Electrochemical Generation of Hypervalent Bromine(III) Compounds

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Abstract: In sharp contrast to hypervalent iodine(III) compounds, the isoelectronic bromine(III) counterparts have been little studied to date. This knowledge gap is mainly attributed to the difficult-to-control reactivity of $\lambda^3$-bromanes as well as to their challenging preparation from the highly toxic and corrosive BrF$_3$ precursor. In this context, we present a straightforward and scalable approach to chelation-stabilized $\lambda^3$-bromanes by anodic oxidation of parent aryl bromides possessing two coordinating hexafluoro-2-hydroxypropyl substituents. A series of para-substituted $\lambda^3$-bromanes with remarkably high redox potentials spanning a range from 1.86 V to 2.60 V vs. Ag/AgNO$_3$ was synthesized by the electrochemical method. We demonstrate that the intrinsic reactivity of the bench-stable bromine(III) species can be unlocked by addition of a Lewis or a Brønsted acid. The synthetic utility of the $\lambda^3$-bromane activation is exemplified by oxidative C–C, C–N, and C–O bond forming reactions.

The chemistry of hypervalent halogen species has experienced tremendous development in the last decades, and hypervalent iodine(III) compounds have become mainstream reagents in contemporary organic synthesis.[1] Recent selected applications of hypervalent iodine(III) compounds involve oxidative heterocycle formation,[2] atom transfer reactions[3] such as alkynylation[4] and trifluoromethylation,[5] oxidative rearrangements,[6] and C–H functionalization.[7] Additionally, electrochemically generated iodine(III) derivatives have been frequently utilized as ex-cell mediators (electro-generated reagents) in organic electroosynthesis.[8] The corresponding isoelectronic hypervalent bromine(III) species feature superior reactivity to that of iodine(III) counterparts owing to the higher oxidizing ability, stronger electrophilicity and better nucleofugality of the bromanyl unit.[9] Not surprisingly, the unique properties of bromine(III) reagents have allowed for the development of unprecedented synthetic transformations such as Hofmann rearrangement of sulfonamides to the corresponding N-arylsulfamoyl fluorides,[10] unusual Bayer–Villiger-type oxidation of open-chain aliphatic aldehydes,[11] oxidative coupling of alkenes and primary alcohols to form conjugated enones[12] as well as transition metal-free regioselective C-H amination of non-activated alkanes.[13] Although these notable accomplishments highlight the remarkable synthetic potential of bromine(III) species,[14] the hypervalent bromine chemistry appears to be significantly less developed as compared to that of iodine(III) compounds. This striking bias apparently is to be attributed to the relatively poor stability and the high oxidizing power of bromine(III) reagents,[15] properties that have created a common perception of difficult-to-control reactivity and poor functional group compatibility. Furthermore, there is an apparent lack of conventional methods for the synthesis of bromine(III) species.

The synthesis of Br$_3^+$ reagents is typically accomplished by a ligand exchange reaction between bromine trifluoride (BrF$_3$) and nucleophilic arenne derivatives such as arylsilanes and aryliodonanes.[13] For example, BrF$_3$ reacts with phenyl trifluorosilane to form a relatively unstable phenyl-$\lambda^3$-bromane[16] that is suitable both as reagent and as entry point for the synthesis of other derivatives via ligand exchange (Figure 1, top).

![Figure 1. New approach to aryl-$\lambda^3$-bromanes.](image-url)
Bromine trifluoride has been also used by Martin et al. for the preparation of chelation-stabilized aryl-\(\lambda^3\)-bromane 3d. However, an important limitation of these approaches is the use of BrF\(_3\), a highly toxic and extremely reactive liquid that requires dedicated equipment (such as PTFE vessels etc.) and specific experimental techniques for its safe handling. Notably, high oxidation potentials of aryl bromides (e.g. 2.0 V vs Ag/0.01 M AgNO\(_3\) for PhBr in CH\(_2\)CN)\(^{34}\) and poor stability of the resulting bromine(III) species complicates the direct two-electron oxidation by chemical oxidants, a method that is routinely employed for the synthesis of hypervalent iodine-two-electron oxidation by chemical oxidants, a method that is the resulting bromine(III) species complicates the direct two-electron oxidation by chemical oxidants, a method that is.

Recently we reported on electrosynthesis of hypervalent iodine(III) species by anodic oxidation of the parent aryl bromide 2 (Figure 1, bottom). The extremely high reactivity of arylbromonium species\(^{13a}\) is tamed by the two coordinating t-butyl groups (Figure 1, bottom). The extremely high reactivity of arylbromonium species\(^{13a}\) is tamed by the two coordinating t-butyl groups.

Gratifyingly, electrochemical oxidation using glassy carbon (GC) as the working electrode and platinum foil as the counter electrode in a TBA-BF\(_4\)/HFIP electrolyte at 10 mA cm\(^{-2}\) afforded the desired 3a in 55% yield (entry 1) after passing 2F per mole of starting material. The molecular structure of 3a was confirmed by single crystal X-ray analysis (Table 1, graphics).

A) Electrochemical oxidation of 3-bromane 3a.

**Table 1: Optimization of the electrochemical synthesis of 3a.**

| Entry | Deviations from standard conditions | 2a [%]\(^4\) | 3a [%]\(^4\) | Mass balance [%]\(^4\) |
|-------|------------------------------------|-----------|-----------|-----------------|
| 1     | none                               | 43        | 55        | 98              |
| 2     | TFE                                | 40        | 52        | 92              |
| 3     | CH\(_2\)CN                          | 93        | 6         | 99              |
| 4     | BOD(+)                             | 54        | 46        | 100             |
| 5     | RVC(+)                             | 60        | 40        | 100             |
| 6     | 0.1 TBA-CIO\(_4\)                  | 50        | 44        | 94              |
| 7     | 0.1 TBA-PF\(_4\)                   | 44        | 55        | 99              |
| 8     | \(j = 5 \text{ mA cm}^{-2}\)       | 51        | 47        | 98              |
| 9     | \(j = 15 \text{ mA cm}^{-2}\)      | 38        | 56        | 94              |
| 10    | \(j = 20 \text{ mA cm}^{-2}\)      | 37        | 60        | 97              |
| 11    | \(q/M\_\text{mol} = 3.0 \text{ F}\) | 30        | 67        | 97              |
| 12    | \(q/M\_\text{mol} = 4.0 \text{ F}\) | 17        | 75        | 63\(^{[9]}\)    |
| 13    | \(q/M\_\text{mol} = 5.0 \text{ F}\) | 18        | 71        | 89              |

\(^{[a]}\) Yields and mass balances determined by \(^1\)H NMR spectroscopy of the post-electrolysis solution using 1,2,3,4-tetrafluorobenzene as the internal standard (0.3 mmol scale). \(^{[b]}\) Isolated yield.
corresponding commercially available 2-bromo-m-xylene
4a-e with KMnO4. Acid 5f was synthesized by chemo-
selective cross-coupling of the two iodo-moieties in 7
(prepared by iodination of 4-bromobenzotriﬂuoride) with
ethyltrimethylsilane under Sonogashira cross-coupling
conditions, followed by oxidative cleavage of the acetylene
subunit in 8 with KMnO4 (Figure 2). Finally, application of the
optimized electrolysis conditions (Table 1, entry 12) to the
oxidation of 2b-g rendered 3-bromanes 3b-g in 24–66% yields. It should also be noted that attempts toward oxidation
of 5a and bromoarene related to 2a carrying one chelating
moiety remained unsuccessful (for details see the Supporting
Information, p. S21).

For characterization of the electrochemical properties of the bromoarene/3-bromane redox couples, all synthesized bromides 2a-g were studied by cyclic voltammetry, using a 0.1 M NBu4BF4/HFIP electrolyte, a glassy carbon working electrode and a Ag/0.01 M AgNO3 reference (E0 = +287 mV vs. Fe/Fe+ couple; for more details, see p. S43). In the range between 0 and 2.7 V, each of the bromoarenes exhibits a single irreversible feature associated with the oxidation of BrI to BrIII. The corresponding half-peak potentials (EP/2) are situated in the range between 1.86 V (2e, R = OMe) and 2.60 V (2g, R = NO2; see table in Figure 3). It follows that i) the anodically generated bromanes can be considered as strong oxidants due to the high EP/2 values and ii) that with the compounds synthesized thus far, the potential of 2 is ﬂexibly tunable within a range of 0.66 V. A Hammett treatment (Figure 3, bottom right) using σp+ substituent coefﬁcients shows that EP/2 is dependent on the electron donating or withdrawing ability of the substituent R and follows a linear trend according to Equation (1),

$$E_{P/2} = 2.25 V + 0.47 V \sigma_{p+}$$

wherein the slope provides a measure of the inﬂuence of the substituents upon the observed potential, while the intercept refers to the EP/2 of the unsubstituted compound of the series.

The stabilization of the characteristic pseudo-trigonal bipyramidal geometry of 3-bromanes 3 by 2-benzobromoxa-
ole rings (for X-ray structure of 3a, see Table 1 graphics) (for X-ray structure of 3a, see Table 1 graphics) endows Martin’s bromine(III) species with remarkable sta-
bility. Given the high oxidizing power and strong electro-
philicity of 3-bromanes, the observed stability is striking. Not only it allowed for the electrosynthesis, isolation and puriﬁcation of 3-bromanes 3a-g, but also made possible their convenient handling and storage for extended periods of time. In the meantime, the synthetic application of 3-bromanes 3a-g would require activation to unlock their intrinsic

Figure 2. Synthesis of bromides 2a-g. [a] Average yield of two runs on 0.3 mmol scale. [b] Yield on 10.0 mmol scale.
reactivity. To this end, oxidative biaryl coupling was chosen as a model reaction to develop the in situ bromane activation (Figure 4). As anticipated, the non-activated 3a did not effect the homocoupling of benzodioxole 9a in DCM at room temperature after 18 h. We envisioned that the reactivity of λ3-bromane 3a could be enhanced by weakening the stabilizing effect of the two chelating ortho-substituents using a suitable Lewis acid. Indeed, a nearly quantitative formation of biaryl 10a (98% yield) was observed after 3 h at −30°C (Figure 4) when 3a was used together with TMSOTf (1:2 ratio, respectively). Alternatively, BF3·OEt2 could be employed for the activation of bromane 2a in HFIP as the solvent (35% yield of 10a). Finally, TIOH as additive (1.05 equiv) also effected the 3a-mediated biaryl formation in DCM (93% yield of 10a). Hence, both Lewis and Brønsted acids are suitable for the enhancement of λ3-bromane reactivity possibly by increase of cationic character of 3a upon interactions with the Lewis basic oxygen atom. Noteworthy, CV studies showed that an in-cell mediated biaryl coupling is not possible, since the substrates are easier to oxidize than the bromoarenes (for details see the Supporting Information, p. S46).

The scope of substrates for the λ3-bromane-mediated biaryl formation was briefly explored using TMSOTf as the activator (Figure 4A). The reaction features remarkable functional group compatibility. Not only halides are tolerated (biaryls 10a–d) but also allylic and propargylic subunits as

![Figure 3. Top: Background and r drop corrected linear sweep voltammograms (LSV) of aryl bromides 2a–g (c=5 mM) recorded at 10 mV/s. Bottom: Plot of the half-peak potentials E1/2 (extracted from the LSVs) vs. the σp* substituent constants.](image)

![Figure 4. Synthetic applications of electrogenerated bromane reagent 3a.](image)
well as primary alcohols (10e,f,g, respectively) are compatible with the 3a-mediated biaryl formation. Biaryl 10h and 10i as well as bi-isoflavone derivative 10j can be also obtained using TMS-OTf activation of \( \lambda^1 \)-bromane 3a (Figure 4A).

We were pleased to find that \( \lambda^3 \)-bromane 3a also effected the oxidative amidation of N,N-dimethylanilines 11a–h with imides (phthalimide and succinimide) as well as with various amidines such as pyrrolidin-2-one, oxindole and cinnamamide (Figure 4B). Relatively electron-rich anilines amides such as pyrrolidin-2-one, oxindole and cinnamamide imides (phthalimide and succinimide) as well as with various propargylic and primary alcohol moieties in anilines (11f–h) as well as with bromine and aldehyde substituents (11i–c).

Finally, \( \lambda^1 \)-bromane 3a was also found to be suitable for the oxidative cyclization of Schiff bases 17a–c to benzoazoles (18a–c; Figure 4C). Further studies to expand the application scope of \( \lambda^1 \)-bromane 3a are ongoing in our laboratories.

In summary, an efficient, reliable, and inexpensive approach to Martin’s hypervalent bromine (III) species is reported. The key step of the synthesis is anodic oxidation of \( \lambda^3 \)-bromane 3a with \( \lambda^2 \)-bromane 3a is compatible with the presence of vinlyc, propargylic and primary alcohol moieties in anilines (11f–h) as well as with bromine and aldehyde substituents (11i–c).

The authors declare no conflict of interest.

Keywords: anodic oxidation - cyclic voltammetry - electrochemistry - hypervalent bromine - oxidative coupling

[1] a) V. V. Zhldankin, Hypervalent Iodine Chemistry: Preparation, Structure and Synthetic Applications of Polyvalent Iodine Compounds, Wiley, Chichester, 2013; b) Hypervalent Iodine Chemistry: Topics in Current Chemistry, Vol. 373 (Ed.: T. Wirth), Springer International Publishing, Cham, 2016; c) A. Yoshimura, V. V. Zhldankin, Chem. Rev. 2016, 116, 3328–3435. 

[2] “Oxidative Heterocycle Formation Using Hypervalent Iodine (III) Reagents”: S. Murarka, A. P. Antonchick, in Hypervalent Iodine Chemistry: Topics in Current Chemistry, Vol. 373 (Ed.: T. Wirth), Springer International Publishing, Cham, 2015, pp. 75–104.

[3] Y. Li, D. P. Hari, M. V. Vita, J. Waser, Angew. Chem. Int. Ed. 2016, 55, 4436–4454; Angew. Chem. 2016, 128, 4512–4531.

[4] “Alkylation with Hypervalent Iodine Reagents”: J. Waser, in Hypervalent Iodine Chemistry: Topics in Current Chemistry, Vol. 373 (Ed.: T. Wirth), Springer International Publishing, Cham, 2015, pp. 187–222.

[5] J. Charpentier, N. Früh, A. Togni, Chem. Rev. 2015, 115, 650–682.

[6] F. Singh, T. Wirth, Synthesis 2013, 45, 2499–2511.

[7] a) Pioneering work in C–H arylation: O. Daugulis, V. G. Zaitsev, Angew. Chem. Int. Ed. 2005, 44, 4046–4048; Angew. Chem. 2005, 117, 4114–4116; b) For a seminal contribution of C–H oxidation, see: a) A. R. Dick, K. L. Hull, M. S. Sanford, J. Am. Chem. Soc. 2004, 126, 2300–2301; c) M. Massignan, X. Tan, T. H. Meyer, R. Kuniyi, A. M. Messinis, L. Ackermann, Angew. Chem. Int. Ed. 2020, 59, 3184–3189; Angew. Chem. 2020, 132, 3210–3215; d) Y. Kita, K. Morimoto, M. Ito, C. Ogawa, A. Goto, T. Dohi, J. Am. Chem. Soc. 2009, 131, 1668–1669; e) A. P. Antonchick, R. Samanta, K. Kulikov, J. Latagahn, Angew. Chem. Int. Ed. 2011, 50, 8605–8608; Angew. Chem. 2011, 123, 8764–8767.

[8] a) M. Elsherbini, T. Wirth, Chem. Eur. J. 2018, 24, 13399–13407; b) R. Francke, Curr. Opin. Electrochem. 2019, 15, 83–88; c) M. Elsherbini, B. Winterson, H. Alharbi, A. A. Folgueiras-Amador, C. Génot, T. Wirth, Angew. Chem. Int. Ed. 2019, 58, 9811–9815; Angew. Chem. 2019, 131, 9916–9920; d) S. Doobary, A. T. Sedikides, H. P. Caldora, D. L. Poole, A. J. J. Lennox, Angew. Chem. Int. Ed. 2020, 59, 1155–1160; Angew. Chem. 2020, 132, 1171–1176; e) J. D. Herszman, M. Berger, S. R. Walvdovg, Org. Lett. 2019, 21, 7893–7896; f) A. Maity, B. L. Frey, N. D. Hoskinson, D. C. Powers, J. Am. Chem. Soc. 2020, 142, 4990–4995; g) R. Möckel, E. Babaoglu, G. Hilt, Chem. Eur. J. 2018, 24, 15781–15785; h) R. Francke, Curr. Opin. Electrochem. 2021, 28, 100719; i) Y. N. Ogbin, M. N. Elinson, G. L. Nikishin, Russ. Chem. Rev. 2009, 78, 89.

[9] a) M. Ochiai, A. Yoshimura, K. Miyamoto, S. Hayashi, W. Nakashishi, J. Am. Chem. Soc. 2010, 132, 9236–9239; b) M. Ochiai, N. Tada, T. Okada, A. Sota, K. Miyamoto, J. Am. Chem. Soc. 2008, 130, 2118–2119.

[10] M. Ochiai, T. Okada, N. Tada, A. Yoshimura, K. Miyamoto, M. Shiro, J. Am. Chem. Soc. 2009, 131, 8392–8393.

[11] M. Ochiai, A. Yoshimura, T. Mori, Y. Nishi, M. Hirobe, J. Am. Chem. Soc. 2008, 130, 3742–3743.

[12] M. Ochiai, K. Miyamoto, T. Kaneaki, S. Hayashi, W. Nakashishi, Science 2011, 332, 448–451.

[13] a) U. Farooq, A.-H. A. Shah, T. Wirth, Angew. Chem. Int. Ed. 2009, 48, 1018–1020; Angew. Chem. 2009, 121, 1036–1038; b) K. Miyamoto, Chemistry of Hypervalent Bromine in PATAPS.
[14] H. J. Frohn, M. Giesen, J. Fluorine Chem. 1998, 89, 59 – 63.
[15] M. M. Hoque, K. Miyamoto, N. Tada, M. Shiro, M. Ochiai, Org. Lett. 2011, 13, 5428 – 5431.
[16] M. Ochiai, Y. Nishi, S. Goto, M. Shiro, H. J. Frohn, J. Am. Chem. Soc. 2003, 125, 15304 – 15305.
[17] a) T. T. Nguyen, J. C. Martin, J. Am. Chem. Soc. 1980, 102, 7382 – 7383; b) T. T. Nguyen, S. R. Wilson, J. C. Martin, J. Am. Chem. Soc. 1986, 108, 3803 – 3811.
[18] N. L. Weinberg, H. R. Weinberg, Chem. Rev. 1968, 68, 449 – 523.
[19] E. A. Merritt, B. Olofsson, Eur. J. Org. Chem. 2011, 3690 – 3694.
[20] a) T. Broese, R. Francke, Org. Lett. 2016, 18, 5896 – 5899; b) O. Koleda, T. Broese, J. Noetzel, M. Roemelt, E. Suna, R. Francke, J. Org. Chem. 2017, 82, 11669 – 11681; c) A. F. Roesel, T. Broese, M. Maík, R. Francke, ChemElectroChem 2019, 6, 4229 – 4237.
[21] H. Lenormand, V. Corc/C216, G. Sorin, C. Chhun, L.-M. Chamoreau, L. Krim, E.-.L. Zins, J.-P. Goddard, L. Fensterbank, J. Org. Chem. 2015, 80, 3280 – 3288.
[22] A. A. Kolomeitsev, F. U. Seifert, G.-V. Röschenthaler, J. Fluorine Chem. 1995, 71, 47 – 49.
[23] Y. Imada, T. Kukita, H. Nakano, Y. Yamamoto, Bull. Chem. Soc. Jpn. 2016, 89, 546 – 548.
[24] Y. Motoyama, M. Okano, H. Narusawa, N. Makihara, K. Aoki, H. Nishiyama, Organometallics 2001, 20, 1580 – 1591.
[25] L. Kraszkiwicz, M. Sosnowski, L. Skulski, Synthesis 2006, 1195 – 1199.
[26] Z. U. Levi, T. D. Tilley, J. Am. Chem. Soc. 2009, 131, 2796 – 2797.