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Electrochemical Synthesis of Cyclic Biaryl λ³-Bromanes from 2,2’-Dibromobiphenyls

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Abstract

The remarkable nucleofugality of diarylbromonium species renders them particularly suitable for generation of arynes for subsequent use in a wide range of synthetic applications. The common approach to generate cyclic biaryl λ³-bromanes is based on thermal decomposition of hazardous diazonium salts. Herein, we disclose a mild and straightforward approach to diarylbromonium species by direct anodic oxidation of 2,2'-dibromo-1,1'-biphenyl. The electrochemical method provides an access to a range of symmetrically and non-symmetrically substituted cyclic biaryl λ³-bromanes in moderate yields.

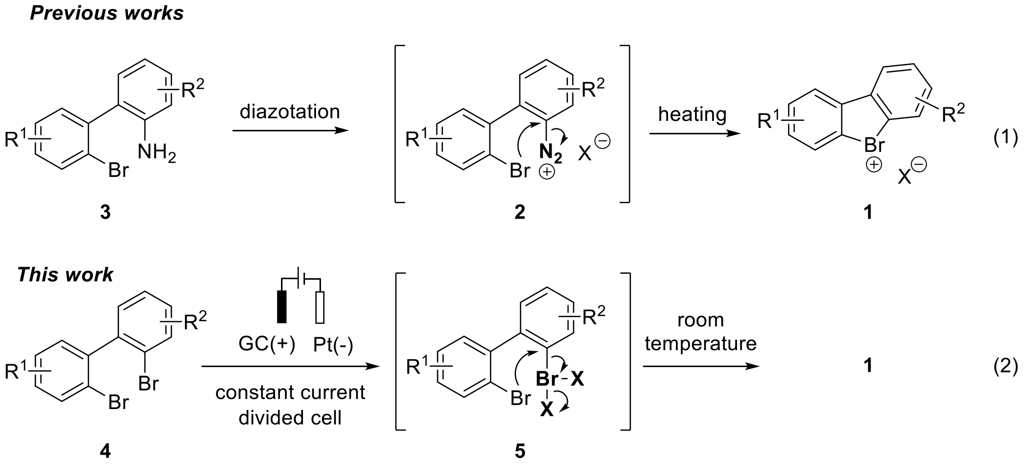
Keywords

Hypervalent bromine; electrochemistry; cyclic biaryl λ^3-bromane; anodic oxidation; cyclic voltammetry

Introduction

Chemistry of hypervalent bromine (III) species has experienced rapid advancements during the recent years [1, 2]. The remarkable nucleofugality of hypervalent bromine(III) has been exploited in the generation of arynes from cyclic diaryl λ^3-bromanes under remarkably mild conditions with subsequent applications of the *in-situ* generated arynes in cycloaddition reactions [3], *meta*-selective reactions with oxygen and nitrogen nucleophiles [4, 5], regiodivergent *meta* or *ortho*-alkynylations [6] and regioselective (di)halogenation [7]. In addition, cyclic diaryl λ^3-bromanes have been successfully employed as halogen-bonding organocatalysts in Michael addition [8] and their chiral variants were efficient in catalyzing enantioselective Mannich reactions or ketimines with cyanomethyl coumarins [9] and malonic esters [10]. These notable examples underscore the remarkable potential of cyclic diaryl λ^3-bromanes in the development of efficient synthetic transformations.

Cyclic diaryl λ^3-bromanes **1** are typically synthesized using a method developed by Sandin and Hay in 1952 that capitalizes on excellent nucleofugality of diazonium leaving group. Accordingly, pre-formed [11] or *in-situ* generated 2,2'-bromodiazonium salts **2** [12-14] furnish cyclic bromine(III) species **1** under thermal decomposition conditions (Scheme 1, eq 1). Diazonium intermediates **2** are obtained by diazotation of 2'-bromo-[1,1'-biphenyl]-2-amines **3** with sodium nitrite and an acid under aqueous conditions. Recently, Wencel-Delord and co-workers disclosed an improved protocol toward diazonium intermediates **2** under non-aqueous conditions (*tert*-BuONO and MsOH in acetonitrile) [4]. Nevertheless, the improved method still required thermal decomposition of diazonium salt to effect the cyclization. In the quest for mild (room temperature) and scalable conditions toward cyclic diaryl λ^3-bromanes **1** we realized that bromanyl moiety possesses comparable leaving group ability to that of diazonium moiety [1, 15]. Hence, the oxidation of 2,2'-dibromo-[1,1'-biphenyl] into mono-λ^3-bromane **5** would set the stage for the key cyclization event (Scheme 1, eq 2). We also reasoned that anodic oxidation of aryl bromide is perfectly suited for the generation of mono-λ^3-bromane **5** under mild conditions [16-18]. Herein we report on the development of electrochemical synthesis of cyclic diaryl λ^3-bromanes under anodic oxidation conditions.



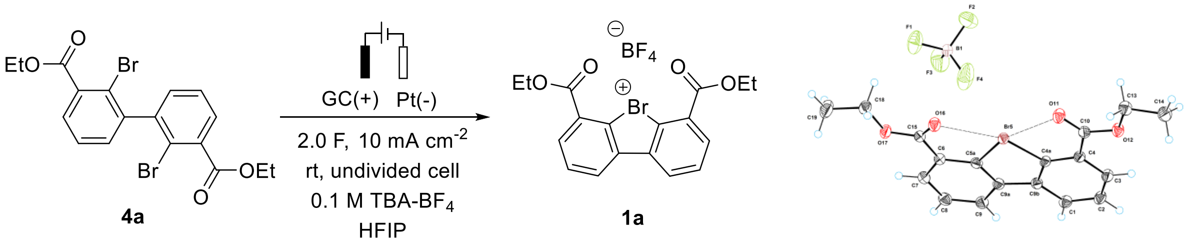
Scheme 1: Synthesis of cyclic diaryl λ^3-bromanes

Results and Discussion

Symmetric 2,2'-dibromo-1,1'-biphenyl **4a** possessing ethoxycarbonyl group *ortho* to the bromine was chosen as a model compound for our study. We anticipated that the presence of the ester moiety would help to stabilize [19] the key λ^3-bromane Br(III) intermediate **5** thus facilitating its formation in anodic oxidation. The anodic oxidation of **4a** under previously published conditions for synthesis Br(III) species [16, 18] (GC as working electrode, Pt foil as counter electrode, 0.1 M TBA-BF4 in HFIP electrolyte and 2F/mol passed charge at current density of 10 mA·cm^{-2}) afforded the desired Br(III) product **1a** in poor 14% NMR yield (Table1, entry 1). Cyclic diarylbromonium salt **1a** was isolated by extractive workup followed by reversed-phase chromatography and its structure was unambiguously confirmed by X-ray crystallography (Table 1 graphics). Gratifyingly, twofold increase in yield was achieved by slight reduction of the current density to j = 8 mA·cm^{-2} (entry 2 vs.1). Further increase in yield of **1a** to 45% was possible by passing higher amount of charge (6.0 F/mol; entry 3). TEA-BF$_4$ appeared to be somewhat superior as the electrolyte to TBA-BF$_4$ and Me$_4$N-BF4 (entry 4 vs. 3 and 5). In all experiments with passed charge amount of 6.0 F/mol (entries 3-5), nearly complete conversion of the starting **4a** and moderate yield of the desired **1a** was observed pointing at possible degradation of starting material or product. Linear sweep voltammetry (LVS) experiments (0.1M TBA-BF$_4$ in HFIP on a Pt disk electrode) revealed that the reduction current increases almost 4 times upon the addition of 5 mM **1a** to the electrolyte (see SI Figure S1). At the same time, passing 6.0 F/mol through a solution of **1a** in 50 mM TBA-BF$_4$/HFIP at j = 8 mA·cm^{-2} led to 60% bromane **1a** degradation, suggesting that cationic **1a**, formed on anode, decomposes on a cathode. To avoid the undesired cathodic decomposition of **1a**, cathode and anode chambers were separated, and further experiments were performed in a divided cell. Gratifyingly, the change of the cell type allowed for more than twofold increase in product **1a** yield from 28% (entry 2, undivided cell) to 60% (entry 6, divided cell). Interestingly, higher amounts of passed charge did not improve the reaction outcome (entry 7). Neither successful was also change of the anode material from GC to RVC or BDD (entries

8-9) or variation of electrolyte amount (entry 10-11; for complete optimization results see SI Table S1).

Table 1: Optimization of electrochemical oxidation/cyclization conditions.[a]

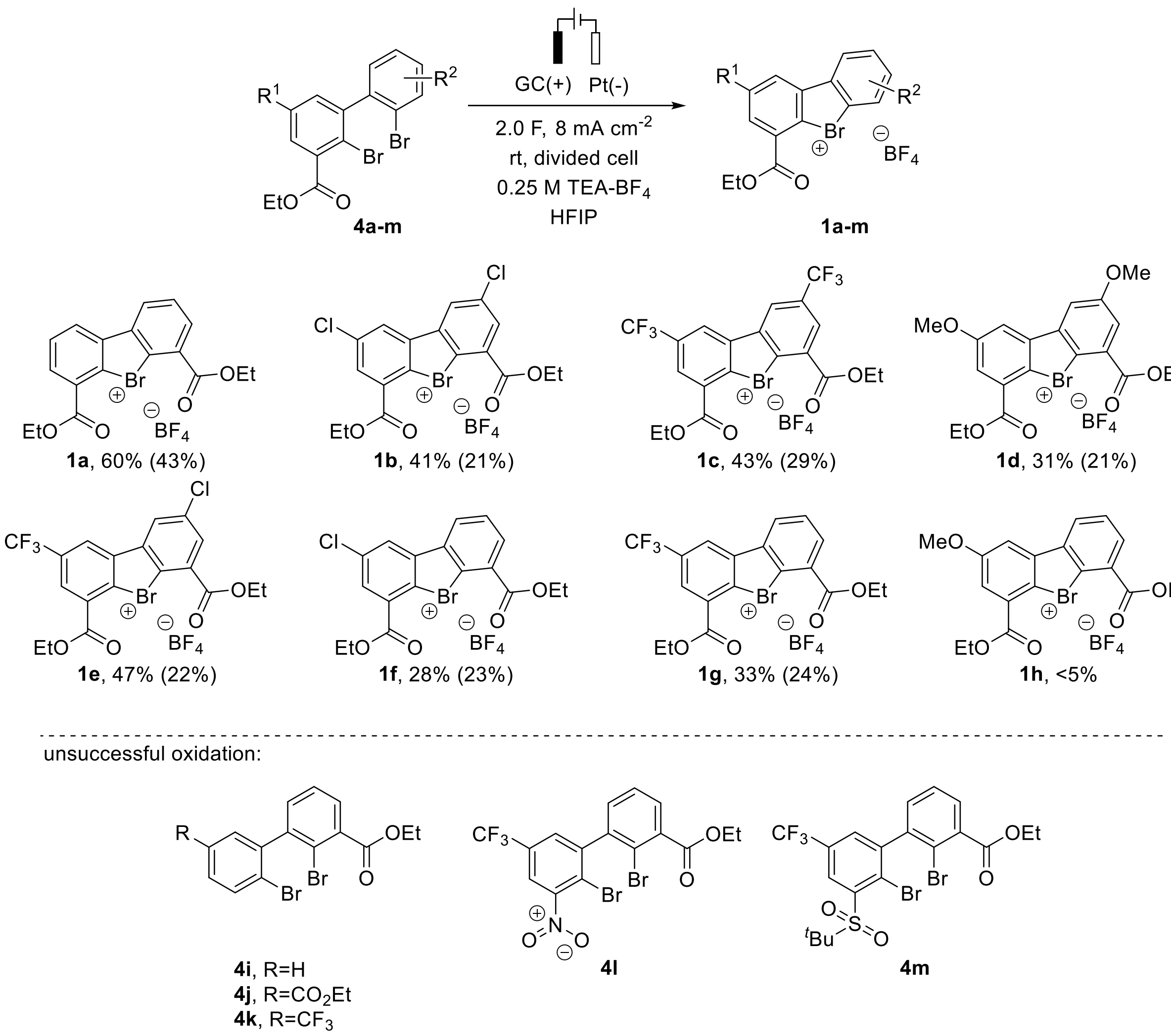


structure confirmed by X-ray

Entry	Deviation from starting conditions	**1a** %	**4a** %	Mass balance, %
1	none	14	61	75
2	*j* = 8 mA cm^{-2}	28	49	77
3	*j* = 8 mA cm^{-2}, *q*/mol = 6.0 F/mol	45	5	50
4	TEA-BF4, *j* = 8 mA cm^{-2}, *q*/mol = 6.0 F/mol	48	5	53
5	Me_4N-BF4, *j* = 8 mA cm^{-2}, *q*/mol = 6.0 F/mol	42	6	48
6	**divided cell, 0.25 M TEA-BF4, *j* = 8 mA cm^{-2}**	**60**	**24**	**84**
7	divided cell, 0.25 M TEA-BF4, *j* = 8 mA cm^{-2} *q*/mol = 3.0 F/mol	41	19	60
8	divided cell, RVC, 0.25 M TEA-BF4, *j* = 8 mA cm^{-2}	62	0	62
9	divided cell, BDD, 0.25 M TEA-BF4, *j* = 8 mA cm^{-2}	57	10	67
10	divided cell, 0.20 M TEA-BF4, *j* = 8 mA cm^{-2}	15	55	70
11	divided cell, 0.30 M TEA-BF4, *j* = 8 mA cm^{-2}	15	63	78

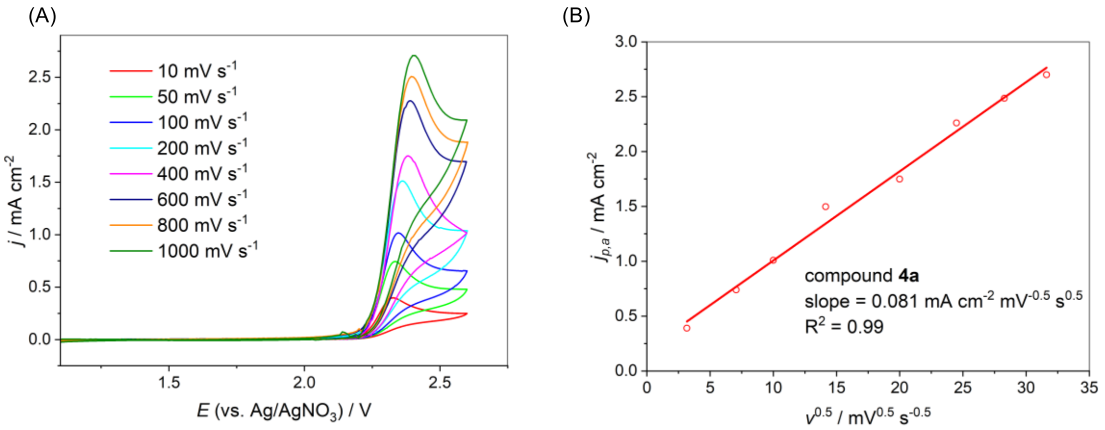
[a] Reactions were performed on a 0.15 mmol scale. Yields and mass balance were determined by ^{1}H-NMR in the crude reaction mixture using 1,2,3,4-tetrafluorobenzene as an internal standard.

With optimised reaction conditions in hand, substrate scope was evaluated (Scheme 2). Symmetrical biaryls with electron deficient substituents such as Cl (**4b**) or CF_3 (**4c**) afforded the respective Br(III) products **1b,c** in slightly reduced yields as compared to that of **1a**. Gratifyingly, electron rich MeO-substituted **1d** could be also obtained under the developed conditions. Unsymmetrically substituted **4e** and mono-substituted dibromides **4f-g** demonstrated reactivity similar to that of their symmetrical analogues **4b-c** with exception of mono-MeO-substituted dibromide **4h**. Notably, the presence of two stabilizing ester moieties is critical for the synthesis of Br(III) species: the removal of one ester group (**4i-k**), or its replacement by NO_2 (**4l**) or $SO_2{}^t$Bu (**4m**) in 2,2'-dibromo-1,1'-biphenyls resulted in starting material degradation with no formation of the desired product.



Scheme 2. Substrate scope. Reactions were performed on a 0.15 mmol scale. Yields were determined by ^{1}H-NMR spectroscopy of reaction mixture using 1,2,3,4-tetrafluorobenzene as an internal standard. Isolated yields are given in parentheses.

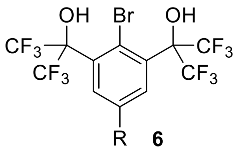
A series of control experiments were performed to rationalize the observed reactivity trends (Scheme 2). The measured redox potentials $E_{P/2}$ for 2,2'-dibromo-1,1'-biphenyls **4a-g** (from 1.77 V to 2.88 V) and unsuccessful substrates **4i-m** (from 1.73 V to 2.54 V) (Table S2) spanned the relatively similar oxidation ranges suggesting that the success of the anodic oxidation likely depends on the structural rather than the electrochemical properties of the starting 2,2'-dibromo-1,1'-biphenyls **4a-m**. Closer inspection of the electrochemical behaviour of **4a** revealed irreversible electron transfer at scan rates up to 1 V s^{-1} (Scheme 3A) indicating that one or more rapid chemical steps are following the electrochemical step [20, 21]. Besides, the observed linear correlation between E_p of the redox event and the square root of the scan rate (Scheme 3B) suggested that **4a** is not significantly adsorbed on the electrode surface [21]. Comparison of j_p vs. $v^{0.5}$ slope with our previously obtained results for the anodic oxidation of aryl bromides **6a** (two-electron oxidation) and **6b** (one-electron oxidation) into the respective bromine (III) species (Scheme 3C) [17] demonstrates more similar behaviour to **6b** suggesting that revealed oxidation is a single electron transfer process. On the other hand, anodic oxidation of **4a** under optimized conditions (entry 6, Table1) using 1 F/mol returned only 35% of **1a** (NMR yield), whereas passing 2 F/mol charge delivered **1a** in 60% yield. The latter data provides an evidence that overall **4a** oxidation to **1a** likely is a two-electron process, suggesting that the second oxidation step may involve disproportionation of putative Br(II) species (see Scheme 3D).

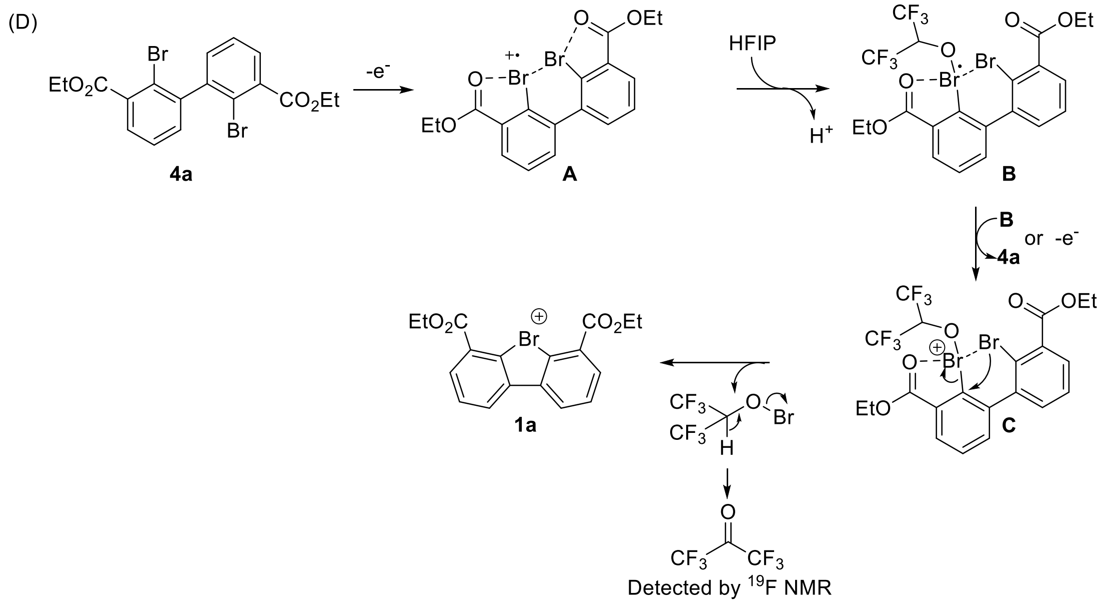


(C)

Entry	Compound	Slope j_p vs. $v^{0.5}$ [mA s$^{0.5}$ mV$^{-0.5}$ cm^{-2}]
1	**6a**	0.156
2	**6b**	0.088

6a, R=H
6b, R=OMe





Scheme 3: A: Background and *iR* drop-corrected CV's of 5mM **4a** at different scan rates (solvent: HFIP, working electrode: glassy carbon, supporting electrolyte: 0.1M Bu_4NBF_4). B: Plot of the peak current densities (j_p) vs. $v^{0.5}$. C: Representative j_p vs. $v^{0.5}$ slope values for oxidation of Martin's bromane precursor **6** (ref. 17). D: Plausible reaction mechanism.

Based on control experiments described above we propose a plausible mechanism as shown in Scheme 3D. The reaction starts with single electron oxidation **4a** on the electrode surface to form cation radical **A**, in which Br(II) is chelation-stabilized by carboxyl group [19] and neighbouring Br substituent [22]. Intermediate **A** rapidly undergoes irreversible chemical reaction by HFIP coordination to transient Br(II) followed by subsequent proton transfer to generate radical **B**. Following disproportionation of radical **B** would lead to the formation of Br(III) species **C** (anodic oxidation cannot be fully excluded), which undergoes intramolecular S_NAr-type substitution to form cyclic λ^3-bromane **1a** and hypobromite **D**. The latter decomposes into hexafluoroacetone, which was observed by ^{19}F NMR [23].

Conclusion

In conclusion, we have demonstrated a conceptual approach to cyclic diaryl λ^3-bromanes by electrochemical oxidative cyclization of 2,2'-dibromo-1,1'-biphenyls. The developed method represents safe, inexpensive and easily scalable alternative to commonly employed thermal decomposition of potentially explosive diazonium salts. The successful electrochemical oxidation requires the presence of two chelating ester groups that stabilize the formed Br(III) species. Further work towards improving substrate scope and understanding the reaction mechanism are in progress in our laboratory.

Supporting Information

Crystallographic data for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC: 2404146

Supporting Information File 1: Experimental procedures, analytical and spectroscopic data for new compounds, copies of NMR spectra, and X-ray crystallographic data

File Name: Supporting information_BJOC.pdf

File Format: PDF

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