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Hypervalent Reactants

Cyclic Diaryl λ^3-Bromanes as a Precursor for Regiodivergent Alkynylation Reactions

Maxime De Abreu, Torben Rogge, Matteo Lanzi, Tomas J. Saiegh, Kendall N. Houk, and Joanna Wencel-Delord**

Abstract: Regiodivergent reactions are a fascinating tool to rapidly access molecular diversity while using identical coupling partners. We have developed a new approach for regiodivergent synthesis using the dual character of hypervalent bromines. In addition to the recently reported reactivity of hypervalent bromines as aryne precursors, the first transition metal-catalyzed reaction is reported. Accordingly, the development of these two complementary transformations allows for the alteration of regioselectivity to furnish both *ortho*- and *meta*-substituted alkynylation products. Mechanistic and computational studies show how these selectivities are controlled.

Rapid construction of molecular complexity under mild and sustainable conditions is one of the key challenges of modern synthetic chemistry. In this context, regiodivergent functionalization of molecules allowing the conversion of a set of substrates into different products depending on the reaction conditions is highly appealing and desirable (Figure 1a).[1,2] While the regiodivergency has been largely investigated in the case of addition reactions to unsaturated compounds or intermolecular cyclizations, coupling type reactions delivering regioisomeric products remain less developed. While the inherent reactivity of heterocyclic compounds facilitates selective functionalization of one or another position of a substrate by modifying either the ligand used or the entire catalytic system, achieving regioselectivity in the case of simple aromatics is clearly more challenging.[3,4] Catalyst-controlled regiodivergent arylation of naphthalene was reported by Sanford, while directed borylation reactions may also occur either in *ortho*- or *meta*-position with respect to a coordinating group, following the choice of a ligand.[5,6] Interestingly, the reaction medium may also clearly impact the selectivity of the reaction, as illustrated by Yin and Liu (Figure 1b).[7,8]

New, sustainable, and mild protocols involving perfect regioselectivity switches are actively sought. Following this challenging goal, we report herein a regiodivergent alkynylation of biaryl compounds. This concept involves two types of reaction conditions, one metal-catalyzed and the other transition-metal-free. Recently, the chemistry of hypervalent bromines, and, in particular, cyclic diaryl λ^3-bromanes, has attracted significant attention.[9] Our group has developed a straightforward and efficient synthetic protocol to access a large panel of such compounds.[10] Subsequently, we have demonstrated that these compounds exhibit complementary reactivity to the corresponding largely explored cyclic diaryl λ^3-iodanes. Indeed, while diaryl λ^3-iodanes react smoothly in metal-catalyzed cross-couplings, undergoing fast oxidative addition into the carbon-iodine(III) bond and subsequent *ortho*-functionalization, the brominated congeners generate aryne intermediates, thus allowing unusual metal-free *meta*-functionalizations (Figure 1c).[11,12] Capitalizing on this observation, we explored whether it is possible to finely tune the reactivity of cyclic diaryl λ^3-bromanes, thus promoting both metal-catalyzed *ortho*-functionalization or/and metal-free *meta*-selective coupling while using the same coupling partner. Notably, while *ortho*-functionalization of cyclic diaryl λ^3-iodanes with N-, O-, S- and P-coupling partners is well demonstrated, alkynylation of these compounds remains exceedingly challenging and limited by the high catalytic loading of Pd-catalyst or/and need of a directing group.[13,14] Aiming at overcoming this limitation, assembling rare *ortho*-halogenated biaryl alkynes and exploring the possibility of a truly efficient regioselectivity switch, we embarked on investigating the reactivity of cyclic diaryl λ^3-bromanes with alkynes. Herein, we report that fully controlled *ortho*- and *meta*-selective functionalization of hypervalent bromines is possible, owing to the perfect control of the distinct mechanisms of both transformations, i.e., oxidative addition vs. aryne chemistry (Figure 1d). Importantly, this work illustrates the previously unrevealed potential of the cyclic diaryl λ^3-bromanes to undergo Pd-catalyzed cross-coupling reactions with ultra-low catalyst

[*] Dr. M. De Abreu, Dr. M. Lanzi, Dr. T. J. Saiegh, Prof. Dr. J. Wencel-Delord
Laboratoire d'Innovation Moléculaire et Applications (UMR CNRS 7042), Université de Strasbourg/Université de Haute Alsace, ECPM
25 rue Becquerel, 67087 Strasbourg (France)
E-mail: joanna.wencel-delord@uni-wuerzburg.de
Dr. T. Rogge, Prof. Dr. K. N. Houk
Department of Chemistry and Biochemistry, University of California Los Angeles, California 90095-1569 (USA)
E-mail: houk@chem.ucla.edu
Prof. Dr. J. Wencel-Delord
Institute of Organic Chemistry, JMU Würzburg
Am Hubland, Würzburg, Germany

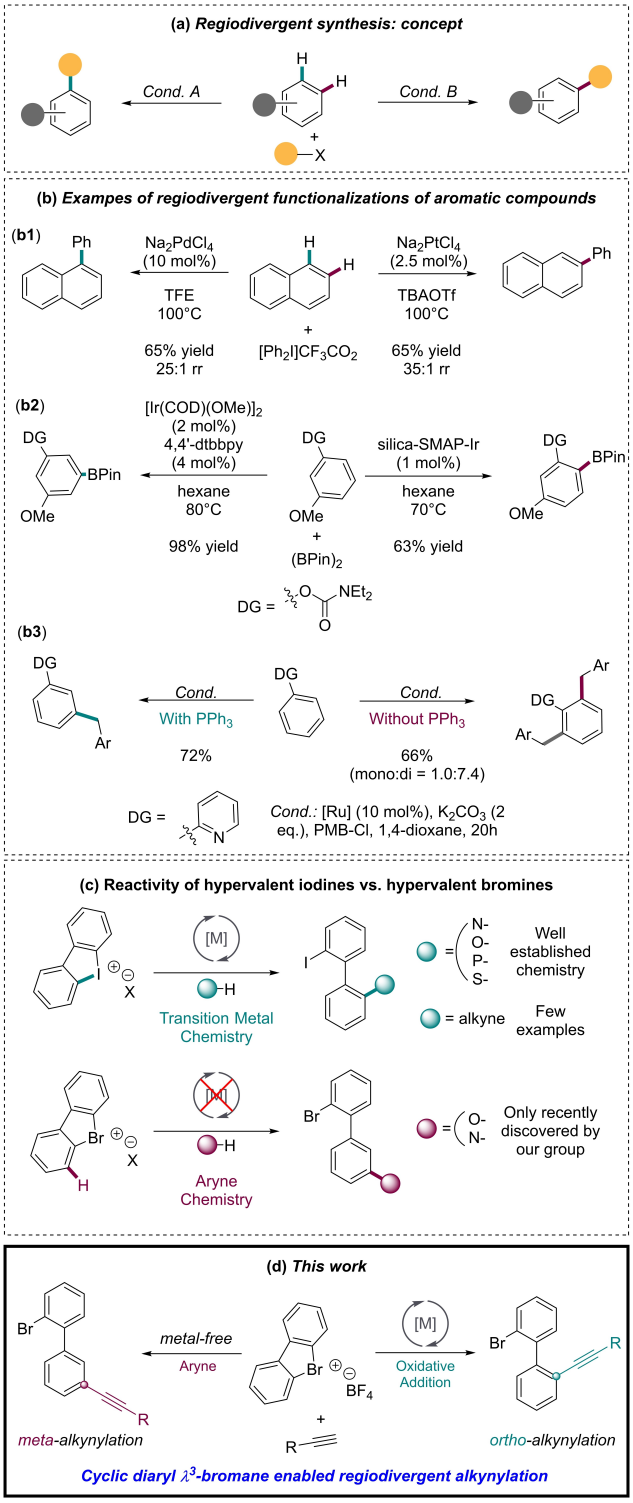
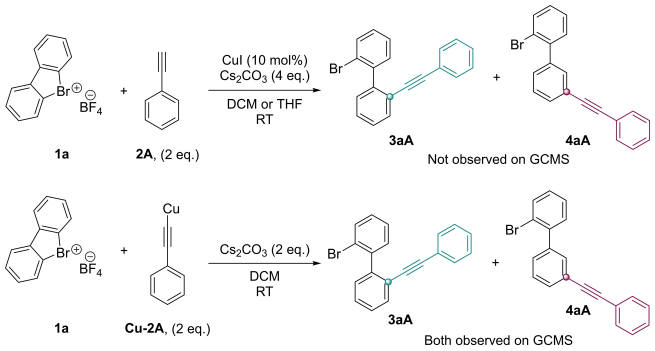


Figure 1. Rapid construction of molecular complexity via regiodivergent reactions.

loading, thus highlighting their superiority with respect to the corresponding diaryl λ^3-iodanes.

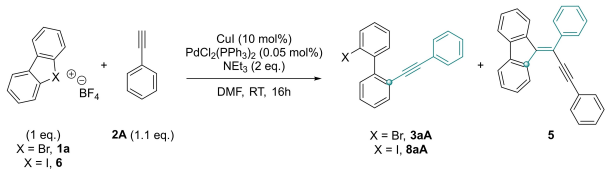
To initiate the exploration of the targeted alkynylation reaction, diaryl λ^3-bromane **1a** was reacted with phenylacetylene **2A** in the presence of a catalytic amount of Cu-catalyst and 4 equivalents of Cs_2CO_3, the key base required to generate the expected aryne intermediate (Scheme 1). However, the coupling reaction was not observed either in dichloromethane (DCM) or in tetrahydrofuran (THF). In contrast, some reactivity could be witnessed while using copper-phenylacetylide as the coupling partner, but both *ortho*- and *meta*-functionalizations occurred (**3aA** and **4aA**, respectively). This preliminary result, although disappointing in terms of efficiency, demonstrated that the desired regioselective *ortho*- and *meta*-alkynylations might be accessible under finely tuned reaction conditions.

In order to enhance the regioselectivity towards *ortho*-coupling, the addition of a Pd-catalyst with low catalyst loading was explored. Delightfully, in the presence of an ultra-low Pd-loading, the desired alkynylation occurred smoothly and fully selectively, providing the *ortho*-product **3aA** in 75 % yield, together with a side product **5** (Table 1, entry 1). The latter is the result of the reaction of the hypervalent bromine with 2 equivalents of alkyne.[15] Optimization of the reaction conditions (for additional information, see SI) revealed that the presence of the Pd-catalyst is critical for this reaction and that dimethylformamide (DMF) is the optimal solvent (Table 1, entries 3 and 4).



Scheme 1. Preliminary phenylethynylation experiments.

Table 1: Selected optimization reactions for the *ortho*-alkynylation.



Entry	Deviation from the standard conditions[a]	Yield **3aA**/**5**[b]
1	None	75 %/12 %
2	With diaryl λ^3-iodane **6** instead of **1a**	9 % (**8aA**)/9 %
3	No $PdCl_2(PPh_3)_2$	–/–
4	With MeCN instead of DMF	Traces/–
5	With $Pd(OAc)_2$ instead of $PdCl_2(PPh_3)_2$	55 %/9 %
6	With $Pd(PPh_3)_4$ instead of $PdCl_2(PPh_3)_2$	59 %/12 %

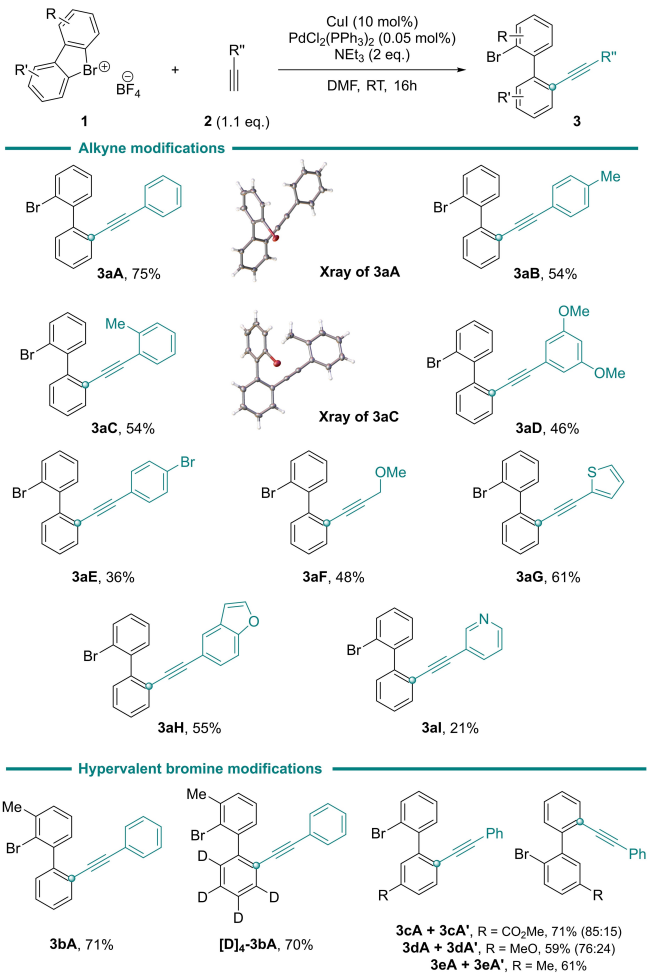
[a] Optimized standard conditions: Hypervalent species 0.2 mmol, CuI 0.02 mmol, $PdCl_2(PPh_3)_2$ 0.0001 mmol, NEt_3 0.4 mmol, phenylacetylene 0.22 mmol, DMF 4 mL at room temperature for 16 h. [b] Isolated yields.

Moreover, the best yield was obtained while using $PdCl_2(PPh_3)_2$ catalyst since other Pd-catalysts ($Pd(OAc)_2$ and $Pd(PPh_3)_4$) led to lower isolated yields (Table 1, entries 5 and 6 respectively). Importantly, the unique character of the hypervalent bromine **1a** was demonstrated while challenging this alkynylation reaction with another hypervalent congener, cyclic diaryl λ^3-iodane **6**. Despite the fact that the reactivity of diaryl λ^3-iodanes in metal-catalyzed cross-couplings has been extensively investigated over the last years, the established protocol failed and the biaryl-iodo-alkyne **8aA** was afforded in only 9% yield together with the dialkynylation side product **5** (Table 1, entry 2). The superiority of the hypervalent bromine with respect to hypervalent iodine may arise from the subdued reactivity preventing the second alkynylation of the biaryl product at the C–Br position that cannot be avoided in the case of the iodinated product **8aA**. With the optimized reaction conditions in hand, the scope of this fully selective *ortho*-functionalization was assessed (Scheme 2). Various aryl acetylene coupling partners could be used, bearing both electron-donating groups such as 4-tolyl, 2-tolyl, and 3,5-dimethoxyphenyl (**3aB**, **3aC** and **3aD**, respectively) and electron-withdrawing substituents such as 4-bromophenyl **3aE**. Encouragingly, a non-aromatic alkyne coupling partner could also be employed, as illustrated by the synthesis of **3aF** in 48% yield.

This reactivity was further expanded towards S-, O- and N-heterocyclic alkyne derivatives, furnishing **3aG**, **3aH**, and **3aI** in synthetically useful yields. Dissymmetrical bromanes turned out to also be potent substrates. Fully regioselective coupling took place for 3-methyl substituted hypervalent bromines, delivering **3bA** and $[D]_4$-**3bA** as single products in very good yields. In contrast, the regioselectivity control was more challenging in the case of dissymmetrical substrates, affording the mixtures of regioisomers **3cA**+**3cA'**, **3dA**+**3dA'** and **3eA**+**3eA'** in good yields.

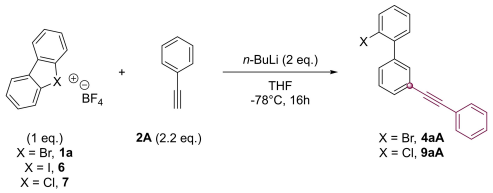
To further explore the reactivity of bromanes with alkynes, we have focused our study on *meta*-selective functionalization. Drawing inspiration from our recent work on bromine(III)-compounds, we hypothesized that the generation of the aryne intermediate should warrant the desired *meta*-selective functionalization. Although the initial attempts with Cs_2CO_3 failed, the desired alkynylation was observed using *n*-BuLi at low temperatures, delivering the expected *meta*-alkynylated biaryl **4aA** in 77% yield (Table 2, entry 1). Further optimization clearly indicated the highest efficiency of this system in THF while increased temperature had a negative impact on the reaction outcome (Table 2, entries 2 and 3). Moreover, *s*-BuLi appeared to be suitable for this reaction although delivering the desired product with a slightly lower 68% yield (Table 2, entry 4).

Remarkably, no product formation was observed while using iodine(III)-congener, while chlorinated congener **7** furnished the expected compound in a decreased yet still synthetically useful 44% yield (Table 2, entries 5 and 6). The lack of reactivity of the cyclic diaryl λ^3-iodane **6** could be explained by the higher activation free energy associated with the aryne formation compared to the cyclic diaryl λ^3-bromane **1a** and chlorane **7**.[16] Finally, a lower excess of alkyne and *n*-Buli (Table 2, entry 7) proved to be detrimental to the reaction, leading to the formation of the desired



Scheme 2. Scope of *ortho*-alkynylation.

Table 2: Selected optimization reactions for the *meta*-alkynylation.



Entry	Deviation from standard conditions[a]	Yield **4aA**[b]
1	None	77%
2	Et_2O instead of THF	-
3	−40 °C instead of −78 °C	44%
4	*s*-BuLi instead of *n*-BuLi	68%
5	With diaryl λ^3-iodane **6** instead of **1a**	–
6	With diaryl λ^3-chlorane **7** instead of **1a**	44% (**9aA**)
7	With 1.5 eq. of **2A** and *n*-BuLi	63%

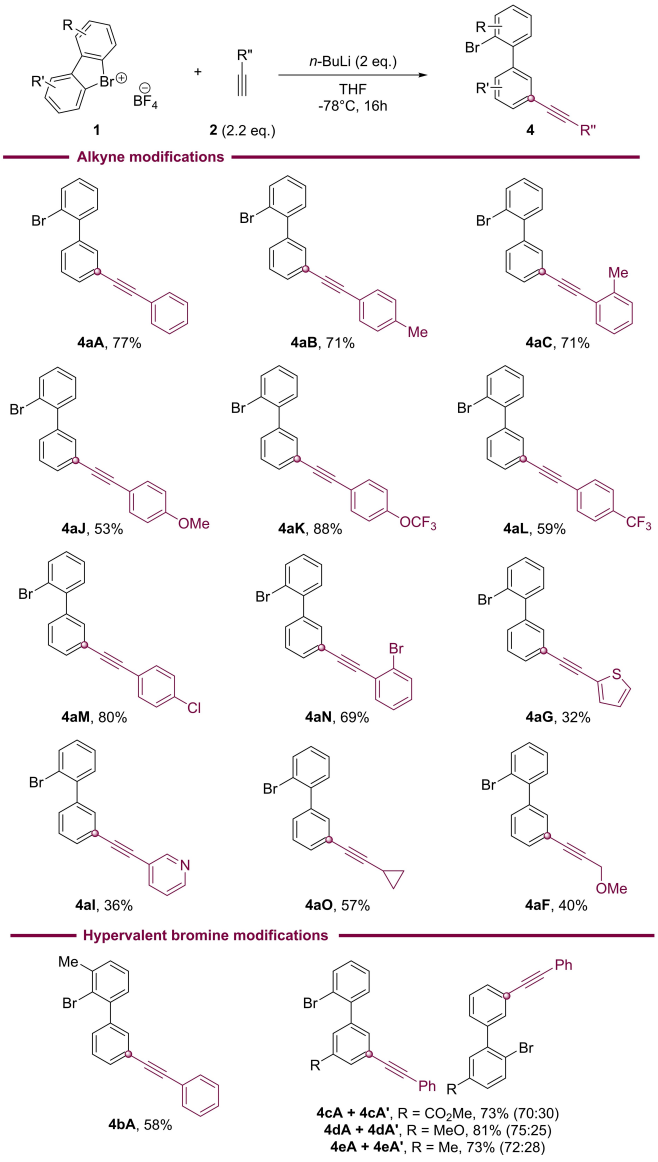
[a] Optimized standard conditions: Hypervalent species 0.2 mmol, *n*-BuLi 0.4 mmol, phenylacetylene 0.44 mmol, THF 3 mL at −78 °C for 16 h. [b] Isolated yields.

product in a 63 % yield and confirming the importance of an excess of both the alkyne and the base in this reaction.

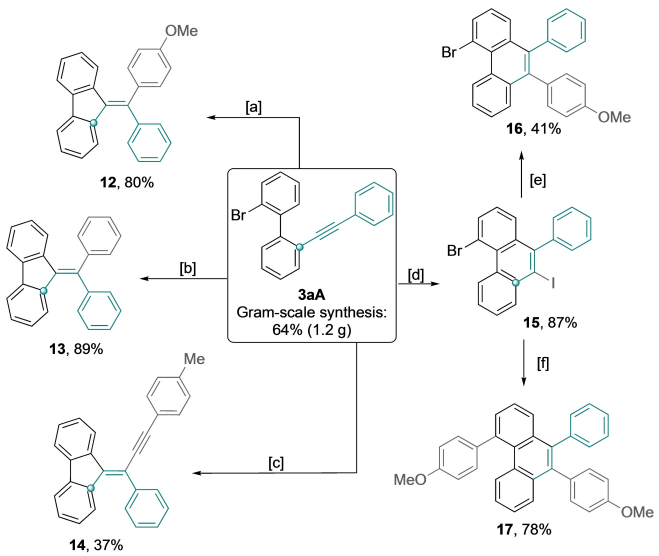
The study of the reaction scope revealed good tolerance towards various aryl-alkynes, bearing both electron-donating and electron-withdrawing groups (Scheme 3). *Ortho*- and *para*-methyl substituents on the alkynes do not hamper the reaction, as **4aB** and **4aC** were afforded an identical 71 % yield. The reaction tolerated an electron-donating group such as *p*-MeO (**4aJ**) with a 53 % yield. Alkynes bearing fluorinated motifs, such as $-OCF_3$ and $-CF_3$ groups, important moieties in medicinal chemistry, performed well under standard reaction conditions.[17] Indeed, *p*-CF_3 substituted product (**4aL**) was furnished in a 59 % yield, whereas a *p*-OCF_3 (**4aK**) substituent led to a very good 88 % yield.

Interestingly, despite the use of *n*-BuLi, halogenated aryl-alkynes performed well, delivering **4aM** and **4aN** in 80 % and 69 % yields. Heterocyclic alkynes (**4aG** and **4aI**) as well as aliphatic alkynes (**4aO** and **4aF**) also showed their reactivity in this metal-free C–C coupling with moderate yields. 3-methyl-substituted hypervalent bromine furnished a single product **4bA** in a 58 % yield while mixtures of two regioisomers were obtained when dissymmetrical bromanes were used although with high yields (**4cA**+**4cA'**, **4dA**+**4dA'**, **4eA**+**4eA'**).

Both reactions could be adapted to the gram-scale without major operational changes.[18] Thus, obtained brominated biaryl alkynes can now be considered interesting building blocks to rapidly access molecular complexity. Indeed, thanks to the mild reaction conditions, the resulting *ortho*- and *meta*-substituted biaryl scaffolds preserve the unaltered C(sp^2)-Br bond, a reactive site for a diversity of post-functionalizations (Scheme 4). Starting from **3aA**, standard Pd-catalyzed cross-coupling reactions, such as a Suzuki coupling, may be performed. In that case, intramolecular carbopalladation occurs first, followed by the arylation reaction, affording **12** in a high 80 % yield and **13** in a very high 89 % yield. Similarly, coupling with alkynes occurs via an oxidative addition of the Pd catalyst into the C–Br bond, followed by its intramolecular insertion in the nearby triple bond leading to an alkenyl-Pd intermediate. The latter reacted with the copper acetylide, affording the dibenzofulvene derivative **14** with a medium 37 % yield. Besides, **3aA** is also a suitable substrate for ICl-induced cyclization thus leading to iodo-bromo-derivative **15** in excellent 87 % yield. Taking advantage of the presence of



Scheme 3. Scope of *meta*-alkynylation.

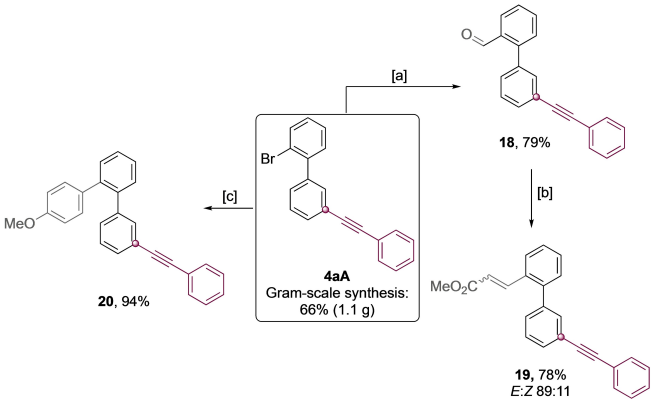


Scheme 4. Post-functionalization reactions of the *ortho*-alkynylated product **3aA**. [a] $Pd(PPh_3)_4$ (3 mol %), K_2CO_3 (10 eq.), 4-CH_3O-$C_6H_4B(OH)_2$ (4 eq.). Toluene/H_2O/EtOH (4 : 1 : 1), 120 °C, overnight; [b] $Pd(PPh_3)_4$ (10 mol %), Cs_2CO_3 (1.9 eq.), $C_6H_5B(OH)_2$ (1.5 eq.), EtOH, 70 °C, 8 h; [c] $PdCl_2(PPh_3)_2$ (4 mol %), CuI (2.5 mol %), 4-Ethynyltoluene (1.2 eq.), NEt_3, 50 °C, 16 h; [d] ICl (1.2 eq.), DCM, −78 °C, 1h; [e] $Pd(PPh_3)_4$ (10 mol %), 4-CH_3O-$C_6H_4B(OH)_2$ (1 eq.), K_2CO_3 (10 eq.), Toluene/H_2O/EtOH (4 : 1 : 1), 120 °C, 24 h; [f] $Pd(PPh_3)_4$ (10 mol %), 4-CH_3O-$C_6H_4B(OH)_2$ (2 eq.), K_2CO_3 (10 eq.), Toluene/H_2O/EtOH (4 : 1 : 1), 120 °C, 24 h.

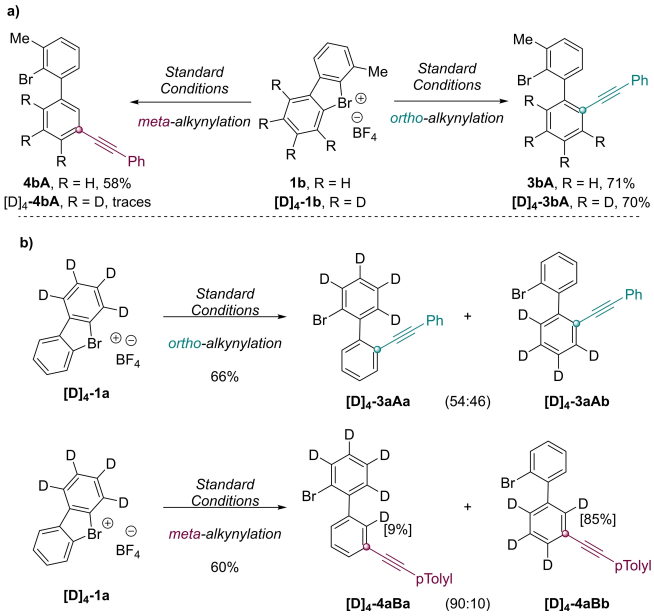
two chemically different halogens, a two-step Suzuki coupling was achieved aiming at the synthesis of functional polycyclic aromatic compounds **16** and **17**.

While considering *meta*-substituted product **4aA**, alternative reactivity could be reached (Scheme 5). Due to the greater distance between the C–Br bond and the alkyne in the *meta*-substituted biaryl, the transformation of the C–Br into an aldehyde via lithium-halogen exchange was possible. This step led to intermediate **18** with a high 79 % yield. The latter was then subjected to a Wittig reaction, affording compound **19** with a high 78 % yield. In parallel, a Suzuki coupling was also possible, leading to compound **20** with an almost quantitative yield.

Subsequently, mechanistic studies were conducted to shed light on these transformations. Deuterated bromane



Scheme 5. Post-functionalization reactions of the *meta*-alkynylated product **4 aA**. [a] *n*BuLi (2 eq.), DMF (10 eq.), THF, −78 °C to RT, 2.5h; [b] methyl (triphenylphosphoranylidene)acetate (1.5 eq.), DCM, RT, 48 h; [c] $Pd(PPh_3)_4$ (3 mol %), K_2CO_3 (10 eq.), 4-CH_3O-$C_6H_4B(OH)_2$ (4 eq.), Toluene/H_2O/EtOH 4:1:1, 120 °C, overnight.



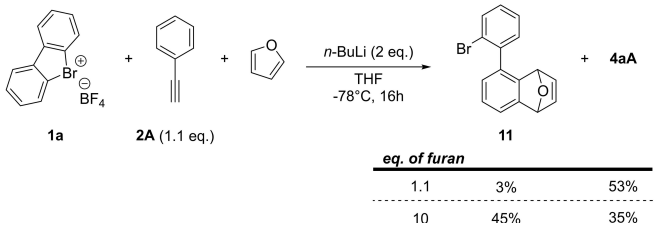
Scheme 6. Mechanistic investigation experiments.

$[D]_4$-**1b** was thus reacted with alkyne **2A** under both *ortho*- and *meta*-selective conditions (Scheme 6a). Not surprisingly, comparable reactivity of **1b** and $[D]_4$-**1b** was observed while targeting *ortho*-functionalization, indicating that the key step of this reaction implies oxidative addition of Pd into the carbon-bromine(III) bond. In clear contrast, in the presence of *n*-BuLi, deuterated $[D]_4$-**1b** was totally inactive whereas its protonated congener **1b** furnished the *meta*-functionalized product **4bA**.[19] This experiment unambiguously illustrates that the *meta*-deprotonation of **1b** is the rate-determining step, clearly supporting the aryne-type pathway. Besides, when using $[D]_4$-**1a** as a substrate, functionalization of either protonated or deuterated rings may be envisaged. Not surprisingly, when using the *ortho*-alkynylation reaction conditions, both products $[D]_4$-**3aAa** and $[D]_4$-**3aAb** were obtained in a comparable ratio. However, when subjecting $[D]_4$-**1a** to the *meta*-alkynylation reaction conditions, two compounds $[D]_4$-**4aBa** and $[D]_4$-**4aBb** were obtained in very distinct ratio (90:10). This result suggests a preference for the functionalization of the protonated aromatic side of $[D]_4$-**1a** and evidence a kinetic isotope effect (KIE) of 9 (Scheme 6b).

Another proof of that hypothesized aryne pathway lies in the successful reaction of the hypervalent bromine with furan, yielding the desired [4+2] cycloaddition product **11** (Scheme 7).

In addition, computational studies with density functional theory (DFT) were performed to explore the key oxidative addition step of the Sonogashira–Hagihara alkynylation of bromane **1a** with $Pd(PMe_3)_4$ as a model catalyst. Calculations at the ωB97X-D/def2-TZVP + SMD(DMF)//TPSS-D3(BJ)/def2-SVP level of theory revealed an oxidative addition via transition state **TS1** with an activation free energy of only 16.1 kcal mol^{-1}, thus supporting a fast reaction at room temperature (Figure 2a).[20,21] Interestingly, when we replaced the hypervalent bromine with a simple bromophenyl substrate, the energy barrier for the oxidative addition increased significantly to 27.9 kcal mol^{-1}, clearly illustrating the key importance of the hypervalent character of the Br-substituent (see Figure S-1 in the SI).

Upon reaction with alkyllithium base, aryne formation was found to take place in a facile concerted deprotonation/C–Br bond cleavage process *via* transition state **TS2** (Figure 2b). In contrast to previous studies on aryne formation by deprotonation of cyclic hypervalent X(III) reagents with carbonate base, which proceeds via a seven-membered cyclic transition state,[15] deprotonations with *in situ*-generated lithium phenylacetylide occur through an acyclic transition



Scheme 7. Cycloaddition with furan – proof of aryne formation.

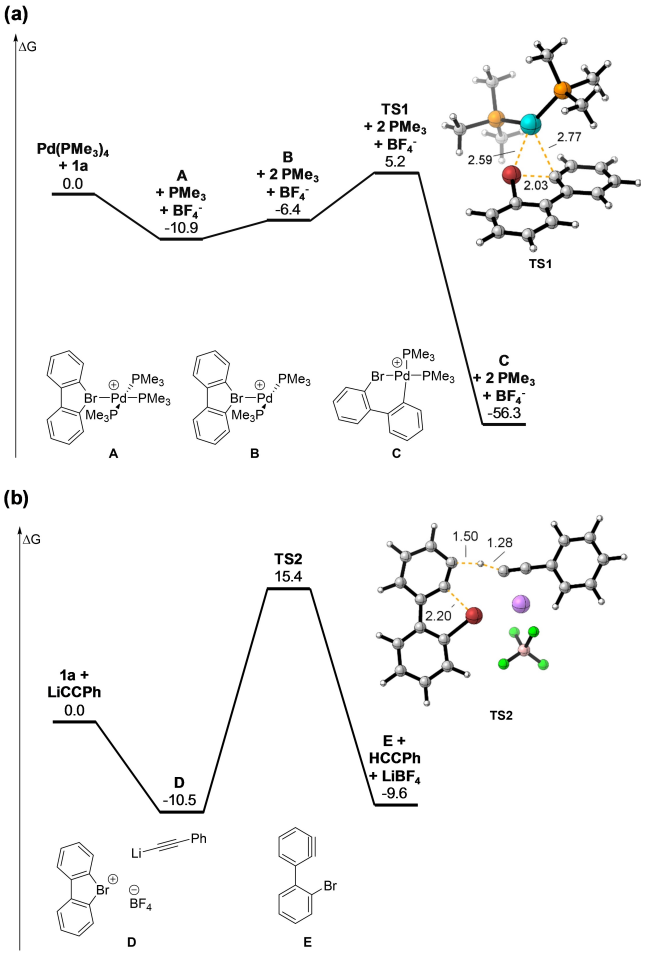


Figure 2. Calculated energy diagram (in kcal mol^{-1}) for (a) the oxidative addition of bromane **1a** to palladium and (b) aryne formation by deprotonation of **1a** with LiCCPh. Distances are given in Å.

state with an activation free energy of 25.9 kcal mol^{-1}. Organolithiums are generally aggregated, and the exact nature of these aggregates, especially in the current case where the cationic bromane could also be incorporated into the aggregate, makes exact modeling of the deprotonation process difficult. In some deprotonations by organolithiums, the rate-determining step has been found to be the disaggregation of a tetramer.[22]

In conclusion, the divergent character of cyclic diaryl λ^3-bromanes has been demonstrated. These compounds are not only unique aryne precursors, but their high reactivity towards palladium catalyst was established. Due to this complementary reactivity, regiodivergent alkynylation reactions furnishing selectively both *ortho*- and *meta*-substituted products were achieved. Such a regiodivergent synthesis combined with the highly modular character of the newly accessed products enables easy and rapid access to molecular diversity starting from a single substrate. Importantly, both reactions illustrate the unparalleled reactivity of hypervalent bromines, clearly exceeding largely explored hypervalent iodines. Experimental mechanistic studies combined with DFT calculations establish the mechanism of both metal-catalyzed and metal-free reactions.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: hypervalent bromine · λ^3-bromane · regiodivergent alkynylation · metal-free alkynylation · biaryl-alkyne

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