Cyclic Diaryl λ3-Bromanes: A Rapid Access to Molecular Complexity via Cycloaddition Reactions

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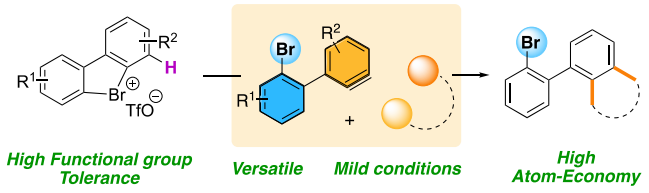
Supporting Information Placeholder



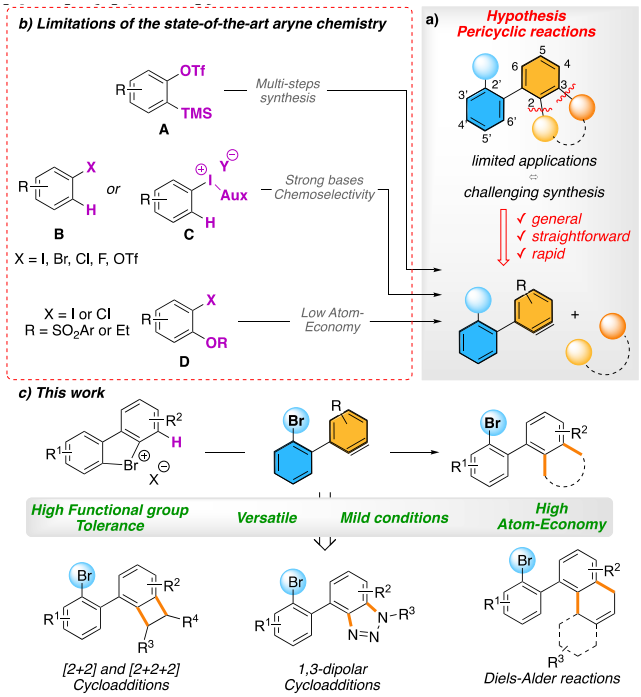
ABSTRACT: Biaryls have widespread applications in organic synthesis. However, sequentially polysubstituted biaryls are underdeveloped due to their challenging preparation. Herein, we report the synthesis of unsymmetric 2,3,2',3',4-substituted biaryls *via* pericyclic reactions of cyclic diaryl λ^3-bromanes. The functional groups tolerance and atom economy allow access to molecular complexity in a single reaction step. Continuous flow protocol has been designed for the scale-up of the reaction, while post-functionalizations have been developed taking advantage of the residual bromide.

The direct access to molecular complexity under sustainable, simple, and mild reaction conditions is a critical challenge of modern organic chemistry. Biaryl compounds are ubiquitous motifs in many fields of chemistry, including medicinal chemistry, agrochemistry, material science, and ligand design. A straightforward synthesis of highly decorated biaryls thus remains an important challenge. [1] In particular, dissymmetrical 2,3,2',3',4-substituted biaryls are poorly explored motifs due to the arduous synthesis *via* standard cross-coupling reactions which require densely decorated precursors. Albeit scarcely investigated, a general and straightforward alternative approach based on a modular functionalization *via* pericyclic reactions of a finely designed biaryl benzyne precursor represents an attractive solution to this synthetic issue (Scheme 1a). [2] However, multiple drawbacks hamper the state-of-the-art of the aryne-based approach (Scheme 1b): 1) lengthy synthetic routes for the preparation of aryne precursors; 2) the limited atom economy resulting from the aryne generation with the removal of leaving groups (-OTf and -TMS; -X and -OR; Aux-I) which translate into significant waste formation and 3) the limited functional group tolerance as the base- and fluorine-sensitive moieties are generally incompatible. [3-5] Accordingly, the implementation of the pericyclic reactions to rapidly access dissymmetrical 2,3,2',3',4'-substituted biaryls diversity requests design of original biaryl aryne precursors, activated under mild reaction conditions and in presence of a weak base.

Despite being known since the 19th century and albeit their unique reactivity, hypervalent bromane (III) reagents have received much less attention compared to the corresponding iodine compounds. [6]

The lack of general and simple synthetic routes deliver-

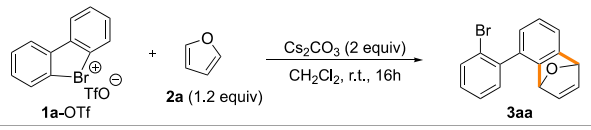
Scheme 1: a) Common aryne precursors; b) Aryne strategy to *ortho*-, *ortho*-, *meta*- substituted biaryls, c) Cyclic diaryl λ^3-bromanes as aryne precursors in pericyclic approach towards *ortho*-, *ortho*-, *meta*- substituted



ing these unique scaffolds has drastically hampered the development of bromane (III) chemistry, [7] and thus the rare advances in this field have been reported only recently. [8] Our group has latterly established a simple, safe, and scalable protocol for the preparation of cyclic diaryl λ³-bromanes in good to excellent yields. [9] The superior electron-withdrawing effect and the nucleofugality of hypervalent bromane (III) compared to the iodine (III) counterpart (approximately 10^6 times higher), confer them a complementary reactivity. [10] Encouraged by the disclosed reactivity of cyclic diaryl λ³-bromanes towards the construction of carbon-oxygen and carbon-nitrogen bonds, we speculate that they could represent a new family of biaryl coupling partners for pericyclic reactions (Scheme 1c). Moreover, cyclic hypervalent λ³-bromane products carry a residual functional bromine atom which opens additional perspectives for further post-functionalizations, while warranting excellent atom economy of the overall process. Thus unique reactivity provides a new strategy for the synthesis of valuable and unprecedented highly decorated dissymmetric 2,3,2',3',4'-substituted biaryls, helicenes [11] and four consequently substituted aromatic units. [4e,12]

Our investigation begun by studying the reaction between the well-known cyclic diaryl λ³-iodanes and furan **2a** (Table 1, entry 2), but no product formation was observed neither by **GC-MS** nor **¹HNMR** (see Supporting Information). Remarkably, while using cyclic diaryl λ³-bromane **1a**-OTf and **2a**, in a presence of cesium carbonate and DCM, the desired product **3aa** was afforded in 92% yield after 16 hours at room temperature (entry 1), unambiguously illustrating the unique reactivity of these reagents.

Table 1. Optimization of the Diels-Alder Reaction with cyclic diaryl hypervalent bromanes[a]

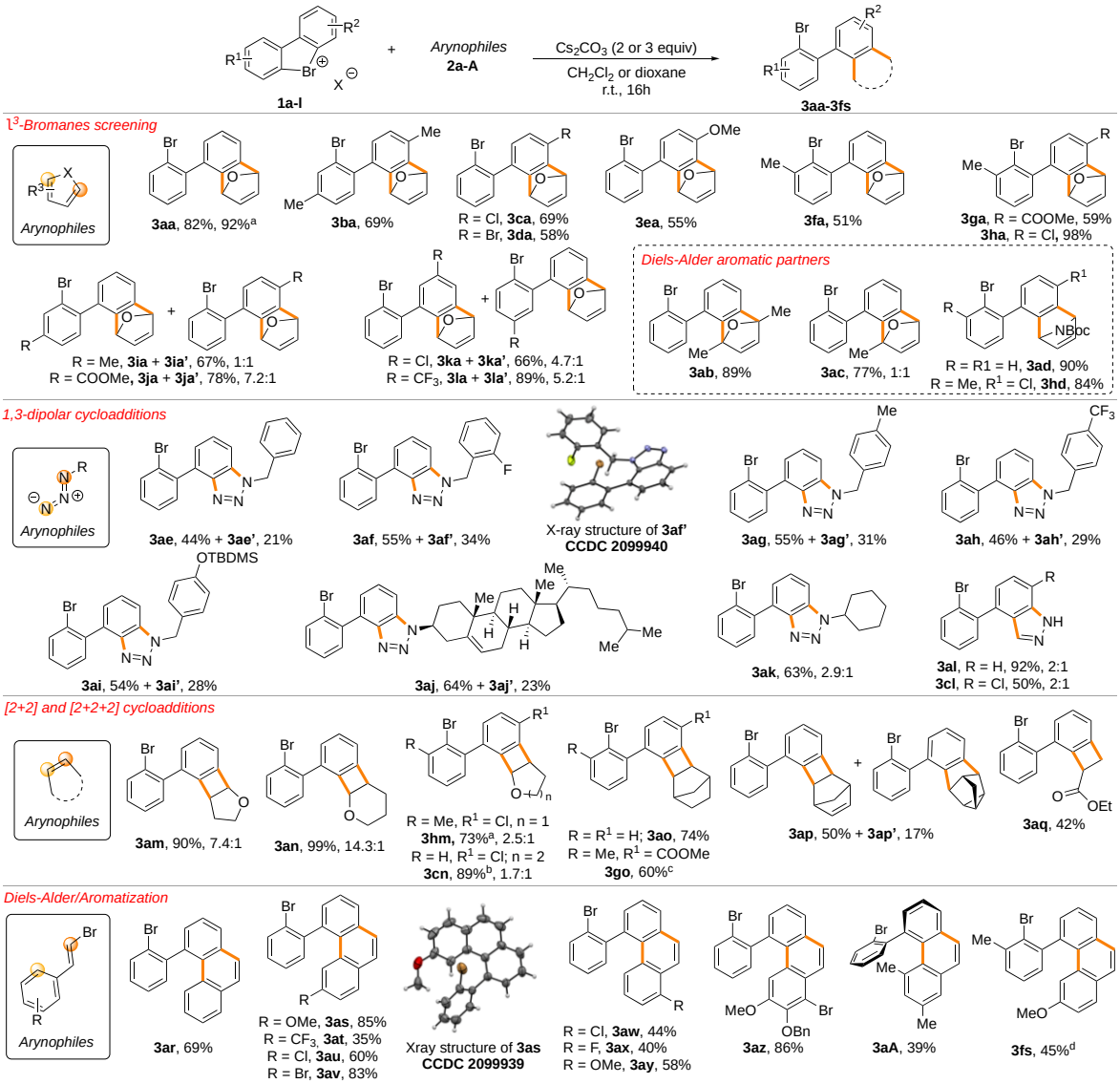


entry	deviation from standard conditions	yield (%)[b]
1	none	92%[c]
2	λ³-**I**-OTf/-OMs instead of **1a**-OTf	-[d]
3	no Cs_2CO_3	-[d]
4	*t*BuONa / K_2CO_3 instead to Cs_2CO_3	59% / 23%
5	CH_3CN / H_2O instead to CH_2Cl_2	69% / 13%

[a] Reaction conditions: λ³-**X**-Y (0.1 mmol), furan (1.2 equiv), r.t. 16h; [b] **¹HNMR** yields using CH_2Br_2 as internal standard; [c] Isolated yield; [d] 5 equiv furan.

No reactivity was observed in the absence of Cs_2CO_3 (entry 3). Further investigation showed that the nature of the base holds a key role. Despite being a stronger base, *t*BuONa provided **3aa** in lower yield, while K_2CO_3 performed poorly (entry 4). Finally, the role of a chlorinated polar solvent, namely CH_2Cl_2, was confirmed (entry 5). Surprising, albeit in low yield, the reaction occurred in water media. [13] With the optimal reaction conditions in hand, the scope of this cycloaddition was explored, focusing on various cyclic diaryl λ³-bromanes **1a-l** and aromatic cyclic Diels-Alder partners **2b-2d** (Scheme 2). The symmetric bromane **1b**, presenting inductive electron-donating methyl groups provided the desired product **3ba** in good yield (69%). Regioselective functionalizations took place in presence of asymmetric substrates, such as **1c**, **1d**, and **1e**, where the enhanced reactivity of one aryl moieties translated into the formation of a unique products in good yields. The introduction of the methyl group in *ortho*-position directs the desired transformation onto one aromatic ring, thus promoting the formation of **3fa** in moderate yield (51%). Bifunctional dissymmetric λ³-bromanes bearing methyl ester and chlorine afforded **3ga** and **3ha** in 59% and 98% yields respectively. Finally, monosubstituted cyclic diaryl λ³-bromanes were tested. A weak electron-donating methyl group, **1i**, unsurprisingly leads to a 1:1 mixture of products **3ia** and **3ia'**, while the enhanced electron-withdrawing character of methyl ester **1j**, chloro **1k** and trifluoromethyl **1l** enabled the preferential formation of one regioisomer with good selectivity. Moreover, substituted furans, **2b** and **2c** and N-protected pyrrole **2d** were well tolerated under our reaction conditions, affording the desired products in good yields. Moreover, the dissymmetric bromane **1h** reacted smoothly with **2d** offering the highly functionalized bromo, chloro cycloadduct **3hd** in 84% yield. Targeting a rapid generation of a broad range of diverse molecules, we have challenged the λ³-bromanes with other arynophiles. Various azides have been successfully coupled with **1a**-OTf, furnishing highly decorated bromo benzotriazole derivatives. Simple benzyl azides **2e** and substituted **2f** – **2i** supplied the desired regioisomeric **3** and **3'** in moderate to good yields, which were straightforwardly separated *via* column providing the pure products. The single-crystal X-ray analysis of **3af'** confirmed the triazole structure and the regioselectivity. Remarkably, thanks to the fluorine-free conditions, the silyl-protected phenols **3ai** and **3ai'** could be obtained in excellent yields, highlighting the complementarity of this protocol. The cholesterol-de derived **2j** and the cyclohexyl azide **2k** react smoothly under the standard reaction conditions. Diazomethane **2l** ($TMSCHN_2$) also proved to be an excellent arynophile, yielding **3al** and **3cl** in 92% and 50% yields respectively, albeit as a mixture of two cycloadducts. In accordance with the aryne distorted and steric models, a moderate regiocontrol has been observed in the 1,3-dipolar cycloaddition where the nucleophilic nitrogen reacts with the more distorted alkyne terminus position furnishing the less steric demanding product as major isomer. [14] While Diels-Alder reactions involving aryne have been largely investigated, [15] the [2+2] reactions have received much less attention despite the interest of the resulting peculiar structures. [16] Rewardingly, the reaction of **1a**-OTf with 2,3-dihydrofuran **2m** and 2,3-dihydropyran **2n** conducted to the selective formation of **3am** and **3an** in excellent yields, furnishing a single regioisomer with a ratio up to 14.3:1. Moreover, strained cycloalkenes, namely norbornene **2o** and norbornadiene **2p**, provided the desired cyclobutene products **3ao** and **3ap** with good yields. Interestingly, an elusive [2+2+2] mechanism has been observed within **1a**-OTf and **2p** yielding the uncommon

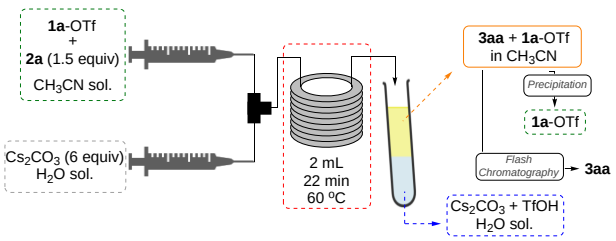
Scheme 3: Scope of the reaction



3ap' in 17% yield. The acrylate **2q** showed sufficient reactivity under our reaction conditions. Asymmetric λ³-bromanes **1h**, **1c** and **1g** provided the highly decorated biaryls **3hm**, **3cn** and **3go** in excellent yields. Finally, structurally condensed polycyclic aromatic compounds, valuable motifs in material science, were targeted. We investigated the reaction of **1a**-OTf with the β-bromostyrenes **2r**. After a minor reoptimization of the reaction conditions, a cascade [4+2] cycloaddition/base-mediated aromatization occurred smoothly, at room temperature, in dioxane yielding the *endo*-product **3ar** as a single regioisomer. Electron-rich bromo styryls showed higher reactivity, delivering **3as** and **3ay** respectively in 85% and 58% yields. The single-crystal X-ray analysis of **3as** confirmed the formation of the *endo*-product. Electron withdrawing groups, such as trifluoromethyl, impact the reaction outcome, delivering **3at** in a decreased yield.

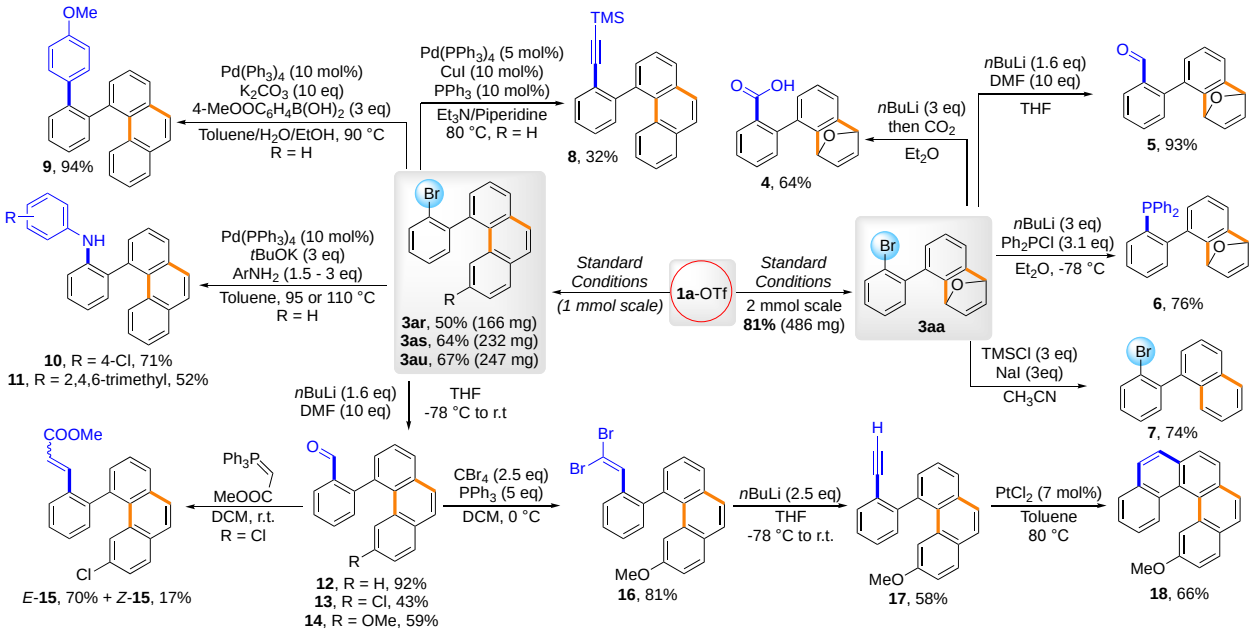
On the other hand, halogenated aromatic rings **2u**, **2v**, **2w** and **2x**, offered synthetically useful bifunctional products in moderate to high yields. The electron-rich, protected bromo caffeic acid derivative **2z** turned out to be suitable for the synthesis of highly decorated phenyl phenanthrene **3az**, providing a functional dibromo compound. Sterically demanding substrate **2A** furnished the conformationally stable atropoisomers **3aA**. Finally, when dissymmetric λ³-bromane **1f** was tested, a selective functionalization occurred, yielding **3fs**. Remarkably, the excellent regioselectivity reached in all of these cases, providing the sterically hindered *endo*-regioisomers as unique product, outcompetes the literature precedents. [17]

Scheme 2: Synthesis of 3aa via flow-chemistry approach



Encouraged by the high versatility observed using cyclic diaryl λ³-bromanes, we endeavored on developing a flow protocol for this reaction (Scheme 3). Despite clear advantageous of flow chemistry approach as scalability, safety

Scheme 4: Synthesis of functional biaryl compounds from 3aa, 3ar, 3as and 3au



and reduction of the reaction time, implementation of this process into the aryne chemistry remains rare and the chemically difficult. [18] The difficulty in our case lays in the use of insoluble Cs_2CO_3, however, attempts to replace it with organic bases failed. (see Supporting Information). Accordingly, the flow-reaction was performed in a biphasic system, which involved a water solution of Cs_2CO_3 and a solution of **1a**-OTf and **2a** in CH_3CN. The optimal flow-reaction conditions enabled the synthesis of 516 mg of **3aa** (66% yield) within 22 min of residence time at 60 °C. Interesting, the substrate **1a**-OTf is stable under these reaction conditions and the unreacted portion was recovered *via* precipitation with Et_2O from the reaction steam. The conspicuous reduction of the reaction time and the use of green solvents make this approach a suitable alternative to the batch protocol, especially for further reaction scale-up.

Beyond the mild reaction conditions for the aryne generation and the high functional group tolerance demonstrated, the cycloadduct products feature a bromine atom which can serve as an additional handle for the incorporation of molecular complexity (Scheme 4). Initially, the robustness of our procedures was confirmed by performing the reactions on 1 or 2 mmol scales, furnishing **3aa**, **3ar**, **3as** and **3au** in multi milligram scale. The functionalization of the **3aa** through lithium-mediated bromine exchange provided the corresponding carboxylic acid **4**, aldehyde **5**, and the new phosphine **6** in 64%, 93% and 76% yields respectively. Moreover, a standard deoxygenation protocol generated **7** in 74% yield. Also, bromo-biphenyl phenanthrenes **3ar, 3as** and **3au** are synthetically interesting scaffolds and the residual bromine enables access to highly adorned structures. Pd-catalyzed cross-couplings, such as Sonogashira and Suzuki reactions granted the introduction of alkyne **8** and aryl **9** moieties with useful yields. Furthermore, a Buchwald-Hartwig Pd-catalyzed couplings delivered **10** and the sterically challenging **11** diaryl amines, in good yields. A lithium exchange protocol using **3ar, 3as** and **3au**, led to the versatile aldehydes **12**, **13** and **14**. A subsequent Wittig reaction involving the aldehyde **13** provided the stereoisomers *E*-**15** and *Z*-**15** in good yield (70% + 17% respectively), which were easily separated by flash chromatography. To further illustrate the utility of the bromine moiety, the synthesis of screw-shaped helicene was envisioned. A standard Corey-Fuchs alkyne synthesis using the aldehyde **14** furnished **17**. Then, a Pt-catalyzed cyclization afforded the desired [5]-helicene **18** in 12% overall yield.

In conclusion, we demonstrated herein the peculiar versatility, chemoselectivity and atom economy of cyclic diaryl λ^3-bromanes as biaryl aryne precursors in cycloaddition reactions for the synthesis of highly decorated dissymmetric 2,3,2',3',4'-substituted biaryl motifs. The mild aryne generation conditions, namely carbonate base and room temperature, allowed a wide arynophiles compatibility, together with great functional group tolerance. Robustness of these aryne precursors guaranteed an efficient biphasic flow protocol for the pericyclic reaction further improving the sustainability. High molecular complexity *via* multiple C-C and C-N bonds formation was attained in a single reaction step, while subsequent functionalizations further expand access to a plethora of complex functional compounds.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, synthesis of reagents, copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

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Notes

The authors declare no conflict of interest.

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