

using lithium bases have also been explored, but are frequently substrate-specific and utilize harsh conditions or hazardous reagents.¹¹

Notably, the aforementioned methods are incompatible with the synthesis of biaryls bearing highly reactive iodine and bromine substituents at specific positions. As a result, numerous polyhalogenated biaryls are commercially unavailable, prohibitively expensive, or yet undiscovered. This highlights the need for more innovative, versatile and efficient protocols to selectively introduce halogen motifs on biaryl scaffolds.

Recently, our group has delved into investigating the chemistry of bench-stable cyclic biaryl hypervalent bromine and chlorine reagents, which remain rare and poorly explored. These unusual reagents, which are safe to handle and easy to prepare (Scheme 1C), undergo unexpected metal-free cycloadditions and *meta*-functionalizations with C-, O- and N-nucleophiles though *in situ* aryne formation at room temperature.¹²

Based on this, we hypothesized that harnessing the unique reactivity of such hypervalent bromine and chlorine compounds as masked biaryl arynes provides a conceptually different strategy to prepare a wide array of polyhalogenated biaryl compounds in a mild and straightforward manner.

It is worth noting that several copper-catalyzed methodologies for the halogenation of analogous cyclic diaryliodonium salts have been reported.¹³ Nevertheless, this approach diverges in its mechanism, yielding selectively *ortho*-functionalized products, while *meta*-functionalization of hypervalent iodines remains extremely rare and requires high reaction temperatures and drastic conditions.¹⁴

In clear contrast, the use of hypervalent bromine and chlorine precursors, which are accessible either through standard Suzuki coupling or metal-free conditions, opens up the possibility of generating biaryl aryne intermediates, which have the potential to undergo vicinal difunctionalization through the concerted addition of both nucleophilic and electrophilic species under extremely mild reaction conditions (Scheme 1C). Such a double functionalization presents however an important challenge. Indeed, while 1,2-difunctionalization of arynes is widely reported, mainly through cycloadditions or reactions with ambiphilic reagents,¹⁵ versatile 3-component strategies remain uncommon.¹⁶ Furthermore, to the best of our knowledge, the 1,2-dihalogenation of arynes is mostly limited to diiodo, dibromo or dichlorinations, and is scarcely reported with mixed halogens.¹⁷ Moreover, the electrophilic intermolecular trapping of arynes originating from cyclic diaryl-bromonium or chloronium salts remains unaccomplished.¹⁸ In this work, we report the first example of a concerted nucleophilic and electrophilic intermolecular 1,2-difunctionalization of our biaryl aryne precursors, allowing the direct, mild and metal-free installation of customized halogen motifs in a fully regioselective manner (Scheme 1D).

Results and discussion

Meta-selective monohalogenations

Our investigation began with the bromination of hypervalent compound **1a** to synthesize product **3b**. Addition of Cs_2CO_3 as mild base prompted simultaneous deprotonation and ring

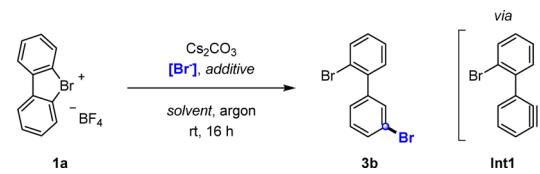
opening of **1a** to generate aryne intermediate **Int1**. *In situ* attack of **Int1** with a nucleophilic bromide source should thus achieve the targeted *meta*-selective bromination.

Preliminary experiments using alkali metal bromides (KBr, NaBr, and LiBr) showed promising results, particularly when employed alongside the corresponding crown ether additives (Table 1, entries 1–4). Increased temperature did not lead to higher yields (entry 5), and swapping solvents (entries 6, and 7) or reagents (entry 8, and 9) led to varying results, frequently producing mixtures of *meta* and *ortho* bromination. Remarkably, the most favourable outcomes were obtained using tetra-*n*-butylammonium bromide (TBAB), furnishing the desired product in quantitative yields and full *meta* : *ortho* selectivities (entries 11–13).

To broaden the generality of this methodology, other halogenation reactions, namely iodination, chlorination and fluorination, were subsequently investigated. Re-evaluation of the most promising conditions in Table 1 showed that tetra-*n*-butylammonium halide salts in THF provided the optimal global reaction conditions for all types of halogenations (see ESI†).

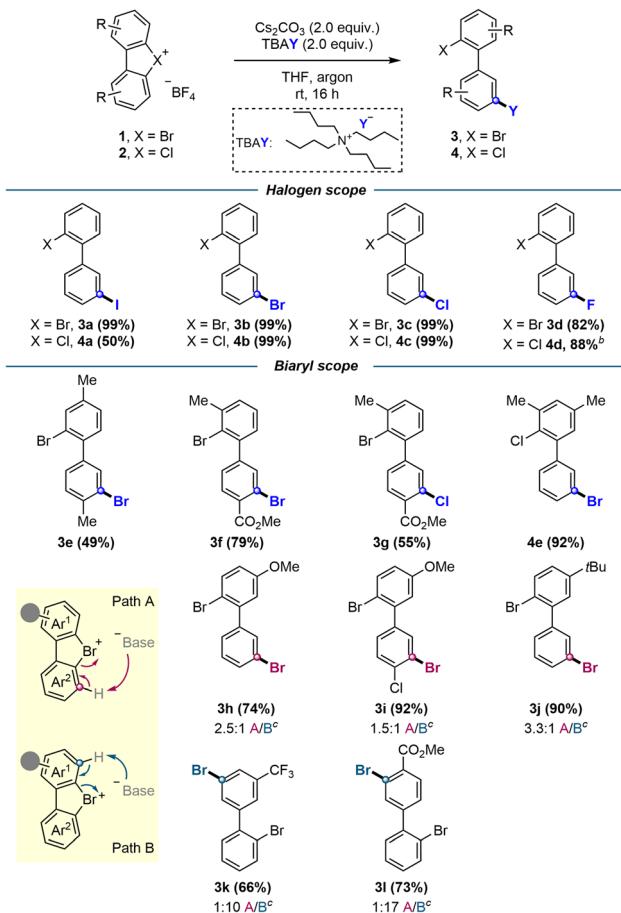
With the optimized conditions in hand, the scope of this transformation was investigated (Scheme 2). We initially explored all possible halogen permutations, achieving quantitative yields for most combinations except fluorination products **3d** and **4d** (82% and 88%, respectively), and iodination product **4a** (50%). Electron donating substituents, including methyl (**3e**, **4e**), methoxy (**3h**), and *tert*-butyl (**3j**), afforded the corresponding products in moderate to excellent yields (49–90%). Likewise, electron withdrawing groups such as $-\text{CF}_3$ (**3k**)

Table 1 Optimization of *meta*-selective bromination^a



Entry	[Br ⁻]	Additive	Solvent	Yield, % ^b
1	KBr	—	DCM	(42)/(54) ^c
2	KBr	18-Crown-6	DCM	(71)
3	NaBr	15-Crown-5	DCM	56
4	LiBr	12-Crown-4	DCM	99 (87)
5	LiBr	—	DCM	67/43 ^d
6	LiBr	—	MeCN	99 (77)
7	LiBr	—	MeCN/H ₂ O 1 : 1	40 + 40 ^e
8	NH ₄ Br	—	DCM/H ₂ O 1 : 1	3 + 34 ^e
9	TBAB	—	DCM	30 + 24 ^e
10	TBAB	—	MeCN	72
11	TBAB	—	MeCN/H ₂ O 1 : 1	99 (99)
12	TBAB	—	THF	99 (99)
13	TBAB	—	AcOEt	99

^a Standard conditions: **1a** (0.10 mmol), Cs_2CO_3 (2.0 equiv.), $[\text{Br}^-]$ nucleophile (2.0 equiv.), additive (2.0 equiv.), solvent (2.0 mL), argon, room temperature, 16 h. ^b Yields determined by ¹H NMR analysis using CH_2Br_2 as internal standard; isolated yields in parentheses. ^c 10 equiv. KBr. ^d 40 °C. ^e Undesired *ortho*-bromination.



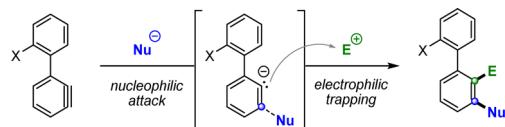
Scheme 2 Scope of meta-selective halogenations. ^aStandard conditions: hypervalent bromine **1** or chlorine **2** (0.10 mmol), Cs_2CO_3 (2.0 equiv.), tetra-*n*-butylammonium halide TBAY (2.0 equiv.), THF (2.0 mL), argon, room temperature, 16 h. Isolated yields are reported unless otherwise stated. ^bYield determined by ¹H NMR analysis using CH_2Br_2 as internal standard. Volatile product, isolated yield: 30%. ^cThe isolated yield encompasses the total yield of both isomers, irrespective of their regiochemical pathway A/B. The subsequent ratio indicates the proportion of this total obtained through pathway A relative to pathway B, and was determined via ¹H NMR analysis.

and $-\text{CO}_2\text{Me}$ (**3l**) led to good yields, and push-pull type structures (**3f**, **3g**, **3i**) yielded the respective halogenations in moderate to high yields (55–92%).

While the nucleophilic attack on the aryne occurs selectively at the *meta* position, the initial deprotonation and generation of the aryne species itself is less regioselective. In non-symmetrical substrates where the aryne formation was possible on both aromatic rings, mixtures of regioisomers resulted from their subsequent *meta*-selective halogenations. Despite this, a preference towards deprotonation and the resulting halogenation on the most electron-poor aromatic ring was observed (Scheme 2, path A *vs.* path B, compounds **3h–l**).

Extension to 1,2-dihalogenations

With the monohalogenation conditions established, we aimed to further expand the methodology to 1,2-dihalogenations by treating the aryne intermediate with both nucleophilic and

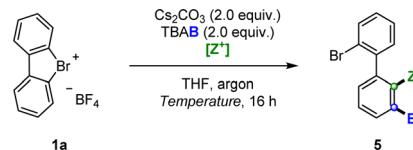


Scheme 3 Predicted aryl carbanion species and subsequent electrophilic trapping.

electrophilic halogen sources in a one-pot procedure. We hypothesized that a *meta*-selective nucleophilic attack on the aryne moiety would generate a highly reactive aryl carbanion species on the adjacent *ortho* position, which, under appropriate conditions, could be trapped by suitable halogen electrophiles (Scheme 3). It must be highlighted that, for the monohalogenation protocol, this reactive carbanion is likely quenched by deprotonating another molecule of starting material in an autocatalytic fashion.

To develop such a rare dihalogenation protocol, we began by screening various electrophilic iodine reagents alongside the optimized monobromination conditions of TBAB in THF (Table 2). Initial attempts yielded limited success with common iodine electrophiles such as NIS, I_2 or $I-Cl$ (entries 1–5). However, the use of nonafluoro-1-iodobutane resulted in a comparatively remarkable outcome, furnishing the desired dihalogenated biaryl **5b** in 86% yield (entry 6).

Table 2 Optimization of regioselective dihalogenation^a



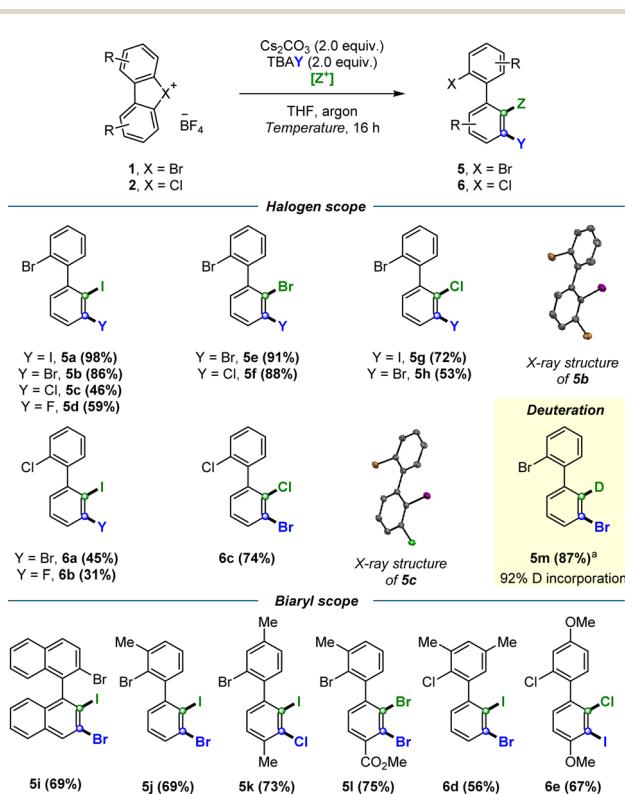
Entry	Z	[Z ⁺] (equiv.)	T, °C	Yield ^b , %
1	I (5b)	I ₂ (1.2)	rt	< 5
2		NIS (3.0)	rt	< 5
3		I-Cl (3.0)	rt	< 5
4		CHI ₃ (3.0)	rt	nr ^c
5		<i>n</i> C ₆ F ₁₃ -I (3.0)	rt	nr
6		nC₄F₉-I (5.0)	rt	(86)
7	Br (5e)	CBr ₄ (5.0)	rt	< 5
8		NBS (5.0)	rt	< 5
9		<i>n</i> C ₆ F ₁₃ -Br (5.0)	rt	6
10		C ₆ F ₅ -Br (20)	rt	17
11		<i>n</i> C ₈ F ₁₇ -Br (15)	50	(16)
12		C₆F₅-Br (15)	50	(91)
13	Cl (5h)	CCl ₄ (5.0)	rt	< 5
14		CCl ₄ (1.0 mL)	rt	nr
15		NCS (5.0)	rt	nr
16		C ₆ F ₅ -Cl (5.0)	rt	< 5
17		C ₆ F ₅ -Cl (15)	50	(30)
18		CCl₄ (15)	50	(53)

^a Standard conditions: **1a** (0.10 mmol), Cs₂CO₃ (2.0 equiv.), TBAB (2.0 equiv.), [Z⁺] electrophile, THF (2.0 mL), argon, Temperature, 16 h.

Yields determined by ¹H NMR analysis using CH_2Cl_2 standard; isolated yields in parentheses. ^c No reaction.

Motivated by this breakthrough, we set out to expand the protocol to bromane and chlorane reagents. However, the screening of Br and Cl electrophiles proved more challenging due to their decreased reactivity compared to their iodine counterparts. While some modest improvements were made using perfluoroalkyl and perfluoroaryl halides as the electrophile sources, the yields remained low (Table 2, entries 9, 10 and 16). Ultimately, temperature was found to be a key factor, as the best results for trapping with Br (entry 12), and Cl (entry 18), were observed when performing the reaction at 50 °C.

Having established the conditions for the regioselective dihalogenations, the scope of the reaction was surveyed for both hypervalent bromine and chlorine substrates (Scheme 4). Biaryls containing halogens in several different arrangements were synthesized in moderate to excellent yields, including *ortho*-iodinated products **5a–d** and **6a–b** (45–98%), *ortho*-brominated products **5e–f** (88–91%), and *ortho*-chlorinated products **5g–h** and **6e** (53–74%). We likewise examined the compatibility of the procedure with electron donating groups such as –Me (**5j**, **5k**, **6d**) and –OMe (**6e**); and electron withdrawing groups such as –CO₂Me **5l**, all of which resulted in modest to high yields (56–75%). We were also able to dihalogenate binaphthyl-derived substrate **5i** in 69% yield, a particularly interesting result



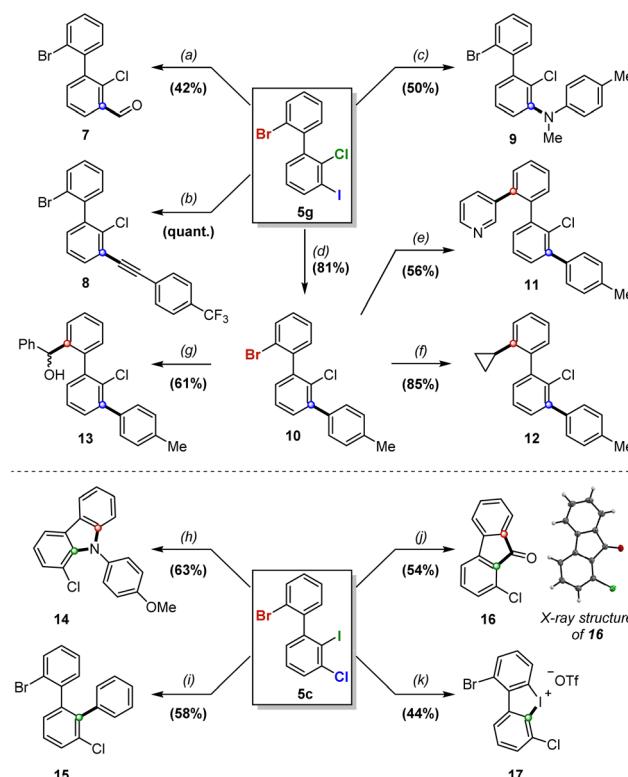
Scheme 4 Scope of the regioselective dihalogenations. Standard conditions: hypervalent bromine 1 or chlorine 2 (0.10 mmol), Cs₂CO₃ (2 equiv.), tetra-*n*-butylammonium halide TBAY (2.0 equiv.), [Z⁺] electrophile [Z=I: nonafluoro-1-iodobutane nC₄F₉–I (5.0 equiv.); Z=Br: bromopentafluorobenzene C₆F₅–Br (15 equiv.); Z=Cl: carbon tetrachloride CCl₄ (15 equiv.)], THF (2.0 mL), argon, temperature [Z=I: room temperature, Z=Br/Cl: 50 °C], 16 h. Isolated yields are reported unless otherwise stated. ^aFollowing standard conditions, electrophile: MeOD (30 equiv.), temperature: 50 °C.

given the potential of such compounds as building blocks for non-*C*₂ symmetrical privileged ligands. Crucially, the potential for this methodology to be extended to other electrophiles was demonstrated *via* the electrophilic trapping with MeOD to furnish deuterated product **5m** in 87% yield and 92% deuterium incorporation. Furthermore, compound **5m** offered additional proof that our electrophiles were indeed functionalizing the desired *ortho* position. X-ray structures were also obtained for selected dihalogenated products, unequivocally confirming the predicted regioselectivity of this transformation.

Chemoselective post-functionalizations

The potential of **5** and **6** as new and unique building blocks was then investigated *via* chemoselective and sequential post-functionalizations on products **5c** and **5g** (Scheme 5).

Compound **5g** was first subjected to several iodine-selective transformations. Grignard formation with i-PrMgCl followed by treatment with DMF furnished benzaldehyde **7** in moderate but non-optimized 42% yield, and Pd-catalyzed Sonogashira, Buchwald–Hartwig and Suzuki–Miyaura cross-couplings yielded



Scheme 5 Chemoselective post-functionalizations of **5g** and **5c**. Conditions: (a) i-PrMgCl, THF, 0 °C then DMF, 0 °C to rt. (b) *p*-(trifluoromethyl)phenylacetylene, Pd(PPh₃)₄Cl₂, K₂CO₃, Cul, DME/H₂O, 100 °C. (c) *p*-ToLNHMe, Pd(OAc)₂, DPEphos, NaOtBu, toluene, 100 °C. (d) *p*-TolB(OH)₂, Pd(PPh₃)₄Cl₂, K₂CO₃, DME/H₂O, 100 °C. (e) 3-pyridylB(OH)₂, Pd(PPh₃)₄, K₂CO₃, dioxane/H₂O, 100 °C. (f) cyclopropylB(OH)₂, Pd(OAc)₂, PCy₃, K₃PO₄, toluene/H₂O, 100 °C. (g) *n*-BuLi, THF, –78 °C then PhCHO, –78 °C to rt. (h) *p*-anisidine, Pd(dppf)Cl₂, NaOtBu, dioxane, 120 °C. (i) PhB(OH)₂, Pd(OAc)₂, PPh₃, K₂CO₃, THF/H₂O, 80 °C. (j) *t*-BuLi, THF, –78 °C then DMF, –30 °C. (k) *m*-CPBA, TfOH, DCM, 0 °C to rt.

the respective functionalized biaryls **8–10** in moderate to quantitative yields, with little to no presence of over-functionalization on bromine.

Selective functionalization on bromine over chlorine can also be achieved, as illustrated with compound **10** via Suzuki–Miyaura cross-couplings with 3-pyridylboronic acid and cyclopropylboronic acid, affording products **11** and **12** respectively in moderate to high yields. Additionally, selective lithium–bromine exchange on **10** was realized, followed by trapping with benzaldehyde, which furnished atropostable biaryl **13** in 61% yield as a mixture of atropodiastereomers.

Compound **5c** proved more challenging to functionalize selectively due to the increased steric hindrance about the biaryl axis. Buchwald–Hartwig amination using *p*-anisidine led to substituted carbazole **14** in 63% yield as a single product, while Suzuki–Miyaura arylation successfully furnished **15** in 58% yield. Interestingly, fluorene derivative **16** was obtained in 54% yield by treatment of **5c** with *tert*-butyllithium, followed by addition of DMF, and its structure was confirmed by X-ray analysis. Finally, we were also able to achieve a selective oxidation on iodine to form appealing cyclic diaryliodinium compound **17** in a considerable 44% yield, which could serve as a unique platform for subsequent transformations.

Conclusions

In conclusion, we have developed a mild, metal-free and highly efficient regioselective (di)halogenation procedure by harnessing the reactivity of cyclic biaryl hypervalent bromine and chlorine compounds. By integrating mild base-mediated aryne formation with *in situ* nucleophilic attack, employing readily available and environmentally benign tetra-*n*-butylammonium halides, we successfully furnished a wide variety of *meta*-halogenated 2-chloro- and 2-bromobiaryls in up to quantitative yields at room temperature. More significantly, we expanded the scope of our methodology to vicinal dihalogenations by achieving an unprecedented electrophilic intermolecular trapping the reactive biaryl carbanion intermediates, effortlessly preparing a range of rare 2,2',3'-trihalogenated biaryl compounds with perfect site selectivity in a simple, mild, one-pot process. Through our innovative and conceptually distinct (di)halogenation protocol, we unlock the opportunity to efficiently and flexibly synthesize a diverse library of tailor-made polyhalogenated biaryls stemming from only a handful of common hypervalent compounds as precursors. This approach thus circumvents the need for complex, multi-step *de novo* syntheses which would be required to produce such a wide variety of rare and valuable compounds. Furthermore, some compounds synthesized utilizing our method may be altogether inaccessible through traditional approaches, underscoring the importance of our protocol in expanding the space of polyhalogenated biaryls. Moreover, the unique potential of these polyhalogenated biaryls as powerful synthetic building blocks was subsequently demonstrated through several chemoselective post-functionalization reactions, thus providing a valuable toolkit for the streamlined synthesis of polyfunctionalized biaryl scaffolds.

Data availability

Detailed experimental procedures, characterization data and crystallographic data are available in the ESI.†

Author contributions

J. W.-D. and P. F. conceived and directed the project. D. C. M. and M. d. A. developed the method and performed the synthetic experiments. D. C. M and P. H. carried out the post-functionalization studies. D. C. M. and J. W.-D. wrote the manuscript with assistance from all authors.

Conflicts of interest

There are no conflicts to declare.

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