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Cyclic Diaryl $\lambda^3$-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 $\lambda^3$-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. In particular, disymmetric 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). 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.

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.

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 $\lambda^3$-bromanes as aryne precursors in pericyclic approach towards ortho-, ortho-, meta- substituted

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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 λ,2-bromanes in good to excellent yields. 9 The superior electron-withdrawing effect and the nucleofugality of hypervalent bromane (III) compared to the iodide (III) counterpart (approximately 106 times higher), confer them a complementary reactivity. 10 Encouraged by the disclosed reactivity of cyclic diaryl λ,2-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 λ,2-bromanes 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 disymmetric 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 λ,2-iodanes and furan 2a (Table 1, entry 2), but no product formation was observed neither by GC-MS nor 1H NMR (see Supporting Information). Remarkably, while using cyclic diaryl λ,2-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**

<table>
<thead>
<tr>
<th>entry</th>
<th>deviation from standard conditions</th>
<th>yield (%)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>92%c</td>
</tr>
<tr>
<td>2</td>
<td>λ,2-OTf /OMs instead of 1a-OTf</td>
<td>d</td>
</tr>
<tr>
<td>3</td>
<td>no Cs2CO3</td>
<td>d</td>
</tr>
<tr>
<td>4</td>
<td>tBuONa / K2CO3 instead to Cs2CO3</td>
<td>59% /</td>
</tr>
<tr>
<td></td>
<td>CH3CN / H2O instead to CH2Cl2</td>
<td>69% /</td>
</tr>
</tbody>
</table>

* Reaction conditions: λ,2-X-Y (0.1 mmol), furan (1.2 equiv), r.t. 16h; b 1H NMR yields using CH3Br2 as internal standard; c Isolated yield; d 5 equiv furan.

No reactivity was observed in the absence of Cs2CO3 (entry 3). Further investigation showed that the nature of the base holds a key role. Despite being a stronger base, tBuONa provided 3aa in lower yield, while K2CO3 performed poorly (entry 4). Finally, the role of a chlorinated polar solvent, namely CH2Cl2, 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 λ,2-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 disymmetric λ,2-bromanes bearing methyl ester and chlorine afforded 3ga and 3ha in 59% and 98% yields respectively. Finally, mono-substituted cyclic diaryl λ,2-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 disymmetric 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 λ,2-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 regiosomeric 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 (TMSCN)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 alkyn terminus position furnishing the less steric demanding product as major isomer. 14 While Diels-Alder reactions involving arynes have been largely investigated, 15 the [2+2] reactions have received much less attention despite the interest of the resulting peculiar structures. 16 Remarkably, 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

![Diagram](image-url)
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 2x 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 a 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 advantages of flow chemistry approach as scalability, safety
and reduction of the reaction time, implementation of this process into the aryne chemistry remains rare and the chemically difficult. The difficulty in our case lays in the use of insoluble Cs$_2$CO$_3$, 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$_2$CO$_3$ and a solution of 1a-O Tf and 2a in CH$_3$CN. The optimal flow-reaction conditions enabled the synthesis of 516 mg of 3aa (66% yield) within 22 min of residence time at 60 °C. Interestingly, the substrate 1a-O Tf is stable under these reaction conditions and the unreacted portion was recovered via precipitation with EtOH 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, the 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 alkynyl 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 Pd-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 $\lambda^3$-bromanes as biaryl aryne precursors in cycloaddition reactions for the synthesis of highly decorated diisymmetric $2,3',2',3''$-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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Notes
The authors declare no conflict of interest.

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REFERENCES


