Recent Advances in Fluoride-Free Aryne Generation from Arene Precursors

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Aryne chemistry has experienced a remarkable renaissance in recent years, with a significant increase in the synthetic applications reported for these highly valuable reactive intermediates. This resurgence of interest is in part due to the introduction of ortho-silylaryl triflates as precursors which can be activated under mild conditions using fluoride. Alternative fluoride-free strategies have received interest in the last decade, with a number of precursors to arynes and their activators reported. These approaches offer alternative modes of reactivity which prove, in some cases, to be orthogonal to those of ortho-silylaryl triflates. This review highlights some of the more recent fluoride-free methodologies developed to access aryne intermediates that start from arene-based precursors.

Introduction

Arynes have attracted a great deal of attention ever since Roberts and co-workers’ classical 14C-labelling experiments with chlorobenzene I, wherein evidence for the existence of a neutral benzyne intermediate II was rationalised by the observance of an equimolar mixture of isotopomeric anilines III and IV (Scheme 1a).1,2 The distinctive reactivity of arynes enables the construction of complex polycyclic and heterocyclic aromatic frameworks in short order and has captivated the interest of organic chemists.2,3 In particular, the ability to form multiple C-C or C-X bonds in a single operation and typically regioselective manner offers a profound strategic advantage.2 The utility of arynes as key reactive intermediates has also been illustrated by their application to the synthesis of complex natural products,21 as well as to the preparation of extended polycyclic aromatic hydrocarbons3 which are of particular interest in materials science.4

The reactive nature of aryne intermediates necessitates in situ generation from stable precursors. Synthetic applications of arynes were somewhat restricted in early years due to severe limitations on functional group tolerance caused by the harsh conditions required for aryne formation. Early precursors included 1-aminobenzotriazoles V, which proceed via nitrene intermediate VI,5 as well as benzenediazonium-2-carboxylates VII, which decompose to form arynes with concomitant release of CO2 and N2 gases (Scheme 1b).6 Other methods, which are still encountered today, required ortholithiation of mono-substituted arenes VIII (typically aryl halides) or metal-halogen exchange of disubstituted arenes IX, both involving the elimination of a good leaving group.

Scheme 1 Experimental evidence for a benzyne intermediate and established methods of aryne generation.

In 1983, Kobayashi and co-workers introduced ortho-silylaryl triflates X as stable precursors that can generate arynes under mild conditions upon the addition of fluoride to trigger a 1,2-syn-elimination (Scheme 1c).7 A variety of functional groups, reagents and catalysts proved to be compatible with this method and as a result the field of aryne chemistry quickly gained a revised interest.2 The development of ortho-silylaryl triflates X, along with the iodoaryl triflates introduced by Suzuki and co-workers in 1991,8 have led to significant advances in the field of aryne chemistry9 and their...
synthetic applications to access valuable and otherwise challenging benzenoid motifs have been presented in many extensive reviews. Areas of particular focus include o-bond insertion reactions for the formation of C-C, C-N and C-O bonds, cyclodDITION processes to prepare bicyclic species, nucleophilic addition to afford substituted benzene derivatives, metal-catalysed reactions and multi-component couplings.

Due to the mild reaction conditions and high functional group tolerance offered by ortho-silylaryl triflates, they are the most widely used aryne precursors in contemporary organic synthesis. However, the development of new methods to access aryne intermediates has continued, including the use of alternative activators and/or precursors, as well as pioneering catalytic strategies. Amongst these new approaches, the hexaethylene-Diels-Alder (HDDA) reaction of polyalkynes, an essentially “reagentless” method of aryne generation, has received considerable attention (Scheme 1d). Pioneered by the groups of Hoye and Lee, the origins of the HDDA reaction lie with independent reports by Ueda and Johnson in 1997. Since Hoye and co-workers coined the term ‘HDDA’ in 2012, there has been a marked increase in reports utilising this approach, showcasing extremely interesting and unusual aspects of aryne chemistry.

This review aims to highlight these recent developments in fluoride-free aryne generation, which supplement the conventional ortho-silylaryl triflates and in certain cases present alternative modes of aryne reactivity. As the HDDA reaction has been the subject of some extensive recent reviews, the focus here will be on new methods involving arene-activated precursors and their different activators.

1,2-Difunctionalised Arene Precursors

In 2013, Hosoya and co-workers reported the generation of aryne intermediates from ortho-borylaryl triflate 1 (Scheme 2a). Treatment with sec- or tert-butyllithium at low temperatures resulted in the corresponding ‘ate’ species 2, which underwent β-elimination to the aryne 3 upon warming to room temperature. Although milder bases such as Cs₂CO₃ and K’OBu were screened, as well as TBAF (a common activator for ortho-silylaryl triflates X), they were all found to be ineffective or resulted in diminished yields. The intermediacy of boron-ate complex 2 was probed by ¹¹B, ¹H and ¹⁹F NMR spectroscopy both before and after the addition of tert-butylithium. The observed changes in chemical shifts provided evidence for the formation of an intermediate for ate complex which was stable below 0 °C and collapsed to form benzene 3 close to room temperature. The ortho-borylaryl triflate precursors were readily accessed from the corresponding phenols through a one-pot Ir-catalysed borylation-triflation sequence. The utility of this method of aryne generation was illustrated by trapping the intermediate with a range of aryrophiles (Scheme 2b). By introducing the coupling partner after the formation of the boron-ate complex, aryrophiles containing base-sensitive functional groups were also amendable to the methodology. Interestingly, aryl triflate 10, containing both boryl and silyl moieties adjacent to the triflate leaving group, was found to exclusively afford the silyl-containing product 11 upon treatment with sec-butyllithium (Scheme 2c). TBAF was also found to be a suitable activator of the boryl group in precursor 10, yielding cycloadduct 11 as the sole product even in the presence of the ortho-silyl group. However, it was found that in the absence of the silyl moiety in arene 10, borylaryl triflate 1 was unreactive towards fluorde, indicating an orthogonal relationship to ortho-silylaryl triflate precursors X.

Furukawa reported in 1987 that ortho-sulfinylphenyl bromide 12 can generate benzene 3 when treated with phenylmagnesium bromide, proceeding via a sulfoxide-magnesium exchange and subsequent β-elimination of the leaving group (Scheme 3a). The resulting benzene intermediate 3 was ultimately trapped with furan 14 to furnish cycloadduct 15 in 73% yield. More recently in 2014, Hosoya and co-workers extended this method of benzene generation to ortho-sulfinaryl triflates 18, using Grignard or organolithium reagents at low temperatures. Hosoya rationalised that the reactivity would be enhanced, relative to 12, by replacing the aryl halide with a triflate leaving group, consequently obviating the previous requirements of heating and extended reaction times. Analogous to the synthesis of ortho-silylaryl triflates, ortho-sulfinaryl triflates are prepared from the corresponding ortho-bromoaryl triflates (Scheme 3b). Dilithiation of bromophenol 16 is followed by C-thiolation to yield aryl sulfide 17, which undergoes subsequent triflation and mono-oxidation with m-CPBA to afford the desired sulfinyl...
chloride initiates iodine-magnesium exchange, followed by β-elimination of one of the triflate groups to reveal 3-triflyloxybenzyne 22. The utility of this method was illustrated by trapping the intermediate at −30 °C with a range of arynophiles, including azide (23a), furan (23b) and nitrone (23c) derivatives, amongst others, which afforded the corresponding cycloaddition products in good to excellent yields (Scheme 4a). Presumably, the lower nucleophilicity of TMSCH₂MgCl is beneficial in the prevention of side reactions with electrophilic arynophiles, such as in the preparation of the nitrone derivative 23c. Elsewhere, the triflyloxy substituent was found to significantly accelerate aryne generation, as demonstrated by a competition reaction with the analogous 3-methoxybenzyne precursor 24 (Scheme 4b). Exposure of an equimolar mixture of the aryne precursors 21 and 24 to TMSCH₂MgCl exclusively furnished the cycloadduct 25 in 94% yield, with quantitative recovery of 3-methoxybenzyne precursor 24, indicating no aryne generation from 24 under the reaction conditions. These results were rationalised due to the differences in the inductive electron withdrawing abilities of the methoxy and triflyloxy groups, with the triflyloxy substituent thought to accelerate the initial iodine-magnesium exchange.

Fluorosulfonyl analogues of ortho-silylaryl triflates are known to be similarly capable of generating benzene upon exposure to fluoride. For example, in 2011 the group of Akai discovered that ortho-silylaryl nonafluorobutanesulfonyl fluoride, spontaneously generated arynes by dequatering the fluoride produced during the sulfonylation reaction. In addition, Novák showed that the imidazolylsulfonate group was amenable to fluoride-induced elimination to reveal arynes from the corresponding ortho-silylaryl imidazolylsulfonate precursors. However, in 2015 Hosoya and co-workers reported that common ortho-silylaryl triflates 20 could also be activated in the absence of fluoride, instead using mild base, such as Cs₂CO₃, and a crown ether to couple a range of arynes with various arynophiles (Scheme 5a). Similarly, in 2015, Wang and co-workers found that the analogous ortho-silylaryl
fluorosulfates 27 could also perform as efficient aryne precursors upon the addition of Cs$_2$CO$_3$ and 18-crown-6 (Scheme 5b).\textsuperscript{23} Treatment of substituted fluorosulfate precursors 27 with benzyl azide 28 yielded the corresponding benzotriazoles 29 from the Huisgen cyclisation in good to excellent yields. The ortho-silylaryl fluorosulfates 27 were accessed via the same general synthetic route as the triflate derivatives, using sulfuryl fluoride – an inexpensive insecticide fumigant – for the final sulfonylation rather than trifluoromethanesulfonic anhydride. Notably, the use of Cs$_2$CO$_3$ as an activator enabled fluoride-sensitive functionality to be tolerated in the reaction; for example, benzotriazole 29d was obtained in 78% yield using Cs$_2$CO$_3$, whereas complete removal of the TBS-silyl ether occurred when the same reaction was conducted with CsF. Finally, the comparative stability of ortho-silylaryl fluorosulfate 27 and ortho-silylaryl triflate 20 under basic conditions was assessed. Whilst triflate precursor 20 displayed significant decomposition to the corresponding phenol within a week of exposure to NaOH, the fluorosulfate analogue remained intact after the same period of time.

In 2016, Li and co-workers reported the sequential generation of two aryne intermediates, 22 and 31, from the domino aryne precursor 30 (Scheme 6a).\textsuperscript{24,25} Initial treatment of 1,3-bis-triflate 30 with CsF in the presence of sulfonamides afforded 1,3-diaminobenzenes 33 wherein the intermediate aryl anion 32 captured a proton from either the solvent (acetonitrile) or the amine reagent.\textsuperscript{24} A combination of K$_2$CO$_3$ and 18-crown-6 also activated aryne precursor 30; which, coupled with a solvent switch from acetonitrile to toluene, was found to favour the competing thia-Fries rearrangement of 32 to afford 1,2,3-trisubstituted arenes 36 (Scheme 6b). In contrast, mixtures of 1,2,3-trisubstituted 36 and 1,3-

![Scheme 5](image)

Scheme 5 Cs$_2$CO$_3$ as an activator for aryne generation.\textsuperscript{22,23}

![Scheme 6](image)

Scheme 6 K$_2$CO$_3$-mediated diamination of a domino aryne precursor.\textsuperscript{24}

disubstituted arenes 37 were isolated when either KF or CsF were employed, presumably due to the generation of HF during the reaction. A number of N-triflyl anilines 38 were shown to be amenable to the K$_2$CO$_3$/18-crown-6 conditions, with ortho, meta and para substitution tolerated (Scheme 6c).

Li and co-workers extended the scope of the domino aryne precursor 30 to undergo 1,2-diamination with sulfamide nucleophiles 40 (Scheme 7a).\textsuperscript{2} Optimisation of the reaction conditions revealed that K$_2$CO$_3$/18-crown-6 afforded a higher yield of vicinal-diamine 41a (85%) in comparison to common fluoride sources. The high reactivity of the carbonate anion was rationalised as being due to a weakened Ar-C-Si bond, arising as a result of the two strongly electron-withdrawing triflate substituents, making the TMS group more susceptible to nucleophilic attack. Different N-aryl substituents were tolerated on the sulfamides and the corresponding 1,2-diaminobenzenes 41 were isolated in good to excellent yields (Scheme 7a). Interestingly, the nature of the substituent in the 5-position of the aryne precursor 42 was shown to have a
marked effect on the reaction efficiency (Scheme 7b). For example, when methyl substituted precursor 42a was subjected to the reaction conditions, the desired product 43a was isolated in 78% yield; however, the fluorinated analogue afforded 43b in just 22% and the silyl derivative 43c was not even observed.

Elsewhere in 2016, Keay and co-workers proposed the intermediacy of an aryne, generated from aryl phosphine 44 in the presence of NaH and DMF, to account for the unexpected formation of 3-(dimethylaminomethyl)-2-hydroxy-6-methoxybenzaldehyde 51 (Scheme 8). It was postulated that an initial base-induced phospha-Brook rearrangement and β-iodide elimination furnished aryne 45. Next, incorporation of two equivalents of DMF leads to (bis)aminobenzaldehyde 49. Subsequent loss of diphenylphosphine oxide through intramolecular attack of a dimethylamino group and a final aqueous work-up affords phenol 51.

Support for an aryne intermediate was provided by the appearance of cycloadduct 53 in a reaction conducted in the presence of furan; 53 was isolated together with phenol 51 in a combined yield of 53% (Table 1, entry 1). In addition, replacement of DMF – integral to the proposed mechanism of formation of phenol 51 – with HMPA resulted in the exclusive formation of cycloadduct 53, wherein the phosphinate group had been cleaved to reveal the benzyl alcohol (entry 2).

Further evidence for the instability of the P-O bond under the reaction conditions was afforded when a model benzyl phosphinate, lacking the aryl phosphine oxide and iodide necessary for aryne formation, exclusively produced para-methoxy benzyl alcohol 54 in 77% yield (entry 3). Finally, triflate and bromide leaving groups (entries 4 and 6) were found to be effective for the aryne generation. In contrast, no reaction was observed with the chloro derivative (entry 5).

### Monofunctionalised Arene Precursors

In 2002, Uchiyama and co-workers reported the deprotonative zincation of *meta*-functionalised haloarenes 56 as a method for generating 3-substituted benzynes 60 (Scheme 9a). Regioselective metalation was observed at the C-2 position of 56 by using lithium dialkyltetramethylpiperidino-zincates (R₂Zn(TMP)Li) and the reactivity of the resulting arylnitrene intermediate 59 was found to be dependent on the nature of the alkyl ligands. For example, in the presence of the diene 61, zincation with Me₂Zn(TMP)Li led to the corresponding cycloadduct 57, indicating the intermediacy of an aryne 60.
However, treating 56 with t-Bu2Zn(TMP)Li did not lead to aryne formation; instead, iodoarene 55 was isolated upon exposure of the resulting arylzincate 58 to iodine. In a related approach, benzene intermediates could be formed from o-dihalobenzene analogues through an initial halogen-zinc exchange, followed by elimination. Uchiyama extended the deprotonative zination method to incorporate mono-substituted arene precursors 62, as trflate and most halide substituents were found to function both as ortho directors and as good leaving groups, yielding cycloadduct 63 in quantitative yields (Scheme 9b). Iodide proved to be the exception to this approach, presumably due to preferential iodine-zinc exchange.

Daugulis and co-workers reported base-mediated benzyne generation from mono-substituted aryl chlorides and triflates 66 to achieve C(sp²)-C(sp²) coupling with arenes and heteroarenes 64 (Scheme 10a).28,29 Lithium 2,2,6,6-tetramethylpiperidide (TMPLi) was found to be the optimum base and played a dual role in the reaction. Firstly, TMPLi deprotonates 66, leading to an ortho elimination to form the benzene intermediate 3. Secondly, the base removes the most acidic proton on the arene/heteroarene substrate 64, which facilitates reaction with the aryne. The bulky nature of the TMP base also reduces its deleterious nucleophilic attack with the benzene intermediate 3. The authors noted that a limitation of using aryl chlorides as aryne precursors was the need to optimise the temperature for each individual reaction (Scheme 10b). Furthermore, substrates containing base-sensitive functional groups were found to be incompatible with the reaction conditions. However, in some cases the use of commercially available aryl chlorides may be advantageous. For example, when non-acidic arenes 64 are used as coupling partners, aryl triflates result in low product yields due to fast aryne formation relative to arene deprotonation. In contrast, aryl triflates can be employed at even lower temperatures than aryl chlorides, which affords a greater functional group tolerance (Scheme 10c). Furthermore, the facile loss of triflate from 66 allows dihalogenated arene coupling partners to be used (70b and 70c). Interestingly, common benzyne precursor 2-trimethylsilylphenyl triflate 20 was found to undergo the TMPLi-mediated arylation of benzo[1,2-b]thiophene 71 with the TMS group remaining intact (70e). Finally, Daugulis showed that the aryllithium intermediate 67 arising from the C-C coupling step (see Scheme 10a) could be trapped with a number of different electrophiles, including 1,2-diiodoethane 72a, DMF (72b), pivaldehyde (72c) and TMSCl (70e) (Scheme 10d).

More recently, Stuart and co-workers reported the generation of arynes under fluoride-free conditions via ortho-C-H deprotonation of unsymmetrical aryliodonium salts 75 (Scheme 11a).30 This concept can be traced back to a report in...
1974 from Akiyama and co-workers, wherein sodium 5-phenyltetrazolide was arylated in the presence of di(p-tolyl)iodonium bromide. The diaryliodonium salts are readily obtained from either commercially available aryl boronic acids or aryl iodides via one-pot syntheses and offer an alternative to the more common 1,2-difunctionalised arylene precursors discussed in the previous section. Stuart found that treatment of a range of ortho-, meta- and para-substituted aryl(mesityl)iodonium tosylate salts with LiHMDS in the presence of excess furan led to the corresponding cycloadducts in good to excellent yields (Scheme 11b). Compared to traditional methods of arylene formation that operate via ortho-deprotonation of aryl halides, this method offers significantly milder conditions – weaker bases and warmer temperatures – which increases functional group tolerance. Furthermore, excellent regio- and chemoselectivity was observed with regards to the site of deprotonation and choice of leaving group respectively, which offers attractive orthogonal reactivity to aryl halide precursors.

Electron withdrawing substituents at C-2 (79b-d) were selected for deprotonation at C-2, consistent with the regioselectivity seen with 1,3-dihaloarenes. Perhaps surprisingly, modest levels of selectivity towards deprotonation at C-2 (4.2:1) were also observed when an inductively donating methyl group was incorporated at C-3. This ortho-deprotonation strategy was also applied to the cycloaddition of benzyl azide with the arylene derived from aryliodonium precursor, which yielded benzoazetazole as a 3:8:1 mixture of regioisomers in 63% yield (Scheme 11c). The same arylene was successfully trapped with nucleophilic amines affording regioisomeric mixtures of products, consistent with the intermediacy of an arylene.

Shortly after Stuart’s report, Wang et al. also demonstrated the ability of diaryliodonium triflate salts to function as arylene precursors; effecting efficient N-arylation of a range of secondary amines in the presence of KOT-Bu (Scheme 12). Elsewhere, Tilley and co-workers have recently developed a new method for the generation of arynes via ortho-deprotonation of aryl halides that uses a mild base, KOT-Bu, and proceeds at ambient temperature to afford the corresponding alkyl aryl ethers. This approach was also applied to the arylation of a secondary amine. However, despite the improvements relative to traditional approaches towards aryl halide deprotonation, this method does require an additional electron withdrawing substituent to the halide to acidify the ortho-C-H, thereby rendering this a 1,3-difunctionalised precursor.

**Catalytic Aryne Generation**

Catalytic arylene generation has emerged in recent years as an attractive strategy to access transition metal-associated arynes, with a few pioneering reports having demonstrated this principle. As the metal can initiate both arylene formation and catalyse subsequent bond-forming transformations, the generation of metal-associated arynes is
a highly attractive concept which can further advance the exploitation of arynes in synthesis.

In 2008, Kim and co-workers established that certain ortho-bromobenzoates generate triphenyles under Pd catalysis, with an aryne intermediate suggested to account for the products. Oxidative addition into the C-X bond of ortho-halobenzoate 90 is believed to be followed by δ-carbon elimination and loss of CO₂ from ary palladium intermediate 91 to generate Pd-associated aryne 92 (Scheme 14a). Triphenylene 93 is then the product of a Pd-catalysed [2+2+2] cyclotrimerisation of Pd-aryne 92, with the active catalyst regenerated by reductive elimination of the corresponding alkyl halide (‘RX’). Aryne formation was found to be dependent upon the nature of the benzoate substrate, with significant amounts of the dimeric biaryl species 94 isolated when methyl 2-iodo and ethyl 2-bromobenzoates (90b and 90d respectively) were subjected to the reaction conditions (Scheme 14a). The ethyl bromobenzoate (90d) was markedly less reactive than the methyl esters (90a+b), which may be due to a more facile δ-elimination of the methyl group, whilst the chloro derivative (90c) underwent decomposition. Allyl ester 90e yielded small amounts of triphenylene 93e (25%), but interestingly no biaryl compound 94e was isolated. It was suggested that this substrate operated through a slightly different reaction mechanism, invoking an initial π-allyl palladium complex followed by decarboxylation to the Pd-associated aryne 92e.

Substituted ortho-bromobenzoates 90f and 90g (Scheme 14b) were also found to be amenable to the methodology; 42% of trimethoxytriphenylene 93f and 44% of trianaphthylene 93g were isolated along with <5% of the minor regioisomers (93f′ and 93g′). The corresponding biaryls 94f and 94g were also observed, as well as the products from reductive dehalogenation (95f and 95g). Intriguingly, when 2-bromoterephthalate 90h was subjected to the reaction conditions the corresponding triphenylene 93h was not isolated. Rather, the dimer 94h (24%) and dehalogenated compound 95h (30%) were obtained.

Greaney and co-workers also used the formation of triphenylene as a model reaction to validate intermediate Pd-aryne formation, developing a Pd(II)-catalysed C-H activation strategy starting from benzoic acids (Scheme 15a). It is proposed that the reaction proceeds via an ortho-C-H activation of benzoic acid 96 to afford oxapalladacycle 97. Decarboxylation from the palladacycle furnishes Pd-associated aryne 98, which undergoes a [2+2+2] trimerisation to generate triphenylene 93. Pd(OAc)₂ was an efficient catalyst, whilst the precise nature and stoichiometry of the oxidant, Cu(OAc)₂, proved to be essential in promoting catalyst turnover and minimising the formation of by-products. The intermediacy of an aryne was supported by identical regioselectivities observed with para- and meta-substituted starting materials 99 and 102 (Scheme 15b). For example, para-substituted benzoic acids 99 can produce only one arylene isomer 100, which could lead to a pair of regioisomeric triphenyles 101 and 101’. However, the unsymmetrical isomer 101 was obtained as the sole product. In contrast, meta-substituted benzoic acids 102, can afford two possible aryne intermediates (100 and 103), allowing potentially three different regioisomeric triphenyles (101, 104 and 104’). Nonetheless, only one isomer (101) was observed, which indicated activation of the distal C-H bond (H₃) to the meta substituent.
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in 102. Therefore, it was reasoned that both the meta- and para-substituted benzoic acids 99 and 102 proceeded via arylene intermediate 100. Finally, the authors noted that a limitation of the methodology was that ortho-substituted precursors were generally ineffective at arylene generation. However, one example was obtained with ortho-toluic acid 105, yielding 23% of the unsymmetrical triphenylene 101a. Although the yields were generally moderate, this report demonstrates the exciting principle of catalytic arylene generation utilising a cheap monofunctionalised starting material.

More recently, in 2014, Greaney and co-workers introduced 2-bromoarylboronic esters 106 as alternative catalytic arylene precursors (Scheme 16a). The arylboronic esters can be obtained from the corresponding readily available 2-bromoarylboronic acids in a single step, or in two steps from the 2-bromoiodoarene derivatives. A mixture of Pd(dba)2 and DPEPhos was found to catalyse both the arylene generation (via an intramolecular Suzuki-Miyaura reaction) and subsequent cyclotrimerisation to form triphenylenes 101 and 101’ in a 3:1 ratio from a number of para-substituted arylboronic esters 106. Drawing parallels to the approach used by Wenger and co-workers to prepare stoichiometric Ni- and Pd-coordinated benzenes from ortho-metalated phenyl boronic esters,33 a mechanism involving a Pd-coordinated arylene was proposed to account for the regiochemical outcome (Scheme 16b).35 Oxidative addition into thearyl bromide 107 is followed by a base-mediated intramolecular transmetallation step, involving boron-ate complex 109, to form Pd-associated arylene 100. Ligand exchange between two equivalents of 100 and subsequent cyclo palladation results in the formation of the isomeric pallacycles 111 and 112. Here the authors assume a 1:1 ratio of isomers given that meta-substituents typically do not exert any regiocontrol in arylene chemistry. Pallacycle 112, which contains a C2-symmetry axis, can only lead to the unsymmetrical triphenylene 101, via reductive elimination of palladated intermediate 113, regardless of the orientation of the final arylene insertion. In contrast, pallacycle 114 can form the C3-symmetrical triphenylene 101’, as well as the unsymmetrical product 101, thereby accounting for the overall 3:1 (101:101’) statistical product distribution. Finally, a 3:1 ratio of regioisomers was also observed when the analogous 4-methyl-2-(trimethylsilyl)benzene triflate was treated with CsF and CsOEt.
catalytic Pd(PPh$_3$)$_4$, providing empirical support that a Pd-associated aryne intermediate is operative in this method.

An early example of catalytic aryne generation was reported by the group of Hu in 2006, utilising 2-haloaryl tosylates and chlorides 115 as precursors (Scheme 17a). In the presence of hindered aryl Grignard reagents 116, a palladium-catalysed domino reaction of the 1,2-bisfunctionalised precursors 115 exclusively yielded fluorene 117, with an aryne intermediate postulated to account for the observations. Fluorene generation (Scheme 17b, Path A) was proposed to occur via $\beta$-halogen elimination from an aryld palladium intermediate 119 to generate Pd-associated aryne 120. Transmetalation with aryl Grignard 126, followed by carbopalladation of aryne 123 yields the aryld Pd species 124 that undergoes a final Pd-catalysed sp$^3$ C-H activation to furnish the fluorene 125. This pathway was found to be in competition with a standard cross coupling reaction (Path B), which produced biaryl product 121 via transmetalation of the common aryld palladium intermediate 119 with Grignard 126 and subsequent reductive elimination. The reaction conditions were found to exert a remarkable control over the reaction course: the use of phosphine or NHC ligands for Pd and/or sterically less bulky Grignard reagents favoured almost exclusive biaryl formation, whilst the absence of ligand and the employment of 2-mesitylmagnesium bromide resulted in fluorenes 117. Lastly, in order to probe the feasibility of an alternative pathway to explain fluorene formation – a tandem cross coupling-C-H activation mechanism – biaryl tosylate 127 was treated with Pd(OAc)$_2$ and 2-mesitylmagnesium bromide 128, with and without MgCl$_2$ (Scheme 17c). Only trace amounts of fluorene 129 were observed, which provided support for the domino reaction mechanism (Path A) and the intermediacy of arynes 120 and 122.

In 2012, Suzuki and co-workers unveiled an alternative transition metal-free strategy for the generation of arynes, instead exploiting catalytic amounts of alkynyllithium reagents 130 and using 2-iodoaryl triflates 131 as precursors (Scheme 18a). This built upon work by the same group, who had previously shown that arynes could be produced by treating 2-iodoaryl sulfonates with stoichiometric n-BuLi at $-78^\circ$C; the electron-withdrawing triflates and tosylates are thought to facilitate initial lithium-halogen exchange. In their most...
recent work, the authors rationalised that the rate of aryne formation could be moderated by slowing the iodine-lithium exchange. This was achieved using poorer nucleophiles, such as alkynyllithium reagents 130, with subsequent elimination of the triflate group from 132 generating benzene 3 (Scheme 18a). Next, if the alkynyllithium 130 was present in a stoichiometric amount then it would intercept the electrophilic benzene 3 (i.e. ‘Nu’ would be ‘CICR’). However, by using 130 in catalytic quantities then another less nucleophilic species 133 could also be employed in the reaction, affording aryllithium intermediate 134. Finally, iodination of 134 with iodoalkyne 136 furnishes functionalised iodoarene 135 and regenerates the alkynyllithium catalyst 130.

Support for the intermediacy of an aryne was provided when regioisomeric benzyl ethers 137 and 139 were treated with lithiated TMS-acetylene and yielded the same alkynylated product 138 (Scheme 18b); nucleophilic addition favoured at the more electrophilic C-1 position of the common α-alkoxybenzyne intermediate 140. Elsewhere, chemoselectivity could be exploited for controlled arylene formation using bis(iodide) substrate 141, which contained both triflate and tosylate leaving groups (Scheme 18c). For example, the tosyl group was untouched when 141 was treated with 1.2 equivalents of LiCICSiMe3 at −78 to −55 °C, affording 142 in 86% yield. However, when an excess of alkynyllithium reagent was employed in the reaction at 0 °C, the bis(alkynyl) derivate 143 was isolated in 82% yield. Similarly, an asymmetric bis-alkynyl mixture was effected in one-pot through careful reagent control; monitoring the reaction by TLC and introducing the second alkynyllithium species after the formation of the monoadduct (Scheme 18d). Finally, a range of lithiated carbon nucleophiles were shown to be effective, generating the corresponding C-C coupled products (145a and 145b) in moderate to good yields (Scheme 18e). ortho-Dihaloarenes (145c and 145d) could also be accessed by treating iodoaryl triflate precursor 137 with lithium halides.

Conclusion

The field of arylene chemistry has flourished in recent years due to the development of protocols, predominantly involving fluoride-mediated ortho-silylaryl triflate precursors, which act under mild conditions. However, despite the significant advances there are still drawbacks associated with these approaches. As a result, a number of alternative fluoride-free precursors have been developed, with most based on the same general principle as Kobayashi’s precursor; 1,2-ambiphiles containing a good leaving group. These methods aim to overcome certain issues associated with ortho-silylaryl triflates, including shortening synthetic sequences to access the precursors through the use of more readily available or monofunctionalised starting materials. However, developing a general method for arylene generation that overcomes all of the limitations of ortho-silylaryl triflates remains a salient challenge. The fluoride-free methodologies described here are typically restricted by the substrate scope, reaction class or tend to be base-mediated, albeit employing weaker bases compared with traditional strategies involving aryl halides. However, with pioneering reports on arylene generation from mono-substituted arenes and an interest in the potential for catalytic generation of arenes, one can expect more efficient and milder methodologies to appear in the near future that tolerate a broader substrate scope. This would, in turn, ensure arenes remain an indispensable tool for synthetic chemists.

Conflicts of interest

There are no conflicts of interest to declare.

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Graphical Abstract & Text:

Aryne chemistry has flourished in the past few decades. This review highlights new aryne precursors that operate under fluoride-free conditions as alternative methodologies to the popular fluoride-mediated ortho-silylaryl triflates.