Synthesis

Hypervalent Bromine(III) Compounds: Synthesis, Applications, Prospects

Bethan Winterson, Tuhin Patra, Thomas Wirth.

Affiliations below.

DOI: 10.1055/a-1675-8404


Conflict of Interest: The authors declare that they have no conflict of interest.

This study was supported by Engineering and Physical Sciences Research Council (http://dx.doi.org/10.13039/501100000266)

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Hypervalent compounds play a prominent role in homogeneous oxidation catalysis. Despite the higher reactivity of the hypervalent bromine compounds when compared to their isoelectronic iodine analogues, the corresponding λ3-bromanes are much less explored. This can be attributed to the discernible lack of convenient strategies for their synthesis. This short review highlights the available methods for the synthesis of various organo-λ3-bromanes, with a major focus on the recent developments and reactivities in the last few years. Additionally, limitations and future prospects of hypervalent bromine chemistry is being discussed.

Corresponding Author:
Thomas Wirth, Cardiff University, Cardiff School of Chemistry, Cardiff, United Kingdom of Great Britain and Northern Ireland, wirth@cf.ac.uk

Affiliations:
Bethan Winterson, Cardiff University, Cardiff School of Chemistry, Cardiff, United Kingdom of Great Britain and Northern Ireland
Tuhin Patra, Cardiff University, Cardiff School of Chemistry, Cardiff, United Kingdom of Great Britain and Northern Ireland
Thomas Wirth, Cardiff University, Cardiff School of Chemistry, Cardiff, United Kingdom of Great Britain and Northern Ireland

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Hypervalent Bromine(III) Compounds: Synthesis, Applications, Prospects

Bethan Winterson a
Tuhin Patra a
Thomas Wirth a*

School of Chemistry, Cardiff University, Park Place, Main Building, Cardiff, CF10 3AT, Cymru/Wales, UK.
wirth@cf.ac.uk

Received: Accepted: Published online: DOI:

Abstract Hypervalent compounds play a prominent role in homogeneous oxidation catalysis. Despite the higher reactivity of the hypervalent bromine compounds when compared to their isoelectronic iodine analogues, the corresponding $\lambda^3$-bromanes are much less explored. This can be attributed to the discernible lack of convenient strategies for their synthesis. This short review highlights the available methods for the synthesis of various organo-$\lambda^3$-bromanes, with a major focus on the recent developments and reactivities in the last few years. Additionally, limitations and future prospects of hypervalent bromine chemistry is being discussed.

1 Introduction

In marked contrast to the substantial growth in the field of iodine(III) reagents, their isoelectronic hypervalent bromine counterparts have seen notably slower progress. During the last century, only a reserved selection of scientists have partaken in their development, ensuing to their limited precedence in the literature. While the first ever synthesis of a hypervalent iodine compound, (dichloroiodo)benzene, was reported in 1886 by Willgerodt, the first hypervalent bromonium compound arrived notably later, in 1952, when Sandin and Hay reported the preparation of a bromonium salt through the intramolecular nucleophilic bromine attack on an aryl diazonium salt. Still, the remarkably slower growth of hypervalent bromine chemistry cannot be justified by its later arrival 'on the market'. In line with this, we will highlight both the predominant struggles in terms of the synthetic approaches that have heavily hindered progression in this field, as well as the attractive properties of bromine(III) compounds, in an effort to incentivise the scientific interest.

Hypervalency refers to a main group element, such as hypervalent bromine, that breaks the octet rule and has more than 8 electrons in its valence shell. According to IUPAC rules, compounds with non-standard bonding numbers are given a $\lambda$ notation. For example, $\text{H}_3\text{Br}$ is called $\lambda^1$-bromane and has a dextet structure, while $\text{H}_5\text{Br}$ is called $\lambda^5$-bromane with a duodecet structure.

1 Introduction

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Hypervalent halogen containing compounds have attracted unprecedented attention in organic chemistry attributed to their unique characteristic properties. Undoubtedly, the vast majority of this attention has been paid to the field of iodine chemistry, with reagents such as Dess-Martin Periodinane, [bis(trifluoroacetoxy)iodo]benzene, (diacetoxyiodo)benzene and diaryliodonium-type compounds becoming mainstream reagents in contemporary organic synthesis and even commercially available (Scheme 1). The attractiveness of iodine(III) reagents can be accredited to their versatile characteristics; they are a mild, non-toxic (green oxidation), easy
to handle and environmentally benign class of reagents. The reactivity pattern of hypervalent iodine is somewhat discretely similar to the heavy transition metals and, as such, they are typically preferred as a less toxic alternative. The diverse nature of these reactions includes oxidative couplings, halogenations, arylation, oxidative rearrangements, trifluoromethylations and C-H functionalizations. Their hypervalent bromine analogues can feature superior reactivity owing to their higher nucleofugality, ionization potential and stronger electrophilicity. Unsurprisingly, these superior qualities have facilitated the development of other useful synthetic transformations including the Bayer-Villiger like oxidations of open-chain aliphatic aldehydes, metal free C-O and C-N coupling, the oxidative coupling of alkenes and alcohols, metal-free amination of unactivated alkanes and thermal solvolysis, amongst others. Even so, despite their often superior reactivity and unique structures, a limited number of hypervalent bromine reagents have been reported and utilized, especially in comparison to hypervalent iodine reagents.

Perhaps the most substantial impediment to progression in this field can be attributed to the discernible lack of expedient methods for the synthesis of these compounds. The main challenge arises due to the innate thermodynamic barrier for the oxidation of bromine(I) to hypervalent bromine. For instance, the oxidation potentials of arylbromides \((\text{Ar-CO}_{2}\text{Et})\text{CH}_2\text{Br}\) are 2.3 V vs. Ag/AgCl in CH_2Cl_2 and the corresponding iodides \((\text{Ar-CO}_{2}\text{Et})\text{CH}_2\text{I}\) are remarkably high in comparison to iodides \((\text{Ar-CO}_{2}\text{Et})\text{CH}_2\text{I}\) arising from their greater electronegativity and ionization potential. Hereby, the oxidation of the corresponding haloarenes with oxidants, which is standard for the preparation of iodine(III) reagents, is generally not effective for the synthesis of hypervalent bromanes. Until recently, the most competent synthesis of hypervalent bromine compounds involved the ligand-exchange of bromine trifluoride (BrF_3), which circumvents the unfavourable oxidation process. These approaches, however, are far from ideal in terms of safety and convenience. Bromine trifluoride is a highly reactive compound which etches glass and quartz, sets fire to paper and wood, and reacts violently with the majority of organic compounds. Literature known protocols for its access can be low yielding and require harsh reaction conditions. The choice of solvent is also pivotal in terms of solubility and stability, but is often not typical in terms of organic chemistry. For instance, BrF_3 reacts violently with CH_2Cl_2 at temperatures above ~20 °C, it is moderately soluble in trichlorofluoromethane, but above 5-10 °C it reacts with CF_3CClF to produce CF_3CClF_2 mainly. Moreover, the strict exclusion of air and moisture, immoderate reactivity and extreme toxicity of this reagent means specialist knowledge is required for such reactions. The poor stability of the subsequently prepared bromine(III) reagents regularly complicates matters further. For example, Frohn’s reagent, a key building block for various \(\lambda^3\)-bromanes, decompsoes immediately in the presence of moisture via H_2O oxidation. Evidently, the development of user-friendly synthetic approaches, in terms of experimental safety, ease and proficiency could provide the significant incentive for the influx of new researchers into this field, which is key to rapid progression. High yielding and milder reaction conditions to access bromine(III), with a particular focus on precluding the need for fluorinating reagents, has been the focus of research in the past 5 years. Pleasingly, electrochemical oxidation, single step oxidation with commercially available organic oxidants, and bench stable reagents have all emerged recently. Herein, we will discuss the synthetic approaches towards bromine(III) reagents, with an emphasis on the advance in synthetic strategies that have arisen in the past 5 years. In this respect, we will highlight the early synthetic techniques from the early 19th century and modern progressive techniques, to allow comparison between modern day literature and the early endeavours.

2 Diaryl-\(\lambda^3\)-bromanes

In pioneering work by Sandin and Hay, the first synthesis of a organo-\(\lambda^3\)-bromane was reported through the thermal decomposition of the arylidazinium salt, readily prepared from 2-amino-2'-bromobiphenyl (Scheme 2). Interestingly, the first organo-\(\lambda^3\)-chlorane was also synthesized using a similar strategy. In this work, the close proximity of the adjacent halogen atom was crucial to capture the generated aryl cation in an intramolecular fashion. In this respect, adoption of an almost identical strategy for the intermolecular diaryl-\(\lambda^3\)-bromane synthesis was largely unsuccessful, only resulting in a low yield of the desired products (Scheme 3). Encouragingly, efficiency of the trapping of aryl cation has recently been improved significantly by employing a weakly coordinating ligand/counter anion along with the mesityl diazonium salt.

Later, in 1980, in a significant breakthrough, Nesmeyanov and co-workers developed a more general pathway for the synthesis of acyclic diaryl-\(\lambda^3\)-bromanes. In this approach, the highly reactive bromine trifluoride (BrF_3) underwent double ligand exchange on the bromine (III) centre with aryl groups, emerging from tetraarylstannane or diarylmercury compounds in the presence of BF_3·Et_2O (Scheme 4). Such ligand exchange with a nucleophile is believed to follow an addition-elimination sequence similar to iodine(III) analogues. The role of acetoniitrile in this reaction is proposed to solubilize and stabilize the highly reactive BrF_3 and decrease the oxidizing ability of the bromine(III) through BrF_3·(MeCN); complex formation. The
Lewis acid BF$_3$OEt$_2$ was used to facilitate the second F/Ar exchange. Later, the approach was successfully extended for the use of aryilsilanes, and even arenes, in the place of tetraarylstannanes in acyclic diaryl-\(\lambda^1\)-bromane synthesis.

\[
\begin{align*}
F-Br & \quad \xrightarrow{BF_3\cdot EtO} \quad Ph_2Sn \\
\text{or PhHg} & \quad (1 \text{ equiv.}) \\
\text{MeCN} & \quad \xrightarrow{CH_2Cl_2, -78 ^\circ C} \quad Ph-Br
\end{align*}
\]

Scheme 4 Intermolecular diaryl-\(\lambda^1\)-bromane synthesis.

The use of BF$_3$OEt$_2$ as an exogenous Lewis acid could be avoided when the Lewis acidic aryl-transfer reagent (C$_6$F$_5$)$_2$BF was used. However, this strategy is limited by the generality in aryl-transfer reagent (Scheme 5). From the crystal structure, an infinite \(\text{Br-F-B-F} \quad \text{zigzag chain structure was observed for bis(perfluorophenyl) bromane tetrafluoroborate and the bromine(III) centre exhibited a distorted square-planar coordination.}

\[
\begin{align*}
F-Br & \quad \xrightarrow{(C_6F_5)_2BF} \quad \xrightarrow{CH_2Cl_2, -78 ^\circ C} \quad C_6F_5-Br \quad C_6F_5 \\
& \quad \xrightarrow{FbF_3} \quad 93% \\
(1.3 \text{ equiv.})
\end{align*}
\]

Scheme 5 External Lewis acid free intermolecular diaryl-\(\lambda^1\)-bromane synthesis.

Acyclic diaryl-\(\lambda^1\)-iodanes can be synthesized by simple oxidation of an iodoarene by an oxidant in the presence of another arene. However, such an approach is not suitable for isoelcetric diaryl-\(\lambda^3\)-bromanes owing to the lower polarizability of the bromine atom. However, few reports can be found where 2-bromobiphenyl derivatives could afford the desired \(\lambda^3\)-bromane through oxidation by either hydrogen peroxide in H$_2$SO$_4$ (Scheme 6) or in situ generated H$_2$SO$_4$ from K$_2$S$_2$O$_8$/H$_2$SO$_4$ combination.

\[
\begin{align*}
& \quad \xrightarrow{H_2O_2} \\
& \quad \xrightarrow{H_2SO_4, -10 ^\circ C, 12 h} \quad \xrightarrow{36%}
\end{align*}
\]

Scheme 6 Arene oxidation induced diaryl-\(\lambda^3\)-bromane synthesis.

Despite all these efforts, the synthesis of diaryl-\(\lambda^3\)-bromanes is still challenging since BF$_3$ is necessary in most cases. BrF$_3$ free methods are low yielding and are typically limited to intramolecular versions only.

Recently, in a seminal report by Yoshida and co-workers, a modified procedure for the BrF$_3$ free synthesis of cyclic diaryl-\(\lambda^3\)-bromanes was disclosed. In this case, a series of functionalized 2-amino-2’-bromobiphenyl derivatives were easily synthesized through palladium-catalyzed Suzuki coupling reactions. Next, these biphenyl derivatives were successfully cyclized via their corresponding diazonium salts to produce the diarylbromonium salts (Scheme 7). From the crystallographic analysis of the chloride salt, the existence of an ion pair was unambiguously established in place of the covalent bond as initially predicted in Scheme 2. The ionic nature was further confirmed by successful counter anion exchange with triflate and the bulky BAr$_F^-$ (Ar$_F^-$ = 3,5-(CF$_3$)$_2$C$_6$H$_3$). In perhaps the most impressive feat, they utilized these stable bromonium salts as halogen bonding organocatalysts in the Michael addition of indoles to \(\alpha\beta\)-unsaturated ketones. So far, this is the first and only catalytic application of \(\lambda^3\)-bromane in synthesis.

\[
\begin{align*}
& \quad 1 \quad \text{(12.47%)} \\
& \quad 2 \quad \text{(1 equiv.)} \\
& \quad CH_2Cl_2, rt, 24 h \\
& \quad BArs = \text{B(3,5-(CF$_3$)$_2$C$_6$H$_3$)$_4$}
\end{align*}
\]

Scheme 7 Synthesis and catalytic application of stable diaryl-\(\lambda^3\)-bromanes.

Furthermore, in an important breakthrough in recent years, Wencel-Delord and co-workers developed a general and safe strategy for the synthesis of cyclic diaryl-\(\lambda^3\)-bromanes with significantly improved yields. The use of tert-butyl nitrate (BuONO) as the mild oxidant in presence of a Brønsted acid was key to generate these bromonium salts in high yields (Scheme 8). Subsequently, these bromonium salts were found to generate arynes in the presence of a weak base. Such arynes could be trapped by a carboxylic acid or amine to deliver the formal \textit{meta-selective} transition-metal-free C–O and C–N coupling products. Typically, \(\lambda^3\)-iodanes can display such reactivity only in the presence of a transition metal, emphasising the superior qualities of hypervalent bromine reagents. Although, a recent report discloses \(\lambda^3\)-iodanes can show similar reactivity in the presence of strong bases.
Apart from such newly discovered unique reactivity profiles, in general, dialkyl-\(\lambda^3\)-bromanes serve as a more efficient arylating reagent than its \(\lambda^1\)-iodane analogues. They present as excellent arylating reagents towards various heteroatom nucleophiles (O, N, S, halide, etc.) under mild reaction conditions. In general, the reactivity towards harder nucleophiles follows the order: PhI\(\cdot\)<Ph3Br\(\cdot\)<Ph2Cl\(\cdot\) owing to the enhanced nucleofugality along the line.\(^{35}\) In general, for 4-substituted unsymmetrical dialkyl-\(\lambda^3\)-bromane, nucleophiles prefer to attack a phenyl ring carrying the electron-withdrawing groups. However, for 2-substituted unsymmetrical dialkyl-\(\lambda^3\)-bromanes, an ortho effect plays a crucial role and the 2-substituted phenyl ring is attacked by the incoming nucleophile.\(^{24,36}\)

### 3 Dialkyl-\(\lambda^3\)-bromanes

Dialkyl-\(\lambda^3\)-bromanes are powerful arylating reagents in organic chemistry. However, given the lack of reports in recent years, this small section proves to merely introduce the reader to their existence, benefits and synthetic problems. Alkyl-\(\lambda^3\)-bromanes are generally considered as unstable transient intermediates. As a result, only a limited number of methods are known for their synthesis and characterizations. Open-chain dialkyl and alkyl(aryl)-\(\lambda^3\)-bromanes were largely unknown until the late 20th century. In 1969, the first symmetrical dialkyl and alkyl(aryl)-\(\lambda^3\)-bromanes were reported by Ohal and co-workers through the self-condensation of alkyl halides with a strong Lewis acid, such as SbF5SO2, under inert atmosphere at low temperatures.\(^{37}\) The formation of dimethyl, diethyl and disopropyl(hexafluoroantimonate)-\(\lambda^3\)-bromanes were characterized by low temperature NMR, IR, and laser Raman spectroscopy.\(^{38}\) Symmetrical dialkyhalonium ions could be obtained by the reaction of alkyl halides with an excess of SbF5SO2. Anhydrous hexacoordinate antimonates (HF-SbF5) or anhydrous silver hexafluoroantimonate in a SO2 solution. Both symmetrical and unsymmetrical dialkyhalonium ions could be obtained by the alkylation of alkyl halides with methyl or ethyl fluoroantimonate in a SO2 solution. Dialkyhalonium salts prepared this were generally clean and not contaminated with any-by-products. While the reaction of alkyl fluoroantimonates with methyl-, ethyl- or disopropyl bromide gave the corresponding dialkyhalonium ions, the reaction of tertary alkyl halides gave an alkylcarbenium ion and a symmetrical dialkyhalonium ion. Both unsymmetrical and symmetrical dialkyhalonium compounds undergo immediate hydrolysis in atmospheric moisture, which hampers their practicality. Moreover, the non-symmetrical \(\lambda^3\)-bromane were kinetically labile and susceptible to disproportionation and self-condensation, even at low temperature (\(-30^\circ\)C). In general, the relative stability of dialkyhalonium ions prepared followed the order R\(\cdot\)I > RBr > RCl, indicating that the larger halogen atom was more capable to accommodate charge. Despite the instability, compound 2 could be isolated as a stable solid at room temperature under argon. The chemical reactivity as well as synthetic application of the prepared dialkyhalonium ions was demonstrated by the alkylation of \(\pi\)-donor aromatics, olefins, as well as a wide variety of \(n\)-donor bases. For example, compounds 2 and 3 facilitated the Friedel-Crafts alkylation of benzene or toluene at \(-50^\circ\)C in SO2:CFI within 5 minutes and the isomer distributions in showed no significant differences from typical Friedel-Crafts reactions. Notably, dimethyl-\(\lambda^3\)-iodane could not facilitate the same reaction, even at \(20^\circ\)C, emphasising the increased reactivity of the dialkyl-\(\lambda^3\)-bromanes compared to the corresponding iodanes. Nevertheless, further investigation of these types of compounds is mainly restricted by their facile decomposition.

In 1937, Roberts and Kimball first proposed that a cyclic three-membered bromonium ion was formed as an intermediate during the electrophilic addition of Br2 to a double bond.\(^{39}\) Subsequently, similar reactions have been invoked for the preparation of cyclic dialkyl-\(\lambda^3\)-bromanes. Ohal and colleagues presented the synthesis of a cyclic dialkyl-\(\lambda^3\)-bromane 6 by treating 2-fluoro-3-bromo-2-methylbutane 5 with SbF5 in a sulfur dioxide solution at \(-60^\circ\)C (Scheme 10).\(^{40}\)

![Scheme 8 Cyclic diaryl-\(\lambda^3\)-bromanes as aryne precursors.](image)

![Scheme 9 Synthesis of dialkyl-\(\lambda^3\)-bromane.](image)

![Scheme 10 Synthesis of a cyclic dialkyl-\(\lambda^3\)-bromane by Ohal and co-workers.](image)

When 2-fluoro-3-bromo-2-methylbutane was ionized in a SbF5:SO2 solution at \(-78^\circ\)C, a stable solution of the (trimethyl)ethylenobromonium ion was obtained. Although NMR evidence for the existence of such species was reported, solid-state structures for the \(\lambda^3\)-bromane were not since subsequent nucleophilic attack to yield the product were rapid. In terms of modern synthetic developments, these procedures have diminished appeal, particularly in terms of safety. Antimony pentfluoride and its derivatives are highly corrosive chemicals which require specialist equipment for handling, which limits the user-friendliness of such techniques. Later, Brown and co-workers reported the solid state structure of a three membered cyclic \(\lambda^3\)-bromane, notably in the absence of SbF5 (Scheme 11).\(^{41}\) The bromination of adamantylidene adamantane in chlorinated hydrocarbons yielded a bright yellow solid, which could be easily

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**Note:** The above text is a natural reading of the provided document and does not include any tables, figures, or images. It has been formatted to maintain the original structure and content of the text. The author acknowledges the use of a specific chemical compound (SbF5) in their synthesis. The synthetic procedure involves the use of SbF5 in the presence of SO2 at low temperatures, leading to the formation of a cyclic dialkyl-\(\lambda^3\)-bromane. The product is stable under these conditions, making it a useful reagent in organic synthesis. The text highlights the challenges and limitations associated with the use of antimony pentfluoride, emphasizing the need for specialized equipment and handling procedures. The synthesis and properties of the cyclic dialkyl-\(\lambda^3\)-bromane are discussed in detail, with a focus on its reactivity and potential applications in organic chemistry.
handled without special precautions. The compound was unstable in polar protic solvents and tended to lose Br₂, converting back to the starting alkene, but it had both stability and modest solubility in CH₂CN, CH₃NO₂, and dichloroethane. In this case, the incorporation of the adamantyl group was to sterically shut down subsequent nucleophilic substitution reactions.

Overall, in recent years, there has been no significant progression in the synthesis of dialkyl-λ³-bromanes, despite their synthetic prowess. Given their emergence as powerful alkylating reagents, certainly a safer, more stable, and versatile bromine(III) type alternative to these reagents would be of huge progress to this area.

4 Dihetero-λ³-bromanes

As it can be found from the previous two sections, the stability of organo-λ³-bromanes is dependent on the presence of aryl groups with the bromine(III) centre. To complement this, several attempts were made to investigate the synthesis and reactivity of dihetero-λ³-bromanes containing one aryl group. The first report for dihetero-λ³-bromane synthesis came from the Martin group in 1980. In this case, the highly reactive liquid, BrF₃, was employed to oxidize the bromoarene 7 in (CFCl₂)₂ at a low temperature for the generation of air and moisture stable solid 8 (Scheme 12). The crystal structure revealed two inequivalent O–Br bonds with bond length slightly longer than the covalent bond lengths (1.81 Å). The two appended "Martin" alkoxyl ligands bind in the apical site of the bromine(III) centre to form a linear O–Br–O hypervalent bonding. An intermolecular oxygen binding to the Lewis acidic bromine(III) centre from another molecule forms an overall dimeric structure and provides higher stability. Compound 8 can tolerate mild acidic or basic conditions. It can oxidize heteroatomic nucleophiles such as PhSH, PhNH₂, NaI, HBr etc.

Despite its high stability, an important limitation of Martin’s λ²-bromane is the use of BrF₃. In 2021, this issue was addressed by Francke, Suna and co-workers. In this ground-breaking example, the simple electrochemical oxidation of arylobromides possessing two coordinating hexafluoro-2-hydroxypropyl substituents delivered the stable λ³-bromane derivatives in high yields (Scheme 13).

With just the use of an undivided cell under constant current conditions, with glassy carbon (GC) as the working electrode, platinum as the counter electrode, TBABF₄ as the supporting electrolyte and HFP (hexafluoroisopropanol) as the solvent, the easy scale-up for the synthesis of the bench-stable λ³-bromane on a multi-gram scale was possible. Moreover, the reactivity of such λ³-bromanes was investigated for oxidative C–C, C–N, and C–O bond forming reactions to complement this simplified synthetic route. The reactivity of Martin’s λ³-bromane is sufficient for oxidative alkylation and benzoxazole formation and could be further enhanced by Lewis or Brønsted acid additives, as demonstrated by its successful application in the biaryl coupling.

Excluding Martin’s λ³-bromane, the chemistry of difluoro-λ³-bromanes is quite well established in the literature. In 1984, Frohn and co-workers revolutionized the field of hypervalent bromine chemistry by introducing difluoro-λ³-bromanes. These were prepared from aryl silanes and BrF₃ through ligand exchange (Scheme 14). In the absence of any other convenient procedure, Frohn’s reagent serves as a pivotal platform for the synthesis of various λ³-bromanes without using highly reactive BrF₃ in subsequent steps. Generally, Frohn’s reagents are stable in room temperature, but require inert atmosphere to prevent instantaneous decomposition to O₂, HF and the corresponding bromoarenes even in the presence of atmospheric moisture. The fluorine ligands can be easily displaced by any other nucleophiles which are stable against oxidation. Easily oxidized substrates such as aromatic alcohols and aldehydes are often converted to their fluoromethyl aryl ether and difluoromethyl aryl ether, respectively, after oxidation followed by 1,2-aryl migration.

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**Scheme 1** Structure of a three membered cyclic λ³-bromane synthesized by Brown and co-workers.

**Scheme 2** Synthesis of stable dialkoxyaryl-λ³-bromane.

**Scheme 3** Electrochemical synthesis of Martin’s bromane.

**Scheme 4** Synthetic route for difluoro-λ³-bromanes and their decomposition pathway.
In a sharp contrast to the high stability and applicability of diacyloxy-λ³-iodanes, the use of diacyloxy-λ³-bromanes is mainly limited by their high moisture sensitivity. [(Bis( trifluoroacetoxy)]-λ³-bromane was first synthesized by Frohn and Giesen from Frohn’s reagent through ligand exchange with trifluoroacetic anhydride (Scheme 15). However, its reactivity was not explored.

Later, Ochiai and co-workers followed the similar procedure to synthesize the corresponding acetoxyl derivative. Such compounds are discretely similar to the very stable, heavily utilized and commercially available (diacetoxyiodo)benzenes. They explored the reactivity of this diacetoxybromobenzene in alkene aziridination reactions (Scheme 16). The aziridination reaction proceeds with TINH₂ or sulfamate esters in a highly stereospecific fashion with retention of the stereochemistry in olefins at room temperature using olefins as the limiting reagents. Interestingly, (diacetoxybromo)arenes were also used in C-H amination reactions of alkanes in presence of a suitable sulfonamide source.

In a seminal report in 2021, Miyamoto, Ochiai and co-workers reported the synthesis of air/moisture stable λ³-bromanes (Scheme 17). The methodology represents the first versatile synthetic methodology towards the synthesis of benchtop stable λ³-bromanes. Analogous to Martin’s approach, the bromine(III) centre is effectively stabilized by intramolecular R-Br-O bonding, both electronically and sterically, but in this case via a 1,2-benzembronoxol-3-(1H)-one (BBX) ligand. The clever use of a N-triflylimino group as an exocyclic changeable ligand allowed the introduction of diverse functionalities through electrophilic substitution reactions on the bromine(III) centre. Using this strategy, a variety of Br-hydroxy-, -acetoxyl-, -alkynyl, -aryl, and bis[(trifluoromethyl)sulfonyl]methylide λ³-bromane derivatives were prepared. Intriguingly, all of these λ³-bromanes were found to be air-, moisture-, and benchtop-stable. The extra stabilization of the bromine(III) centre by intramolecular R-Br-O hypervalent bonding was further confirmed by X-ray crystallography, NMR and IR spectroscopy of N-triflylimino-λ³-bromane. The hydroxy-BBX-λ³-bromane could be stored in refrigerator (4 °C) indefinitely, though it slowly decomposes with a half-life time (t½) of 7.5 days in 1:1 CDCl₃:CH₂Cl₂ solution with evolution of O₂ gas.

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5 Alkenyl-λ³-bromanes

Hypervalent 1-alkenyl(phenyl)-λ³-iodanes enjoy their rich chemistry in modern organic synthesis. The tenacious leaving group affinity of phenyl-λ³-iodanyl groups mean they serve as superb precursors for the generation of alkyldiene carbenes and undergo unusual vinylic nucelofilic displacement by a wide array of nucelophiles. On the other hand, the chemistry of the analogous alkenyl-λ³-bromanes has been remarkably under explored in comparison because user-friendly synthetic methods are not well-established. Most of the proficient synthetic techniques towards these compounds rely on difluoro-λ³-bromanes as key reagents, yielding alkenyl-λ³-bromanes, often with limited stability. Their thermal stability varies over a broad range depending on the nature of the ligands and propensity for polymerization. From an historical perspective, the first preparation of an alkenyl-λ³-bromane was performed in 1985 by Olah and co-workers, which was only characterized by NMR.

The method proceeded via the alkylation of the corresponding vinyl bromides (Scheme 18). For instance, treatment of vinyl bromide, in SO₂ClF at −78 °C, with a fourfold excess of a freshly prepared CH₂=CHF:SbF₅ complex yielded a yellow coloured solution of methyl[vinyl][vinyl]λ³-bromane, whose ¹³C NMR spectrum at −90 °C showed three absorptions at δ = 132.9 (C(q)), 120.9 (C(β)), and 44.1 (Me) ppm. Similarly, the ethylenyl bromonium ion was prepared by using the CH₂=CH₂F:SbF₅ complex in a SO₂ solution. However, these alkenyl-λ³-bromanes were unstable due to their high tendency for polymerization and they consequently decomposed over several hours (roughly 4 h), even at −78 °C. Facile anti-β-elimination of the hydrogen and bromomethyl group, yielding the corresponding alkynes, is the rationality behind the low thermal stability of such reagents. Hence, because of the lack of stability...
of such compounds they were not demonstrated in synthetic applications.

![Scheme 18](image)

Noteworthy, the corresponding alkenyl-\(\lambda^1\)-iodanes could not be prepared under these conditions, associated with the preferential oxidation of vinyl iodides under the alkylation conditions. In reality, this method has relatively low practical value for application because of the low stability and tedious preparation of such compounds. But, considering the sustained success in the development of procedures for the synthesis of alkenyl-\(\lambda^1\)-bromanes, it is obvious that the work served as a pivotal building block for the development of these compounds. Procedures following the ligand exchange of difluoro-\(\lambda^3\)-bromanes with alkynes generally afford the alkenyl-\(\lambda^1\)-bromanes in greater yields compared to the alkylation of vinyl bromides. The first fully characterized, stable alkenyl-\(\lambda^1\)-bromanes were prepared by Ochiai and colleagues in 2005 from difluoro-\(\lambda^3\)-bromanes with the corresponding alkynes (Scheme 19).\(^{32}\) In marked contrast to the Olah’s efforts, the prepared (E)-\(\beta\)-halovinyl(aryl)-\(\lambda^1\)-bromanes (14) had much higher thermal stabilities and could even be stored at ambient temperature.

In this reaction, exposure of 1-decynyl to difluoro-\(\lambda^3\)-bromane (1.5 equiv) and BF₃·Et₂O (1.5 equiv) at −78 °C in dichloromethane under argon yielded 62% of \(\beta\)-fluoro-1-decenyldifluoro-\(\lambda^3\)-bromane stereoselectively in an E/Z ratio of 96:4, after repeated decantation with hexane. (E)-\(\beta\)-ethoxy-7% and (E)-\(\beta\)-chloro-1-decenyldifluoro-\(\lambda^3\)-bromane (4%) were obtained as by-products. The \(\beta\)-ethoxy group originated from BF₃·Et₂O, so the formation of \(\beta\)-alkoxybromanes could be limited using the more sterically demanding BF₃·O(P(Pr))₂. Meanwhile, the \(\beta\)-chlorodecenyldifluoro-\(\lambda^3\)-bromane by-product, arising from chloride transfer from the solvent to reactive intermediates, could be minimized by using less nucleophilic solvents like CH₂Cl₂ or CCl₄ instead of CHCl₃. Ochiai and co-workers prepared compound 15 by the ligand exchange of p-CF₃C₆H₄BF₃ on the bromine(III) atom, with potassium cyclopentanetrifluoroborate (5 equiv.) in MeCN at low temperature in 61% yield (Scheme 20).\(^{30}\) The resulting bromane does not decompose at room temperature for a short period of time (after 3 days, >92% remains). Complexation of 15 with a crown ether could increase the stability: slow evaporation of a n-hexane/ethyl acetate/dichloromethane solution of a 1:2 mixture of 15 and [18]-crown-6 at 4 °C afforded colourless crystals of a 1:1 complex of 15-[18]-crown-6, which were thermally stable and could now be left standing under ambient conditions for two weeks. Even though 15 was stable in the solid-state, solvolysis took place at room temperature.

![Scheme 19](image)

![Scheme 20](image)

Latterly, Ochiai et al. reported the first stereoselective synthesis of (E)-\(\beta\)-alkylvinyl(aryl)-\(\lambda^1\)-bromanes via a boron-\(\lambda^1\)-bromane exchange reaction (Scheme 21).\(^{33}\) The 1-alkenyl-\(\lambda^1\)-bromanes with a \(\beta\)-fluoro or \(\beta\)-chloro group were formed through a stereoselective anti-Markovnikov addition of difluoro-\(\lambda^3\)-bromane to terminal alkynes. For instance, the ligand exchange of Frohn’s reagent with (E)-1-decenyldifluoroborane (generated in situ from the reaction of postassium decenyloborane with BF₃·OEt₂) at −78 °C for 1 h afforded the corresponding (E)-vinyl-\(\lambda^3\)-bromane in 85% yield. A series of vinyl-\(\lambda^1\)-bromanes could be synthesized in high to moderate yields, but they were thermally labile at ambient temperature and moisture sensitive. However, 16 could be stored for several weeks in its solid state at −78 °C. Interestingly, compounds of the type 16 were able to facilitate the efficient Sₐ₂ substitution at a vinlylic carbons, under mild reaction conditions.

![Scheme 21](image)

Weakly nucleophilic anions such as HBF₄, TIOH and Tf₂CH could all function as nucleophiles towards the vinyl-\(\lambda^3\)-bromanes. For example, the in-plane vinylic Sₐ₂ substitution of (E)-vinyl-\(\lambda^1\)-
bromanes with potassium bis(triflyl) methanide proceeds to give the \((Z)\)-vinylloxy oxosulfonium ylides 17 exclusively. Noteworthily, \((E)\)-\(\beta\)-alkynyl-\(\lambda^3\)-iodanes failed to undergo similar vinylic S2 reactions with the same weak nucleophiles, which likely signifies the higher nucleofugality of aryl-\(\lambda^3\)-bromanyl groups in comparison to aryl-\(\lambda^3\)-iodanyl groups. In general, all of the significant experimental methods for the preparation of alkynyl-\(\lambda^3\)-brromanes involve difluoro-\(\lambda^3\)-bromane as the principal reagent. Clearly, these synthetic methods would benefit from the exclusion of fluorinating reagents in order to increase the safety and synthetic convenience for researchers. Nevertheless, the recently conveyed methods are generally high yielding and give rise to sufficiently stable alkynyl-\(\lambda^3\)-bromanes, such that novel and synthetically valuable procedures could be demonstrated.

6 Alkynyl-\(\lambda^3\)-bromanes

The hypervalent 1-alkynyl(aryl)-\(\lambda^3\)-iodanes exhibit diverse reactivity for modern organic synthesis.\(^{54}\) Such compounds are highly electron-deficient owing to the powerful electron-withdrawing nature of the \(\lambda^3\)-iodanyl groups. They serve as efficient Michael acceptors to a variety of soft nucleophiles. The Lewis acid catalyzed ligand exchange on iodine(III), of the structure ArIX, or ArlX, with boranes, silanes or stannanes, are well-established methods for the syntheses of 1-alkynyl-(aryl)-\(\lambda^3\)-iodanes (Scheme 22).\(^{55}\)

\[ \begin{align*}
\text{R} & \equiv \text{SiMe}_3 & \text{PhOBF}_3 & \equiv \text{Ar} \\
\text{R} & \equiv \text{SnBu}_3 & \equiv \text{OTf} & \equiv \text{Ar}
\end{align*} \]

Scheme 22 General methods for the synthesis of alkynyl-\(\lambda^3\)-iodanes.

In marked contrast to 1-alkynyl(aryl)-\(\lambda^3\)-iodanes, the syntheses of 1-alkynyl(aryl)-\(\lambda^3\)-bromanes is much less orthodox, accredited to the quintessentially more difficult preparation and handling \(\text{ArBrX}_2\)'s. Although, the reported synthetic procedure is considerably similar to that of \(\lambda^3\)-iodanes. Until recently, hypervalent 1-alkynyl(aryl)-\(\lambda^3\)-bromanes were not synthesized or characterized. In 2003, Ochiai, Frohn, and co-workers reported the first synthesis of alkynyl-\(\lambda^3\)-bromanes via the Lewis acid catalyzed stannane-bromane(III) exchange of difluoro[p-(trifluoromethyl)phenyl]-\(\lambda^3\)-bromane with 1-alkylstannanes (Scheme 23).\(^{54}\) The ligand exchange with silanes instead of stannanes gave poor results under the same conditions, but 1-alkynyl(trifluoro)borates could also be used to access the desired bromanes. Difluoro-\(\lambda^3\)-bromane was prepared in 72% yield by reacting \(p\)-(trifluoromethyl)phenyl(trimethyl)silane with bromine trifluoride at \(-78\) to \(-25\) °C in dichloromethane. Subsequently, the reaction of difluoro-\(\lambda^3\)-bromane with a trimethylstannyl derivative and \(\text{BF}_3\text{OEt}_2\) at \(-78\) °C afforded the alkynylbromane \(\text{18}\) in 82% yield.

In this reaction, an excess amount of difluorobromane (1.5 equiv) was required. Selective stannane-Br(III) exchange could be achieved with various primary, secondary, and tertiary alklylethenyl stannanes in good yields (76 - 89%). However, the ligand exchange with phenylethylnyl stannane was not successful and gave a tarry matter. Contamination of these oily \(\lambda^3\)-bromanes with a small amount (4-9%) of \((E)\)-\(\beta\)-fluorovinyl-\(\lambda^3\)-bromane was noted in every case. Furthermore, due to their high Michael accepting ability, these bromanes were relatively labile and gradually decomposed to \(p\)-bromo(trifluoromethyl)benzene upon standing at room temperature. But, they could be handled under air for brief moments at a time. The bromanes were also highly water sensitive: the half-life \((t_{1/2})\) of \(\text{18}\) CDCIs was decreased from 13 days to just 25 minutes in the presence of a small amount of water. Despite this, full structural conformation of the prepared bromanes was still possible by the complexation of \(\text{19}\) with a crown ether. The slow evaporation of a dichloromethane: diethyl ether \((1:1)\) solution of a 2:1 mixture of \(\lambda^3\)-bromane \(\text{19}\) and \(\text{18}\)-crown-6 at 4 °C under argon afforded colourless single crystals of a 2:1 complex that was suitable for X-ray crystallography. Complexation of \(\lambda^3\)-bromanes with crown ethers seems to be a valuable technique for stabilizing such structures of this type and has been reported since. As expected, the strong electron-withdrawing nature of the phenyl-\(\lambda^3\)-bromanyl moiety combined with the long C-C triple bond length made these alkynyl bromanes highly efficient Michael acceptors. The compounds underwent tandem Michael-carbene rearrangement in the presence of a variety of nucleophiles under mild conditions. For instance, exposing compounds \(\text{18}\) to \(\text{Bu}_2\text{OTf}\) in dichloromethane at room temperature afforded the alkynyl tosylate in 55% yield, along the cyclic alkynyl tosylate as a minor product (5% yield). In fact, weakly nucleophilic superacid conjugate bases could also participate as a Michael donor, which cannot be observed in iodine chemistry. Attack of the \(\beta\)-acetylenic carbon of by a sulfonate anion generated the alkylidene carbones. A variation of this procedure using alkynyl stannanes as nucleophiles can be used to prepare polyynes.\(^{56}\) More recently, Frohn and co-workers accessed alkynyl(aryl)- and bis(alkynyl)-\(\lambda^3\)-bromonium salts starting from aryldifluoro bromanes (Scheme 24).

Scheme 23 The first synthesis of alkynyl-\(\lambda^3\)-bromanes.

\[ \begin{align*}
\text{R} & \equiv \text{SnMe}_3 & \text{Ar/BrF}_2 (1.5 \text{ equiv}) & \equiv \text{BF}_3\text{OEt}_2 (1.5 \text{ equiv}) & \equiv \text{Ar} \\
\text{R} & \equiv \text{SnBu}_3 & \equiv \text{OTf} & \equiv \text{Ar}
\end{align*} \]
Under similar conditions, the authors were able to access the previously unknown perfluorinated alkynyl(aryl) bromonium versions by boron-bromine(III) exchange, in this case using the electron deficient C$_3$F$_7$BrF$_3$ hypervalent bromine source in place of p-CF$_3$C$_6$H$_4$BrF$_3$ (Scheme 25). For instance, the perfluorinated molecule 23 was obtained by addition of 22 to a cold solution of bromane 21, in 1,1,1,3,3-pentfluorobutane (PPF), and was isolated as a reasonably stable white solid after removal of all volatiles. In the same fashion, the reaction of trans-pentfluoroprop-1-en-1-yI(difluoro)borane 26 with the same bromane (21) yielded the perfluorinated product 27 with retention of configuration. Interestingly, this retained configuration is different from the synthesis of [(CF$_3$CF=CF)$_2$]Br][(CF$_3$CF=CF)$_2$BF] by the reaction of a borane and BrF$_3$, where partial conversion to the cis-isomer transpires.$^{21}$

Transformation of the polarizable triple bond in the perfluoralkynyl moiety, bonded to bromine(III), was possible due to the highly electron-deficient property of the C-C triple bonds. Upon slow addition of the weakly nucleophilic hydrogen fluoride at 24 °C to 23, 38% of 24 was obtained after 12 h. Extension of the reaction time to 60 h resulted in the isolation of bromopentafluorobenzene and 1H,1H-octafluoropentan-2-one 25, likely caused by the presence of trace amounts of water. Formation of the ketone indicates the enhanced electrophilicity of the perfluoralkynyl-λ$^3$-bromanes. Despite the proficiency of the methods for the synthesis of alkynyl-λ$^3$-bromanes, they do not comply with contemporary demands for safe and accessible procedures that are required for the widespread utilization of these compounds. In essence, the prerequisite for fluorinating reagents remains prevalent in all methods, including modern day literature. Certainly, methodology that can avoid the necessitate ligand exchange of ArBF$_3$’s, that are typically troublesome to handle, would improve the expediency of such synthetic techniques.

Unlike hypervalent organo-λ$^3$-iodane, the chemistry of λ$^3$-bromane is greatly underdeveloped despite their synthesis being known since 1952. This can be attributed to the limitations in user-friendly synthetic methods for their syntheses, as well as their lack of stability. Consequently, their reactivity profile is largely under-explored in terms of synthetic application. Overall, the progress in the field of hypervalent bromine chemistry is surprising slow compared to the rapid growth with hypervalent iodine chemistry. However, the recent breakthroughs reported in this year certainly simplify the synthesis techniques significantly, and as such improve the accessibility of different hypervalent bromine compounds. We believe, this will be pivotal in unfolding their unique reactivities and attracting more research groups to explore the largely uncharted field of hypervalent bromine compounds.

Funding Information

We thank EPSRC (PhD studentship B.W. and postdoctoral fellowship to T.P.) for generous financial support.

Acknowledgment

The School of Chemistry, Cardiff University is gratefully acknowledged.

Conflict of Interest

The authors declare no conflict of interest.

References

Thomas Wirth is professor of organic chemistry at Cardiff University. He received his PhD after studying chemistry at Bonn and the Technical University of Berlin. After a postdoctoral stay at Kyoto University as a JSPS fellow, he worked independently at the University of Basel before taking up his current position at Cardiff University in 2000. He was invited as a visiting professor to a number of places: Toronto (1999), Tokyo (2000), Osaka (2004, 2008), Kyoto (2012). He was awarded the Werner-Prize from the New Swiss Chemical Society (2000), the Furusato award from JSPS London (2013), the Wolfson Research Merit Award from the Royal Society (2016) and the Bader-Award from the Royal Society of Chemistry (2016). In 2016, he was elected as a fellow of The Learned Society of Wales. His main interests of research concern stereoselective electrophilic reactions, oxidative transformations with hypervalent iodo reagents and flow chemistry performed in microreactors.