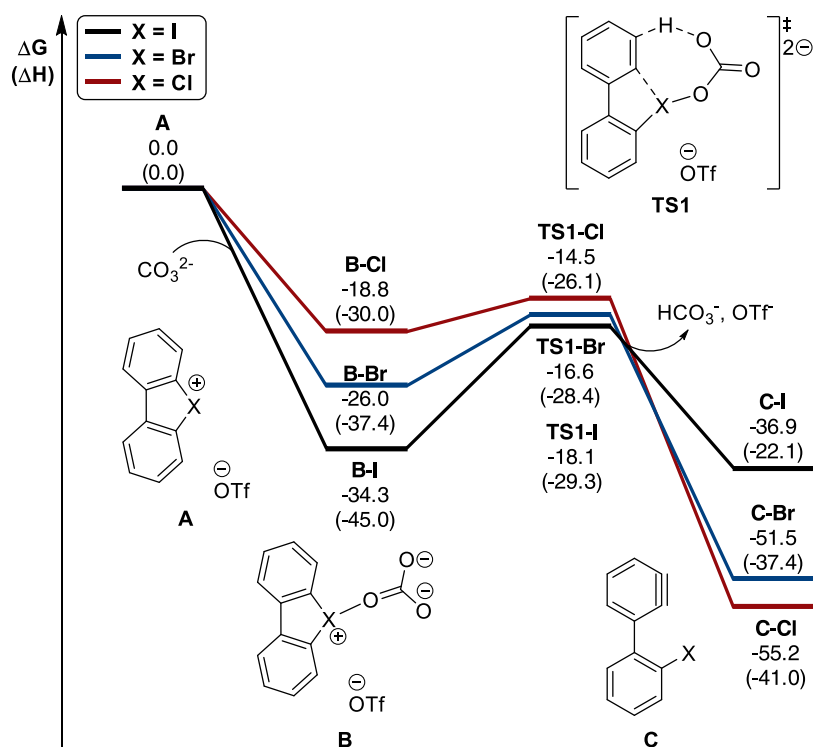


Figure 3. Calculated energy diagram (in kcal mol⁻¹) for the formation of arynes C from hypervalent halonium 2a (red color), 3a (blue) and 4a (black).

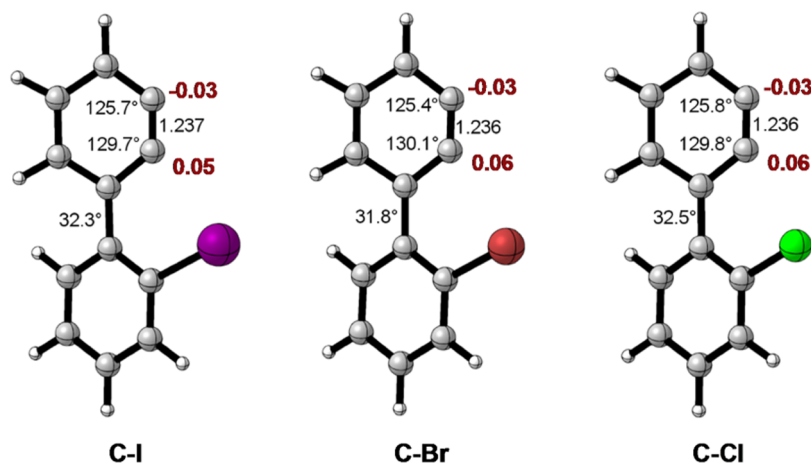


Figure 4. Calculated geometries of aryne intermediates C. Distances are given in Å; values in red correspond to NBO charges.

To better understand the aryne formation process, the initial rates of both C–C and C–O coupling were measured (see the SI, Scheme S-20, and Scheme S-21). Similar rates have been observed within 30 min of the reactions, leading to 50% of conversions. These results support a limited influence of the reaction media on the formation of the aryne intermediate step from 2a-OTf, which can further rapidly react with the phenol.

DFT Calculations. To gain further insights into the formation of arynes from hypervalent compounds 2a–4a and their subsequent reaction with phenols 5, density functional theory (DFT) calculations at the ω B97X-D/def2-QZVPP+SMD(CHCl₃)/ ω B97X-D/def2-TZVP level of theory including corrections for solvation by chloroform were performed (see the SI for full computational details).^{41–43}

Aryne Generation. The formation of highly reactive aryne intermediates from 2a–4a is proposed to take place *via*

deprotonation with carbonate and concurrent C–X bond cleavage. Coordination of carbonate to intermediate A was found to be thermodynamically favorable (Figure 3), and the larger stabilization of B-I compared to B-Br and of B-Cl can be rationalized by the greater electrostatic stabilization due to the significantly larger positive charge of iodine in A-OTf (+1.20 for I compared to +0.87 for Br, and +0.67 for Cl; see the SI, Figure S-3).

Subsequent deprotonation and C–X bond cleavage occur in a concerted process *via* seven-membered cyclic transition state TS1, with an activation free energy of 16.2 kcal mol⁻¹ for I, 9.4 kcal mol⁻¹ for Br and only 4.3 kcal mol⁻¹ for Cl with respect to the corresponding intermediate B. The substantially smaller activation free energy as well as the considerably higher stabilization of C agrees well with the experimentally preferred aryne formation with hypervalent λ^3 -bromane and λ^3 -

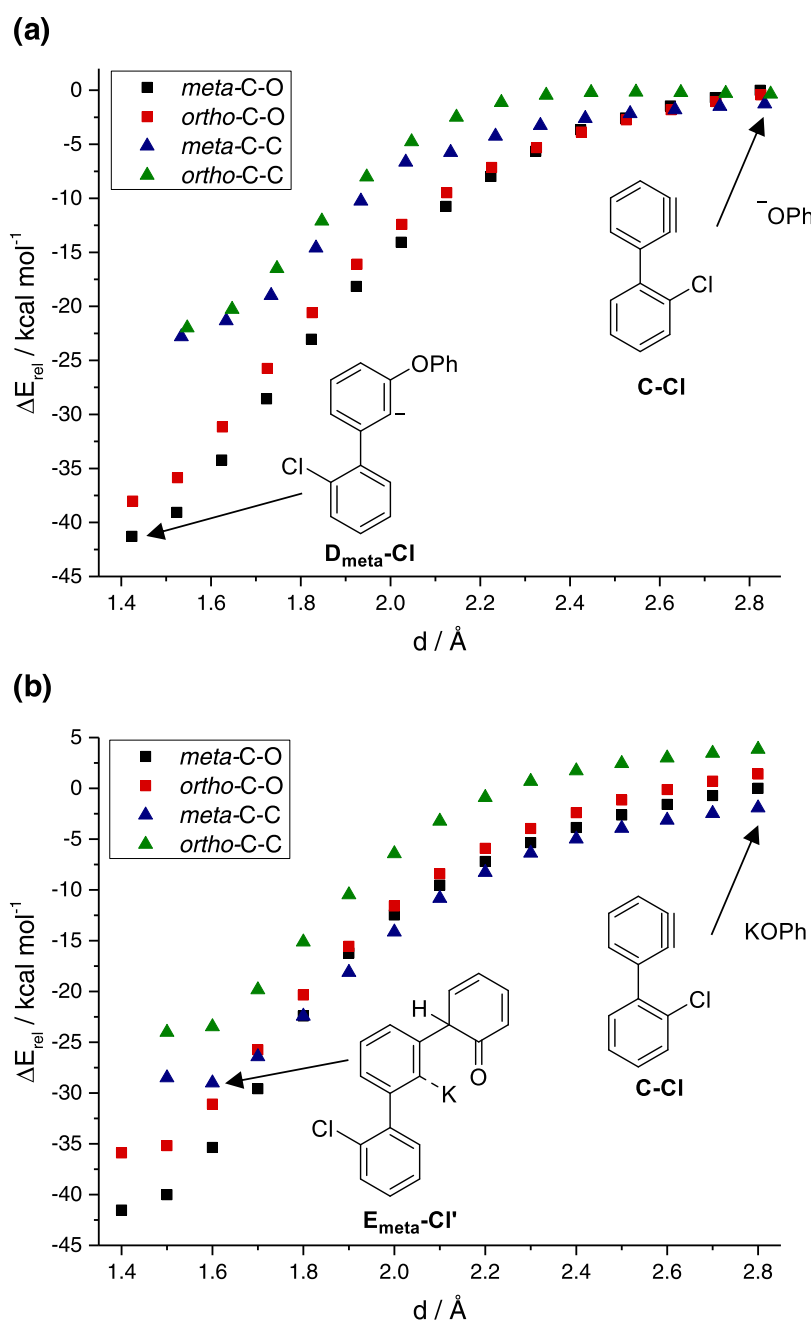


Figure 5. Calculated energy profile (in kcal mol⁻¹) for C–O bond (black and red squares) and C–C bond (blue and green triangles) formation with (a) phenolate and (b) potassium phenolate.

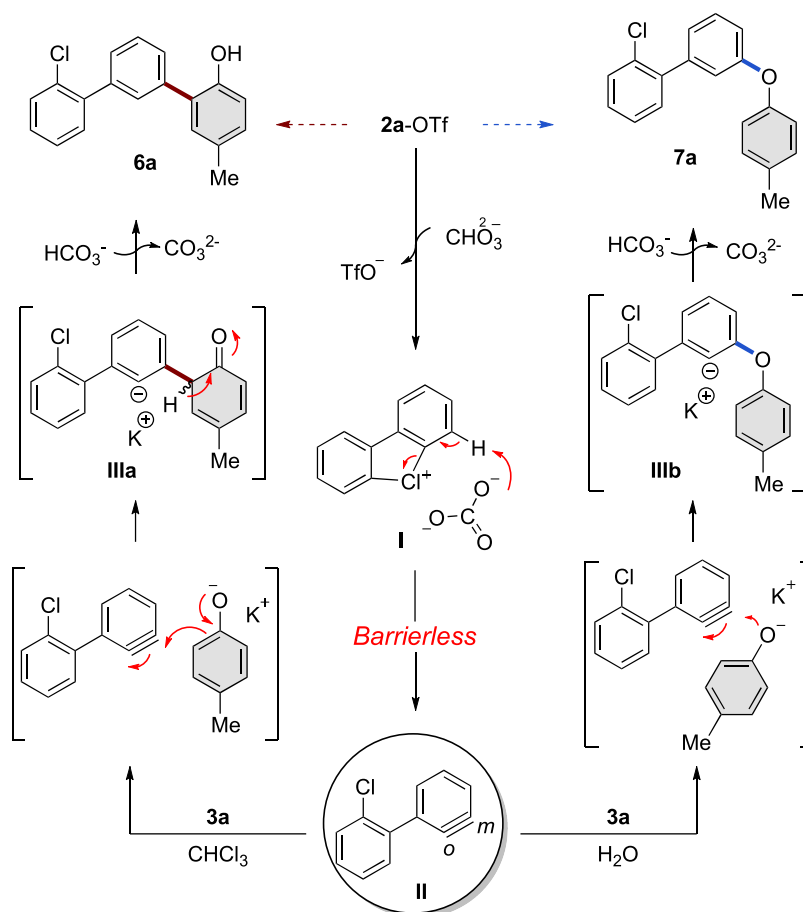
chlorane compounds compared to well-established λ^3 -iodane reagents. Furthermore, the experimentally determined increased reactivity of hypervalent λ^3 -chloranes is consistent with the surprisingly low energy barrier required for aryne formation. The geometries and electronic properties of 3-(*o*-halophenyl)benzynes **C** were found to be largely independent of the halide substituent (Figure 4).

***meta*- vs *ortho*-Selectivity.** While the slightly larger distortion toward linearity at C2, *i.e.*, the aryne C atom in *ortho*-position with respect to the ArX substituent, indicates a marginally preferred nucleophilic attack at C2 due to the more pronounced p-orbital character, partial positive charge, and lesser transition state distortion energy,³⁸ we hypothesize that the significant steric bulk of the ArX substituent overrides the

predicted selectivity, thus leading to the observed attack at *meta*-position.⁴⁴

Chemoselectivity. The C–O vs C–C, condition-controlled chemoselectivity was subsequently investigated. The formation of a solvent-separated potassium and phenolate ion pair is likely to occur in water, whereas in less-polar chloroform, the potassium phenolate ion pair is formed, presumably rendering an attack of the phenolate oxygen onto the benzyne less facile. In contrast, cesium phenolate is expected to form loose ion pairs in chloroform, due to the more complete solvation in part caused by the significantly lower charge density compared to potassium. To shed light on the *meta*-/*ortho*-selectivity of the transformation as well as the solvent-dependent switch from C–O to C–C bond formation, we performed a series of calculations at different C–O and C–

Scheme 7. Proposed Mechanism

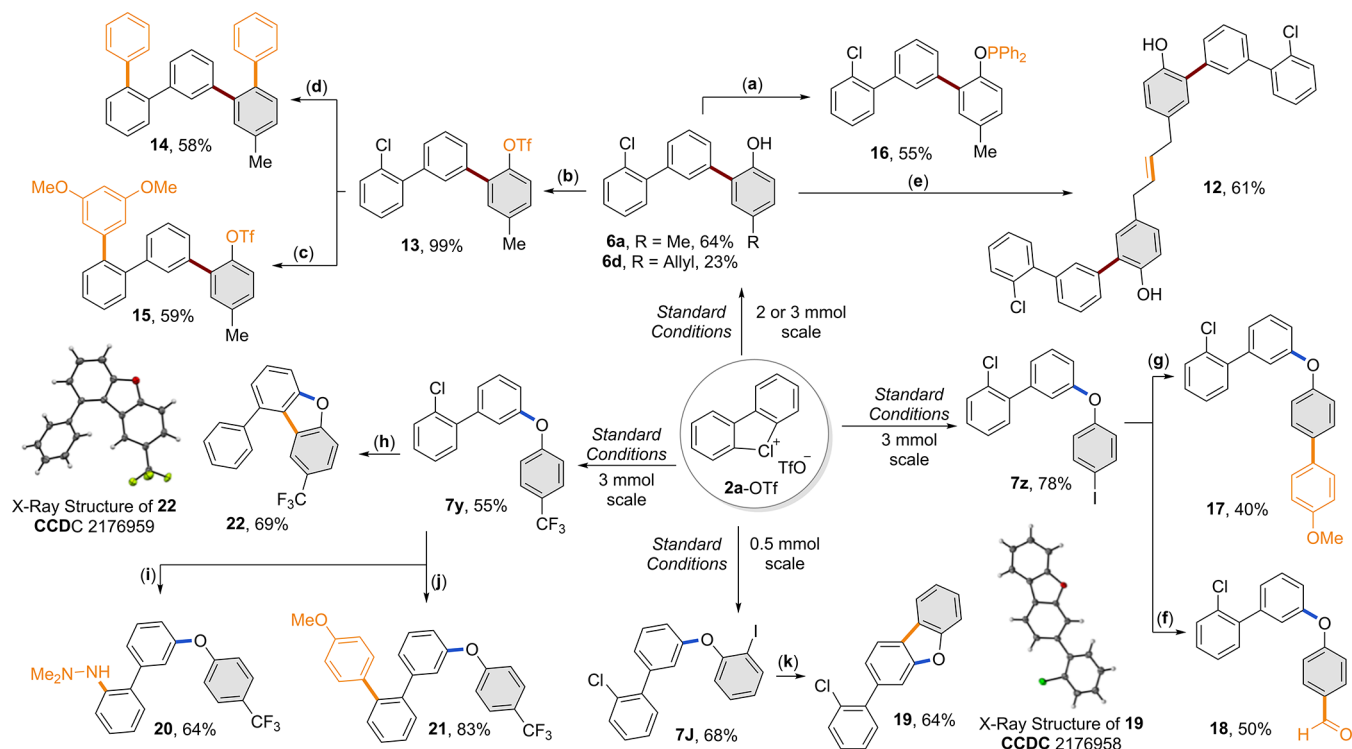


C bond distances, respectively. These computations were performed because there is no electronic energy barrier to the reaction, although there will be a free-energy barrier due to the decrease of entropy for this bimolecular reaction. The barrier will be low (less than the 8–12 kcalmol⁻¹ $-T\Delta S$ of a bimolecular reaction). For the reaction of intermediate C-Cl with phenolate, a clear preference for C–O over C–C bond formation can be observed for all relevant bond distances (Figure 5a).⁴⁵

In addition, C–O as well as C–C bond formation was found to preferentially occur at the *meta*-position, which is in good agreement with the experimental observation. In contrast, replacing phenolate with potassium phenolate led to a distinct change in reactivity, with C–C bond formation at the *meta*-position now preferred over C–O bond formation for bond distances $d > 1.8$ Å (Figure 5b).

Based on this mechanistic evidence, a plausible reaction mechanism for the formation of C–C and C–O coupling is proposed (Scheme 7). Initially, an anion exchange leads to the energetically more stable 2a-carbonate intermediate I, which through a low-barrier process evolves into a seven-membered ring TS. Concerted base-mediated deprotonation and carbon–halogen cleavage generate the aryne intermediate II. The *meta*-selective nucleophilic attack onto the benzyne intermediate II results in the formation of the new C–C and C–O bonds, respectively, yielding intermediates IIIa and IIIb. The rearomatization of the intermediate IIIa and the subsequent protonation of the carbanion generate products 6a and 7a.

Post-Functionalization. The transition metal-free C–C and C–O couplings described here provide sustainable and rapid access to highly modular building blocks, straightforwardly diversifiable into various interesting compounds (Scheme 8). To demonstrate several possible post-modifications, large-scale couplings were first performed. The 15 mmol scale synthesis of the cyclic diaryl λ^3 -chlorane was performed, yielding 3 grams of 2a-OTf in 60% yield within 90 minutes, ensuring a useful and simple approach to these hypervalent reagents. Subsequently, a vast diversification study was carried out to further display the utility of our products. The 2 mmol scale reactions of 2a-OTf with 5a and 5d under the C–C coupling conditions provided 6a and 6d in synthetically useful amounts. Interestingly, exploiting the allyl fragment of 6d, a Grubbs-catalyzed metathesis furnished the highly functionalized dichloro-diphenol compound 12 in 61% yield. A straightforward conversion of the hydroxy group to the corresponding triflate 13 enabled the synthesis of the *m*-quinquephenyl 14 via a double Suzuki reaction in 58% yield, while a Cl-selective palladium-catalyzed Suzuki coupling furnished the product 15 in 59% yield. The peculiar presence of a hydroxyl residue was also exploited for the synthesis of a new phosphine 16, which was prepared in 55% yield. Subsequently, the relevance of C–O coupling product was evaluated. The scale-up reactions up to 3 mmol scales produced the desired products 7y, 7z, and 7j in good to excellent yields (55, 78, and 68%, respectively). Taking advantage of the selective reactivity of the iodine with respect to the chlorine atom, a Suzuki reaction and a lithium base-

Scheme 8. Post-Functionalization^a

^a(a) Ph_2PCl , Et_3N , Tol, reflux, 16 h. (b) TiF_4 , 2,6-lutidine, DCM, 0 °C to r.t., 2 h. (c) $\text{Pd}(\text{OAc})_2$ cat., PCy_3 cat., $3,5\text{-OMeC}_6\text{H}_3\text{B}(\text{OH})_2$, KF, THF, r.t., 72 h. (d) $\text{Pd}(\text{OAc})_2$ cat., PCy_3 cat., $\text{C}_6\text{H}_5\text{B}(\text{OH})_2$, KF, THF, r.t., 72 h. (e) Grubbs I cat., DCM, reflux, 16 h. (f) $n\text{BuLi}$, DMF, THF, -78 °C to r.t., 2 h. (g) $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ cat., NaHCO_3 , $\text{MeOC}_6\text{H}_4\text{B}(\text{OH})_2$, DME/ H_2O , 120 °C, 2 h. (h) $\text{Pd}_2(\text{dba})_3$ cat., SPhos cat., Cs_2CO_3 , dioxane, 150 °C, 16 h. (i) $\text{Pd}_2(\text{dba})_3$ cat., SPhos cat., $\text{Me}_2\text{N-NH}_2$, $t\text{BuONa}$, dioxane, 120 °C, 5 h. (j) $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ cat., NaHCO_3 , $\text{MeOC}_6\text{H}_4\text{B}(\text{OH})_2$, DME/ H_2O , 120 °C, 2 h. (k) $\text{Pd}(\text{OAc})_2$ cat., $\text{P}(\text{Cy})_3$, HBF_4 cat., K_2CO_3 , DMA, 130 °C, 16 h.

mediated exchange were performed starting from **7z**, supplying, respectively, **17** and **18** in 40 and 50% yields. On the other hand, a palladium-catalyzed C–H activation delivered the dibenzofuran **19** from **7J** in 64% yield. Notably, the resulting products contained the residual chlorine substituent as a handle for further post-modifications. Accordingly, a palladium-catalyzed C–N Buchwald–Hartwig reaction and a Suzuki reaction were performed starting from **7y** and granting, respectively, access to **20** and **21** in 64 and 83% yields. Finally, a palladium-catalyzed dechlorination process yielded benzofuran **22**.

CONCLUSIONS

We have here reported a new, simple, and robust synthetic method for the preparation of novel cyclic diaryl λ^3 -chloranes **2**. The higher reactivity of these compounds proved to be complementary to the well-established chemistry of cyclic diaryl λ^3 -iodane and more recent λ^3 -bromane compounds. The increased reactivity of cyclic diaryl λ^3 -chloranes as aryne precursors enhances the unparalleled metal-free *ortho*-arylation of phenols under mild base-mediated reaction conditions. Furthermore, experimental and DFT mechanistic investigations elucidated the origins of the reactivities as well as the chemo- and regioselectivity observed in this work. A variety of synthetic applications show the considerable potential of these new reagents in synthetic organic chemistry.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/jacs.2c10090>.

General procedure, product characterizations, computational methods, energies and geometries of calculated structures (PDF)

Accession Codes

CCDC 2176956–2176959 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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REFERENCES

- (1) Yoshimura, A.; Zhdankin, V. V. Advances in Synthetic Applications of Hypervalent Iodine Compounds. *Chem. Rev.* **2016**, *116*, 3328–3435.
- (2) Zhdankin, V. V.; Stang, P. J. Chemistry of Polyvalent Iodine. *Chem. Rev.* **2008**, *108*, 5299–5358.
- (3) Silva Jr, L. F., Jr.; Olofsson, B. Hypervalent Iodine Reagents in the Total Synthesis of Natural Products. *Nat. Prod. Rep.* **2011**, *28*, 1722.
- (4) Morimoto, K.; Sakamoto, K.; Ohnishi, Y.; Miyamoto, T.; Ito, M.; Dohi, T.; Kita, Y. Metal-Free Oxidative Para Cross-Coupling of Phenols. *Chem. - Eur. J.* **2013**, *19*, 8726–8731.
- (5) Stridfeldt, E.; Lindstedt, E.; Reitti, M.; Blid, J.; Norrby, P.-O.; Olofsson, B. Competing Pathways in O-Arylations with Diaryliodonium Salts: Mechanistic Insights. *Chem. - Eur. J.* **2017**, *23*, 13249–13258.
- (6) Merritt, E.; Olofsson, B. Diaryliodonium Salts: A Journey from Obscurity to Fame. *Angew. Chem., Int. Ed.* **2009**, *48*, 9052–9070.
- (7) Wang, X.; Studer, A. Iodine(III) Reagents in Radical Chemistry. *Acc. Chem. Res.* **2017**, *50*, 1712–1724.
- (8) Winterson, B.; Patra, T.; Wirth, T. Hypervalent Bromine(III) Compounds: Synthesis, Applications, Prospects. *Synthesis* **2022**, *54*, 1261–1271.
- (9) Ochiai, M. Hypervalent Aryl-, Alkynyl-, and Alkenyl- λ^3 -Bromanes. *Synlett* **2009**, *2009*, 159–173.
- (10) Farooq, U.; Shah, A.-H. A.; Wirth, T. Hypervalent Bromine Compounds: Smaller, More Reactive Analogues of Hypervalent Iodine Compounds. *Angew. Chem., Int. Ed.* **2009**, *48*, 1018–1020.
- (11) Miyamoto, K.; Saito, M.; Tsuji, S.; Takagi, T.; Shiro, M.; Uchiyama, M.; Ochiai, M. Benchtop-Stable Hypervalent Bromine(III) Compounds: Versatile Strategy and Platform for Air- and Moisture-Stable λ^3 -Bromanes. *J. Am. Chem. Soc.* **2021**, *143*, 9327–9331.
- (12) Miyamoto, K.; Uchiyama, M. Hypervalent Organo- λ^3 -Chloranes. *Chem. Lett.* **2021**, *50*, 832–838.
- (13) Nakajima, M.; Miyamoto, K.; Hirano, K.; Uchiyama, M. Diaryl- λ^3 -Chloranes: Versatile Synthesis and Unique Reactivity as Aryl Cation Equivalent. *J. Am. Chem. Soc.* **2019**, *141*, 6499–6503.
- (14) Watanabe, Y.; Takagi, T.; Miyamoto, K.; Kanazawa, J.; Uchiyama, M. Shelf-Stable (E)- and (Z)-Vinyl- λ^3 -Chlorane: A Stereospecific Hyper-Vinylating Agent. *Org. Lett.* **2020**, *22*, 3469–3473.
- (15) Sandin, R. B.; Hay, A. S. Stable Bromonium and Chloronium Salts. *J. Am. Chem. Soc.* **1952**, *74*, 274–275.
- (16) Lanzi, M.; Dherbassy, Q.; Wencel-Delord, J. Cyclic Diaryl λ^3 -Bromanes as Original Aryne Precursors. *Angew. Chem., Int. Ed.* **2021**, *60*, 14852–14857.
- (17) Lanzi, M.; Ali Abdine, R. A.; De Abreu, M.; Wencel-Delord, J. Cyclic Diaryl λ^3 -Bromanes: A Rapid Access to Molecular Complexity via Cycloaddition Reactions. *Org. Lett.* **2021**, *23*, 9047–9052.
- (18) Yoshida, Y.; Ishikawa, S.; Mino, T.; Sakamoto, M. Bromonium Salts: Diaryl- λ^3 -Bromanes as Halogen-Bonding Organocatalysts. *Chem. Commun.* **2021**, *57*, 2519–2522.
- (19) Yoshida, Y.; Mino, T.; Sakamoto, M. Chiral Hypervalent Bromine(III) (Bromonium Salt): Hydrogen- and Halogen-Bonding Bifunctional Asymmetric Catalysis by Diaryl- λ^3 -Bromanes. *ACS Catal.* **2021**, *11*, 13028–13033.
- (20) (a) Zhang, X.; Zhao, K.; Li, N.; Yu, J.; Gong, L.; Gu, Z. Atroposelective Ring Opening of Cyclic Diaryliodonium Salts with Bulky Anilines Controlled by a Chiral Cobalt(III) Anion. *Angew. Chem., Int. Ed.* **2020**, *59*, 19899–19904. (b) Li, Q.; Zhang, M.; Zhan, S.; Gu, Z. Copper-Catalyzed Enantioselective Ring-Opening of Cyclic Diaryliodoniums and O-Alkylhydroxylamines. *Org. Lett.* **2019**, *21*, 6374–6377.
- (21) Karandikar, S. S.; Bhattacharjee, A.; Metzke, B. E.; Javaly, N.; Valente, E. J.; McCormick, T. M.; Stuart, D. R. Orbital Analysis of Bonding in Diarylhalonium Salts and Relevance to Periodic Trends in Structure and Reactivity. *Chem. Sci.* **2022**, *13*, 6532–6540.
- (22) Quideau, S.; Deffieux, D.; Douat-Casassus, C.; Pouységú, L. Plant Polyphenols: Chemical Properties, Biological Activities, and Synthesis. *Angew. Chem., Int. Ed.* **2011**, *50*, 586–621.
- (23) Scott, K. A.; Cox, P. B.; Njardarson, J. T. Phenols in Pharmaceuticals: Analysis of a Recurring Motif. *J. Med. Chem.* **2022**, *65*, 7044–7072.
- (24) *The Chemistry of Phenols*; Rappoport, Z., Ed.; The chemistry of functional groups; Wiley: Hoboken, NJ, 2003.
- (25) Huang, Z.; Lumb, J.-P. Phenol-Directed C–H Functionalization. *ACS Catal.* **2019**, *9*, 521–555.
- (26) Eisenhofer, A.; Hioe, J.; Gschwind, R. M.; König, B. Photocatalytic Phenol-Arene C–C and C–O Cross-Dehydrogenative Coupling: Photocatalytic Phenol-Arene C–C and C–O Cross-Dehydrogenative Coupling. *Eur. J. Org. Chem.* **2017**, *2017*, 2194–2204.
- (27) Tian, T.; Li, Z.; Li, C.-J. Cross-Dehydrogenative Coupling: A Sustainable Reaction for C–C Bond Formations. *Green Chem.* **2021**, *23*, 6789–6862.
- (28) Krylov, I. B.; Vil', V. A.; Terent'ev, A. O. Cross-Dehydrogenative Coupling for the Intermolecular C–O Bond Formation. *Beilstein J. Org. Chem.* **2015**, *11*, 92–146.
- (29) Liu, Z.; Larock, R. C. Facile O-Arylation of Phenols and Carboxylic Acids. *Org. Lett.* **2004**, *6*, 99–102.
- (30) Gebara, K. S.; Casagrande, G. A.; Raminelli, C. An Efficient Fluoride-Mediated O-Arylation of Sterically Hindered Halophenols with Silylaryl Triflates under Mild Reaction Conditions. *Tetrahedron Lett.* **2011**, *52*, 2849–2852.

(31) Castillo, J.-C.; Quiroga, J.; Rodriguez, J.; Coquerel, Y. Time-Efficient Synthesis of Pyrido [2,3-*d*]Pyrimidinones via α -Oxoketenes. *Eur. J. Org. Chem.* **2016**, *2016*, 1994–1999.

(32) Röckl, J. L.; Pollok, D.; Franke, R.; Waldvogel, S. R. A Decade of Electrochemical Dehydrogenative C,C-Coupling of Aryls. *Acc. Chem. Res.* **2020**, *53*, 45–61.

(33) Truong, T.; Daugulis, O. Divergent Reaction Pathways for Phenol Arylation by Arynes: Synthesis of Helicenes and 2-Arylphenols. *Chem. Sci.* **2013**, *4*, 531–535.

(34) Yoshimura, A.; Fuchs, J. M.; Middleton, K. R.; Maskaev, A. V.; Rohde, G. T.; Saito, A.; Postnikov, P. S.; Yusubov, M. S.; Nemykin, V. N.; Zhdankin, V. V. Pseudocyclic Arylbenziodoxaboroles: Efficient Benzynes Precursors Triggered by Water at Room Temperature. *Chem. - Eur. J.* **2017**, *23*, 16738–16742.

(35) (a) Kitamura, S.; Hvorecny, K. L.; Niu, J.; Hammock, B. D.; Madden, D. R.; Morisseau, C. Rational Design of Potent and Selective Inhibitors of an Epoxide Hydrolase Virulence Factor from *Pseudomonas Aeruginosa*. *J. Med. Chem.* **2016**, *59*, 4790–4799.

(b) Xu, Y.; Wang, Y.; Wu, D.; He, W.; Wang, L.; Zhu, W. P-Terphenyls From *Aspergillus* Sp. GZWMJZ-055: Identification, Derivation, Antioxidant and α -Glycosidase Inhibitory Activities. *Front. Microbiol.* **2021**, *12*, No. 654963. (c) Guo, R.-T.; Cao, R.; Liang, P.-H.; Ko, T.-P.; Chang, T.-H.; Hudock, M. P.; Jeng, W.-Y.; Chen, C. K.-M.; Zhang, Y.; Song, Y.; Kuo, C.-J.; Yin, F.; Oldfield, E.; Wang, A. H.-J. Bisphosphonates Target Multiple Sites in Both Cis- and Trans-Prenyltransferases. *Proc. Natl. Acad. Sci. U.S.A.* **2007**, *104*, 10022–10027. (d) Kovács, A.; Vasas, A.; Hohmann, J. Natural Phenanthrenes and Their Biological Activity. *Phytochemistry* **2008**, *69*, 1084–1110. (e) Hangeland, J. J.; Doweiko, A. M.; Dejneka, T.; Friends, T. J.; Devasthale, P.; Mellström, K.; Sandberg, J.; Grynfarb, M.; Sack, J. S.; Einspahr, H.; Färnegårdh, M.; Husman, B.; Ljunggren, J.; Koehler, K.; Sheppard, C.; Malm, J.; Ryono, D. E. Thyroid Receptor Ligands. Part 2: Thyromimetics with Improved Selectivity for the Thyroid Hormone Receptor Beta. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3549–3553.

(36) Synthesis of **1a** was conducted under transition metal-free protocol (see the SI, page 14).

(37) Tse, E. G.; Houston, S. D.; Williams, C. M.; Savage, G. P.; Rendina, L. M.; Hallyburton, I.; Anderson, M.; Sharma, R.; Walker, G. S.; Obach, R. S.; Todd, M. H. Nonclassical Phenyl Bioisosteres as Effective Replacements in a Series of Novel Open-Source Antimalarials. *J. Med. Chem.* **2020**, *63*, 11585–11601.

(38) Medina, J. M.; Mackey, J. L.; Garg, N. K.; Houk, K. N. The Role of Aryne Distortions, Steric Effects, and Charges in Regioselectivities of Aryne Reactions. *J. Am. Chem. Soc.* **2014**, *136*, 15798–15805.

(39) Bronner, S. M.; Mackey, J. L.; Houk, K. N.; Garg, N. K. Steric Effects Compete with Aryne Distortion To Control Regioselectivities of Nucleophilic Additions to 3-Silylarynes. *J. Am. Chem. Soc.* **2012**, *134*, 13966–13969.

(40) Shi, J.; Li, L.; Li, Y. O-Silylaryl Triflates: A Journey of Kobayashi Aryne Precursors. *Chem. Rev.* **2021**, *121*, 3892–4044.

(41) Chai, J.-D.; Head-Gordon, M. Long-Range Corrected Hybrid Density Functionals with Damped Atom–Atom Dispersion Corrections. *Phys. Chem. Chem. Phys.* **2008**, *10*, 6615.

(42) Weigend, F.; Ahlrichs, R. Balanced Basis Sets of Split Valence, Triple Zeta Valence and Quadruple Zeta Valence Quality for H to Rn: Design and Assessment of Accuracy. *Phys. Chem. Chem. Phys.* **2005**, *7*, 3297.

(43) Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. Universal Solvation Model Based on Solute Electron Density and on a Continuum Model of the Solvent Defined by the Bulk Dielectric Constant and Atomic Surface Tensions. *J. Phys. Chem. B* **2009**, *113*, 6378–6396.

(44) Cheong, P. H.-Y.; Paton, R. S.; Bronner, S. M.; Im, G.-Y. J.; Garg, N. K.; Houk, K. N. Indolyne and Aryne Distortions and Nucleophilic Regioselectivities. *J. Am. Chem. Soc.* **2010**, *132*, 1267–1269.

(45) Previous studies already showed that additions of nucleophiles to aryynes often do not display a maximum (*i.e.* transition state) on the electronic energy surface, especially with anionic nucleophiles, thereby rendering the geometry optimization of a transition state structure for the comparison of activation free energies unfeasible (Refs. 38 and 44).