Journal Name

ARTICLE

Recent Advances in Fluoride-Free Aryne Generation from Arene Precursors

mReceived 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

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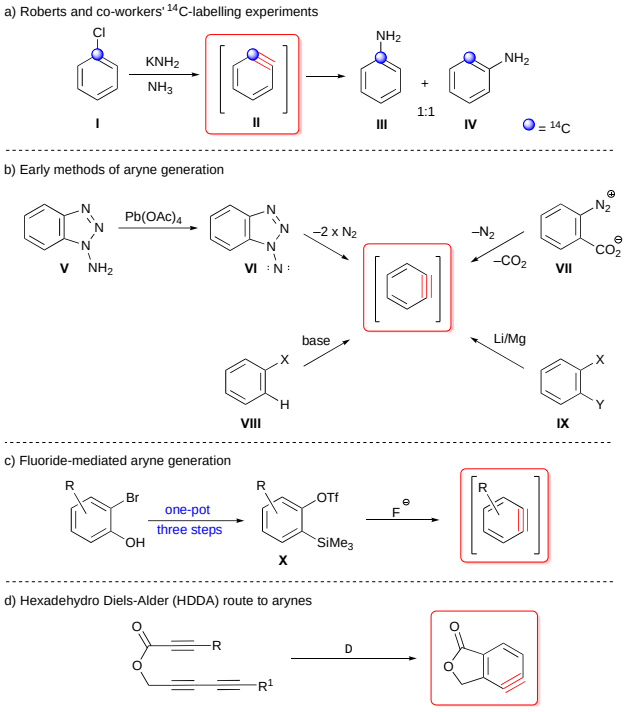
Aryne chemistry has experienced a remarkable renaissance in recent years, with a significant increase in the synthetic applications reported for these highly valuable reactive intermediates. This resurgence of interest is in part due to the introduction of *ortho*-silylaryl triflates as precursors which 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 ^{14}C-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.[2d] 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,[2i] as well as to the preparation of extended polycyclic aromatic hydrocarbons[3] 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 CO_2 and N_2 gases (Scheme 1b).[6] Other methods, which are still encountered today, required *ortho*-lithiation 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 chemistry[9] and their

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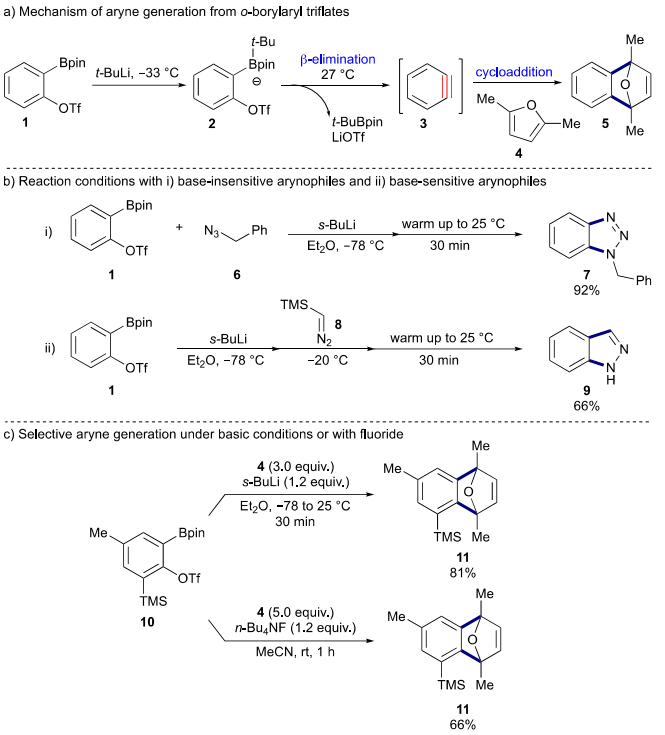
synthetic applications to access valuable and otherwise challenging benzenoid motifs have been presented in many extensive reviews.[2e,10] Areas of particular focus include *σ*-bond insertion reactions for the formation of C-C, C-N and C-O bonds, cycloaddition processes to prepare bicyclic species, nucleophilic 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 hexadehydro-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[11] and Lee,[12] the origins of the HDDA reaction lie with independent reports by Ueda[13] and Johnson[14] in 1997. Since Hoye and co-workers coined the term 'HDDA' in 2012,[11a] there has been a marked increase in reports utilising this approach, showcasing extremely interesting and unusual aspects of aryne chemistry.[2l,p,11,12]

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,[2l,p] the focus here will be on new methods involving arene-based precursors and their different activators.

1,2-Difunctionalised Arene Precursors

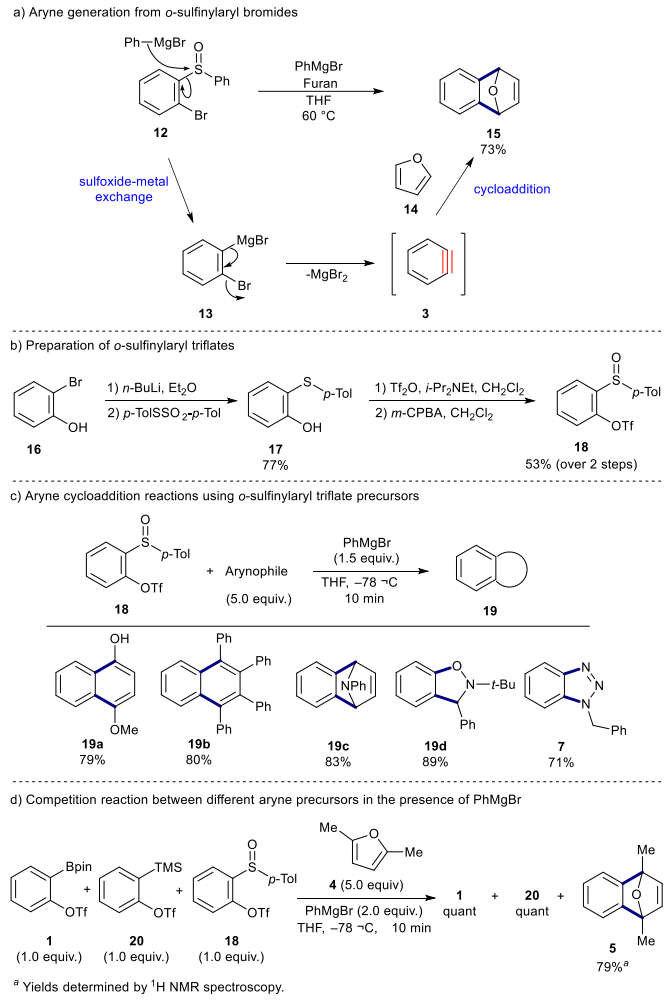
In 2013, Hosoya and co-workers reported the generation of aryne intermediates from *ortho*-borylaryl triflate **1** (Scheme 2a).[15] Treatment with *sec*- or *tert*-butyllithium at low temperatures resulted in the corresponding *'ate'* species **2**, which underwent β-elimination to the aryne **3** upon warming to room temperature. Although milder bases such as Cs_2CO_3 and K^{t}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 ^{11}B, ^{1}H and ^{19}F NMR spectroscopy both before and after the addition of *tert*-butyllithium. The observed changes in chemical shifts provided evidence for the formation of an intermediate *ate* complex which was stable below 0 °C and collapsed to form benzyne **3** close to room temperature. The *ortho*-borylaryl triflate precursors were readily accessed from the corresponding phenols through a one-pot Ir-catalysed borylation[16]-triflation sequence. The utility of this method of aryne generation was illustrated by trapping the intermediate with a range of arynophiles (Scheme 2b).[15] By introducing the coupling partner after the formation of the boron-*ate*



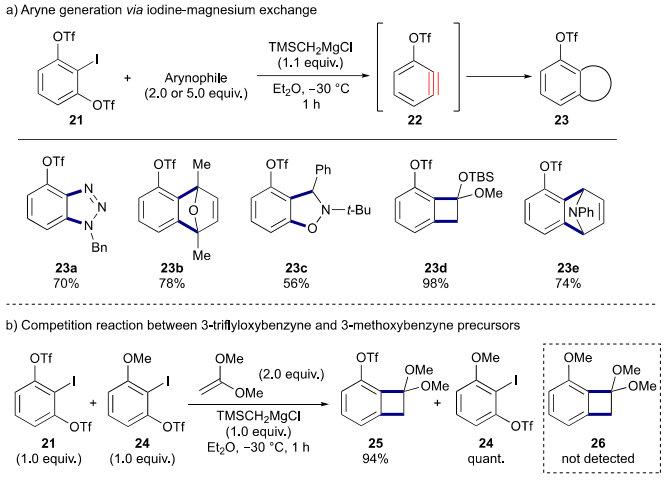
Scheme 2 Aryne generation *via* an intermediate boron-*ate* complex.[15]

complex, arynophiles 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 fluoride, indicating an orthogonal relationship to *ortho*-silylaryl triflate precursors **X**.

Furukawa reported in 1987 that *ortho*-sulfinylphenyl bromide **12** can generate benzyne **3** when treated with phenylmagnesium bromide, proceeding *via* a sulfoxide-magnesium exchange and subsequent β-elimination of the leaving group (Scheme 3a).[17] The resulting benzyne 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 benzyne generation to *ortho*-sulfinylaryl triflates **18**, using Grignard or organolithium reagents at low temperatures.[18] 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*-sulfinylaryl triflates are prepared from the corresponding *ortho*-bromophenols (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



Scheme 3 *ortho*-Sulfinylaryl bromides and triflates as precursors to arynes.[17,18]

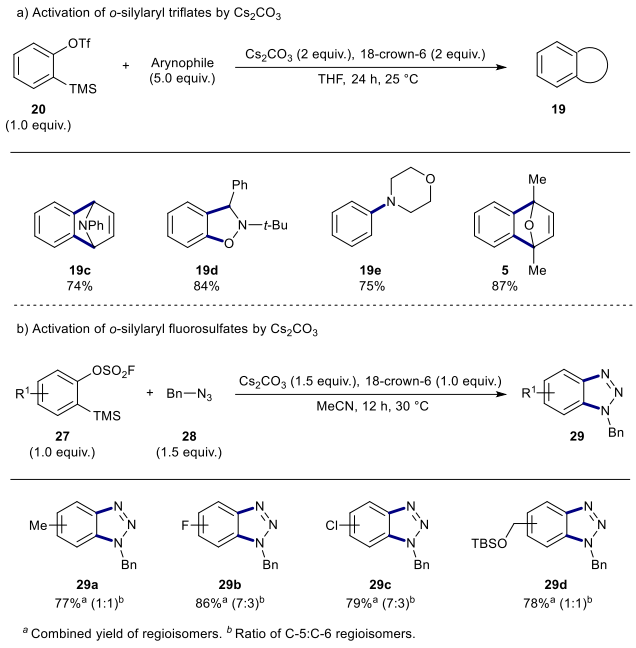


Scheme 4 1,3-Bis(triflyloxy)-2-iodobenzene as a precursor to 3-triflyloxybenzynes.[19]

precursor **18**. Alternatively the *ortho*-sulfinylaryl triflates can be prepared *via* initial *ortho*-lithiation of the phenol. In terms of aryne reactivity, treatment of the precursor **18** with PhMgBr and a number of arynophiles in THF at –78 °C furnished bicyclic compounds **19** in very good yields and in only 10 minutes following cycloaddition with furan (**19a**), cyclopentadienone (**19b**), pyrrole (**19c**), nitrone (**19d**) and azide (**7**) derivatives respectively (Scheme 3c). Finally, a competition reaction involving an equimolar mixture of *ortho*-borylaryl triflate **1**, *ortho*-silylaryl triflate precursor **20** and *ortho*-sulfinylaryl triflate **18** revealed exclusive benzyne generation from the sulfinylaryl precursor when PhMgBr was used as the activator (Scheme 3d). Boryl and silyl precursors **1** and **20** were recovered in quantitative amounts, whilst cycloadduct **5** was formed in 79% yield from *ortho*-sulfinylaryl triflate **18**, thus indicating the potential for orthogonal aryne generation as a result of facile sulfoxide-magnesium exchange in the presence of Grignard reagents.

In 2014, Hosoya and co-workers further exploited the excellent leaving group ability of triflate in the development of an alternative method for aryne generation, using 1,3-bis(triflyloxy)-2-iodobenzene **21** as the precursor, which can be obtained from resorcinol in two steps (Scheme 4a).[19] Treatment of **21** with trimethylsilyl-methyl magnesium 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 $TMSCH_2MgCl$ 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 $TMSCH_2MgCl$ 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.

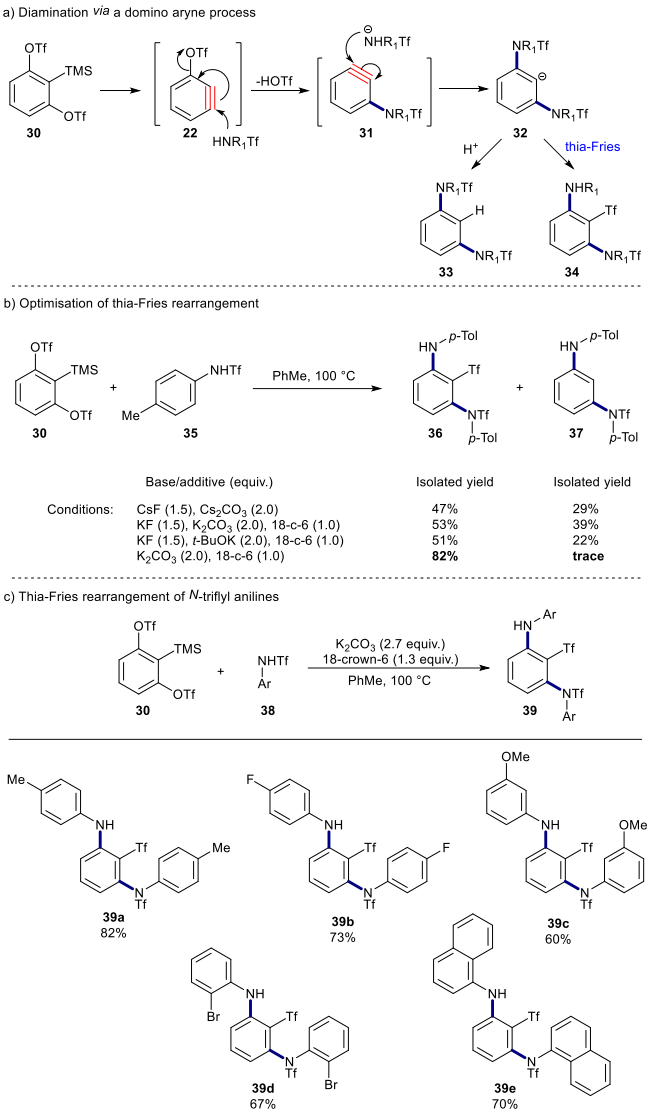
Fluorosulfonyl analogues of *ortho*-silylaryl triflates are known to be similarly capable of generating benzyne upon exposure to fluoride. For example, in 2011 the group of Akai discovered that *ortho*-silylaryl nonaflates, formed *in situ* from *ortho*-silyl phenols and nonafluorobutanesulfonyl fluoride, spontaneously generated arynes by sequestering the fluoride produced during the sulfonylation reaction.[20] In addition, Novák showed that the imidazolylsulfonate group was amenable to fluoride-induced elimination to reveal arynes from the corresponding *ortho*-silylaryl imidazolylsulfonate precursors.[21] 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 Cs_2CO_3, and a crown ether to couple a range of arynes with various arynophiles (Scheme 5a).[22] Similarly, in 2015, Wang and co-workers found that the analogous *ortho*-silylaryl



Scheme 5 Cs_2CO_3 as an activator for aryne generation.[22,23]

fluorosulfates **27** could also perform as efficient aryne precursors upon the addition of Cs_2CO_3 and 18-crown-6 (Scheme 5b).[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_2CO_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_2CO_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.

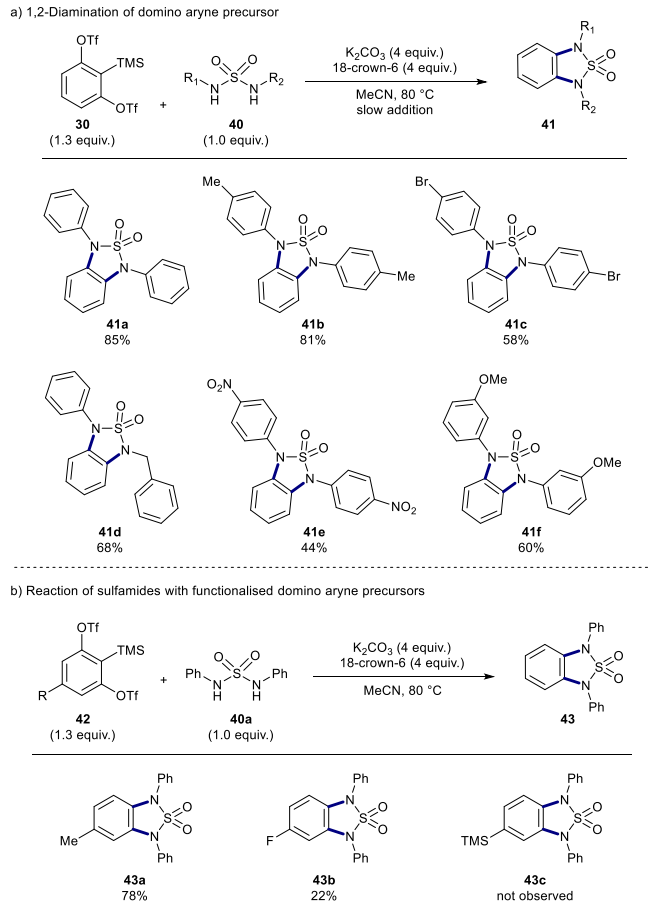
In 2016, Li and co-workers reported the sequential generation of two aryne intermediates, **22** and **31**, from the domino aryne precursor **30** (Scheme 6a).[24,25] Initial treatment of 1,3-bis-triflate **30** with CsF in the presence of sulfonamides afforded 1,3-diaminobenzenes **33** wherein the intermediate aryl anion **32** captured a proton from either the solvent (acetonitrile) or the amine reagent.[24] A combination of K_2CO_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-trisubstitued **36** and 1,3-



Scheme 6 K_2CO_3-mediated diamination of a domino aryne precursor.[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_2CO_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).[25] Optimisation of the reaction conditions revealed that K_2CO_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 ArC-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

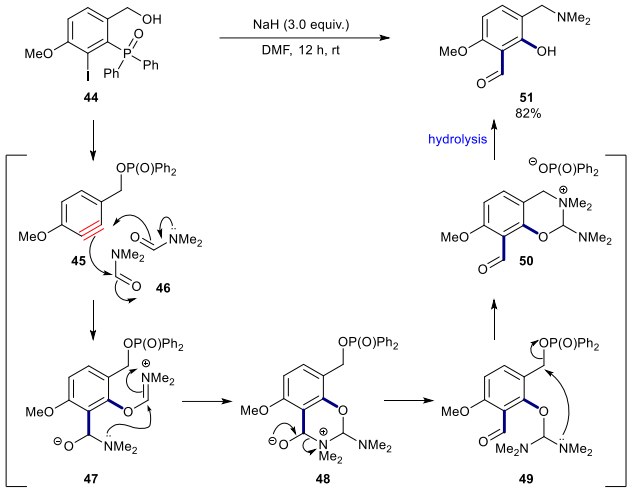


Scheme 7 Vicinal diamination of arenes *via* sequential aryne generation.[25]

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.

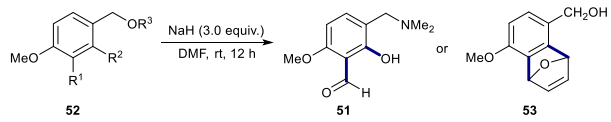
Elsewhere in 2016, Keay and co-workers proposed the intermediacy of an aryne, generated from aryl phosphine **44** in the presence of NaH and DMF, to account for the unexpected formation of 3-(dimethylaminomethyl)-2-hydroxy-6-methoxybenzaldehyde **51** (Scheme 8).[26] It was postulated that an initial 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).



Scheme 8 Base-mediated aryne generation from aryl phosphine oxides.[26]

Table 1 Comparison of the reactivity of substituted benzyl alcohols.[26]



Entry	R^1	R^2	R^3	Product	Yield (%)
1[a]	I	$P(O)Ph_2$	H	**51** + **53**	53%[b]
2[c]	I	$P(O)Ph_2$	H	**53**	44%
3	H	H	$P(O)Ph_2$	**54**	77%
4	Br	$P(O)Ph_2$	H	**53**	79%
5	Cl	$P(O)Ph_2$	H	no reaction	-
6	OTf	$P(O)Ph_2$	H	**53**	84%

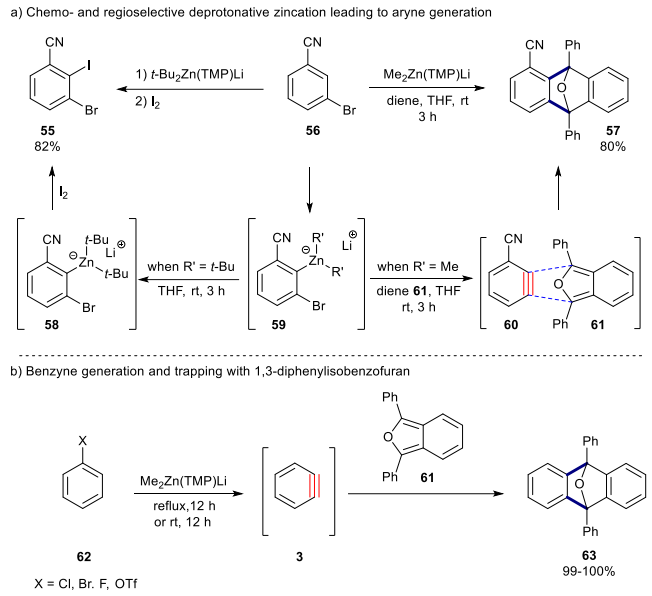
[a]Addition of 10 equiv furan. [b]Combined yield as 1:1 mixture. [c]HMPA used instead of DMF.

[a] Addition of furan (10 equiv.). [b] Combined yield as 1:1 mixture. [c] HMPA used as solvent instead of DMF.

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

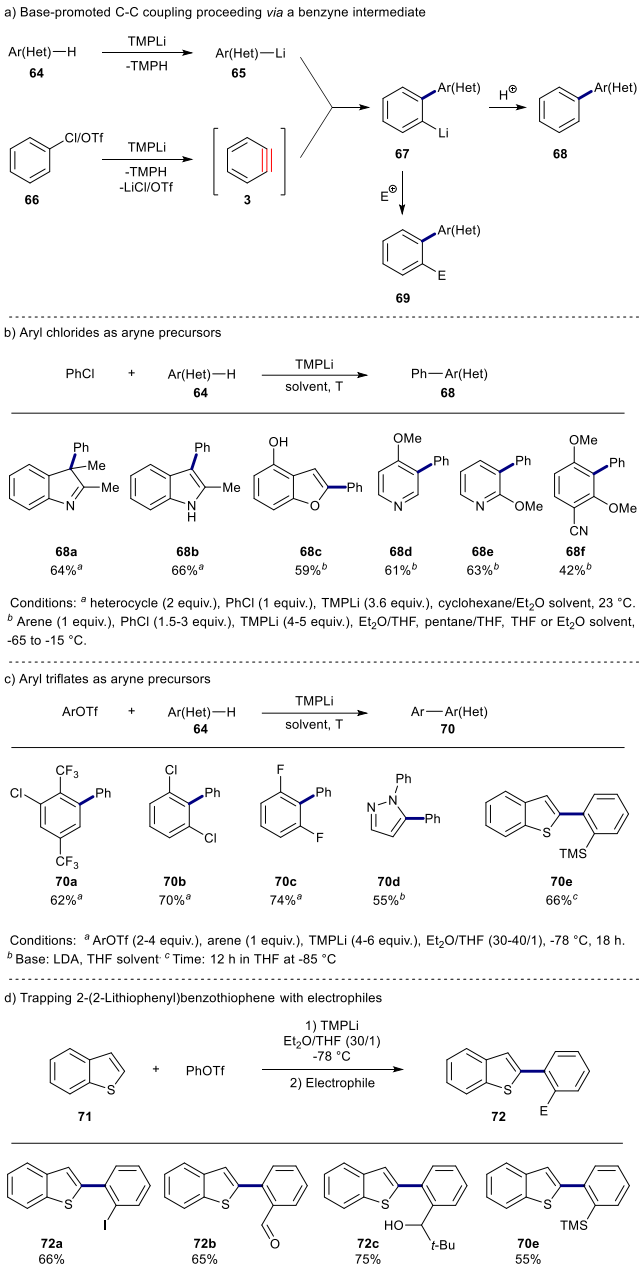
In 2002, Uchiyama and co-workers reported the deprotonative zincation of *meta*-functionalised haloarenes **56** as a method for generating 3-substituted benzynes **60** (Scheme 9a).[27] Regioselective metalation was observed at the C-2 position of **56** by using lithium dialkyltetramethylpiperidino-zincates ($R_2Zn(TMP)Li$) and the reactivity of the resulting arylzincate 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 $Me_2Zn(TMP)Li$ led to the corresponding cycloadduct **57**, indicating the intermediacy of an aryne **60**.



Scheme 9 Benzyne generation with TMP-zincates.[27]

However, treating **56** with *t*-$Bu_2Zn(TMP)Li$ did not lead to aryne formation; instead, iodoarene **55** was isolated upon exposure of the resulting arylzincate **58** to iodine. In a related approach, benzyne intermediates could be formed from *o*-dihalobenzene analogues through an initial halogen-zinc exchange, followed by elimination. Uchiyama extended the deprotonative zincation method to incorporate mono-substituted arene precursors **62**, as triflate 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 $C(sp^2)$-$C(sp^2)$ 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 benzyne 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 benzyne 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

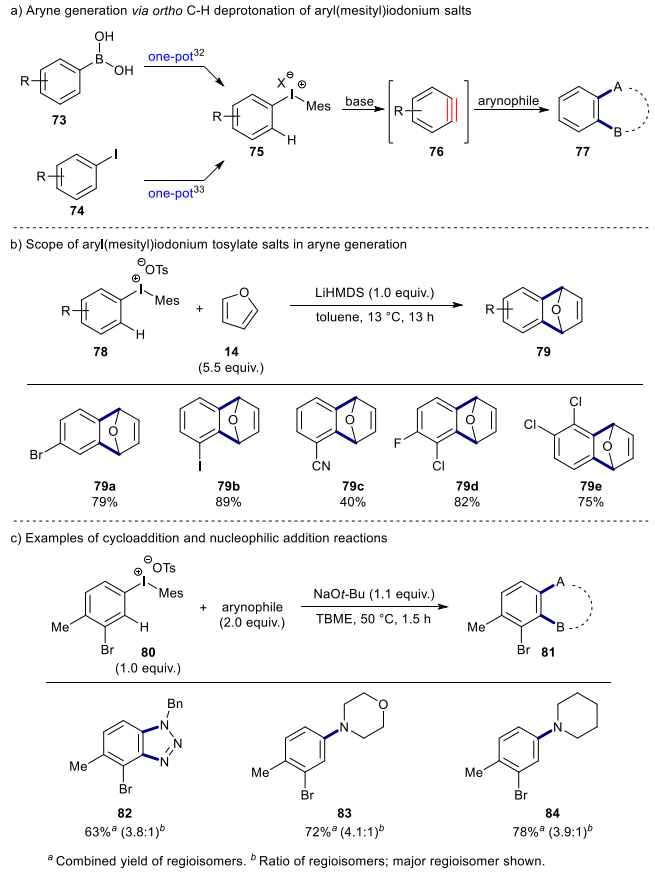


Scheme 10 Base promoted arylation *via* aryne intermediates.[28,29]

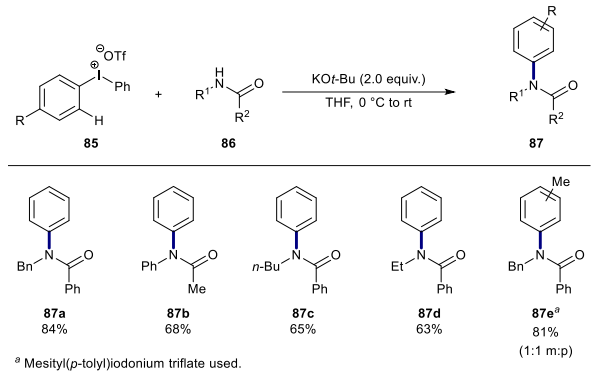
than aryl chlorides, which affords a greater functional group tolerance (Scheme 10c). Furthermore, the facile loss of triflate from **66** allows dihalogenated arene coupling partners to be used (**70b** and **70c**). Interestingly, common benzyne precursor 2-trimethylsilylphenyl triflate **20** was found to undergo the TMPLi-mediated arylation of benzothiophene **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 I_2 (**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

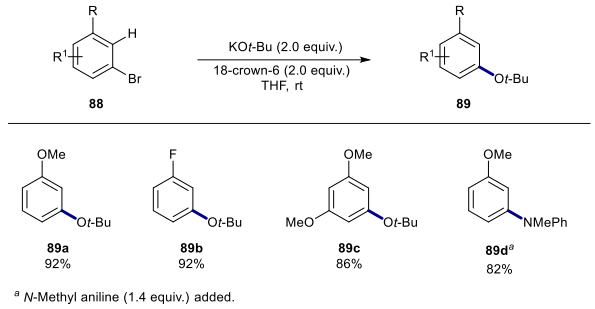
1974 from Akiyama and co-workers, wherein sodium 5-phenyltetrazolide was arylated in the presence of di(*p*-tolyl)iodonium bromide.[31] The diaryliodonium salts are readily obtained from either commercially available aryl boronic acids[32] **73** or aryl iodides[33] **74** *via* one-pot syntheses and offer an alternative to the more common 1,2-difunctionalised aryne precursors discussed in the previous section. Stuart found that treatment of a range of *ortho*-, *meta*- and *para*-substituted aryl(mesityl)iodonium tosylate salts **78** with LiHMDS in the presence of excess furan **14** led to the corresponding cyclo-adducts **79** in good to excellent yields (Scheme 11b).[30] Compared to traditional methods of aryne formation that operate *via ortho*-deprotonation of aryl halides,[2d] 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 (**79a**-**e**) and choice of leaving group (**79a**,**b**,**d**,**e**) respectively, which offers attractive orthogonal reactivity to aryl halide precursors. Electron withdrawing substituents at C-3 were highly selective for deprotonation at C-2 (**79b**-**d**), consistent with the regioselectivity seen with 1,3-dihaloarenes.[2d] 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



Scheme 11 Aryl(mesityl)iodonium tosylate salts as precursors to arynes.[30]



Scheme 12 Diaryl iodonium salts as aryne precursors for *N*-arylation of amides.[34]



Scheme 13 *ortho*-Deprotonation of aryl halides at ambient temperature.[35]

cycloaddition of benzyl azide with the aryne derived from aryliodonium precursor **80**, which yielded benzotriazole **82** as a 3.8:1 mixture of regioisomers in 63% yield (Scheme 11c). The same aryne was successfully trapped with nucleophilic amines (**83** and **84**), affording regioisomeric mixtures of products, consistent with the intermediacy of an aryne.

Shortly after Stuart's report, Wang *et al.* also demonstrated the ability of diaryliodonium triflate salts **85** to function as aryne precursors; effecting efficient *N*-arylation of a range of secondary amides in the presence of KO*t*-Bu (Scheme 12).[34]

Elsewhere, Tilley and co-workers have recently developed a new method for the generation of arynes *via ortho*-deprotonation of aryl halides **88** that uses a mild base, KO*t*-Bu, and proceeds at ambient temperature to afford the corresponding alkyl aryl ethers **89a**-**c**. (Scheme 13).[35] This approach was also applied to the arylation of a secondary amine (**89d**). However, despite the improvements relative to traditional approaches towards aryl halide deprotonation, this method does require an additional electron withdrawing substituent *meta* to the halide to acidify the *ortho*-C-H, thereby rendering this a 1,3-difunctionalised precursor.

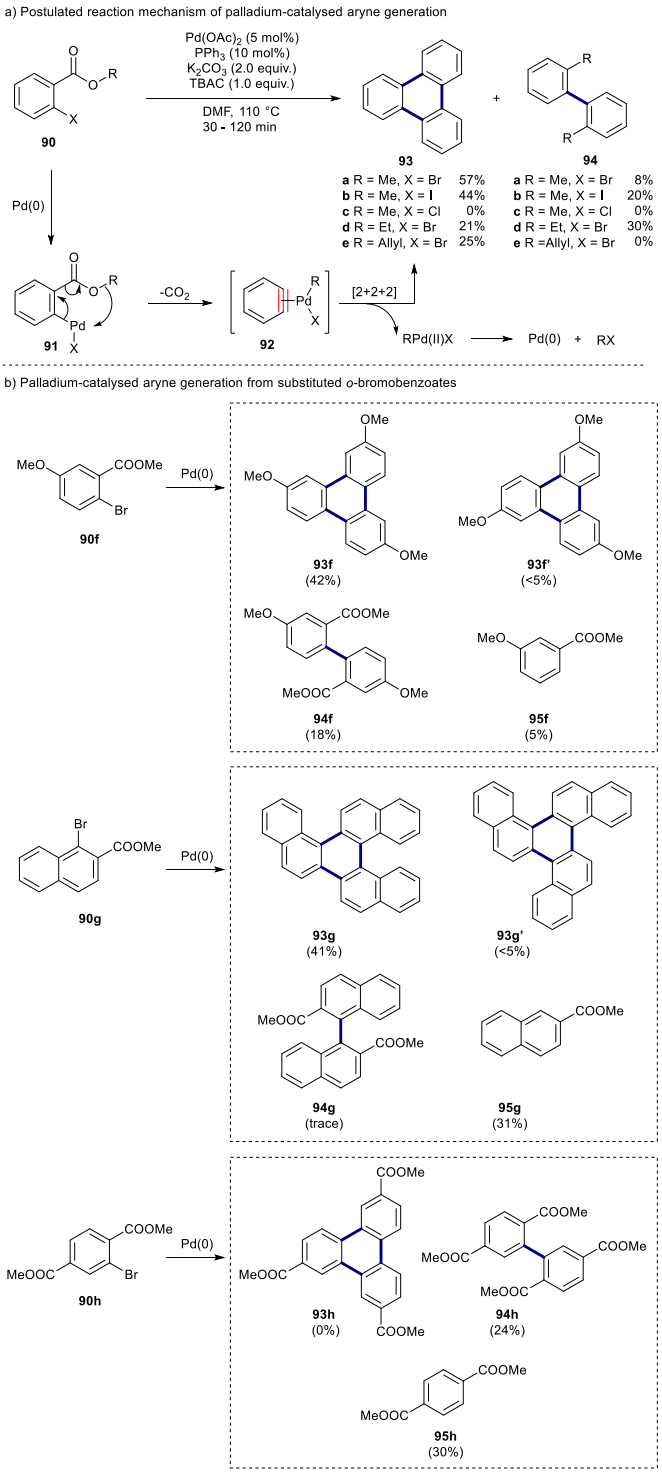
Catalytic Aryne Generation

Catalytic aryne 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.[36-38,40] As the metal can initiate both aryne 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.

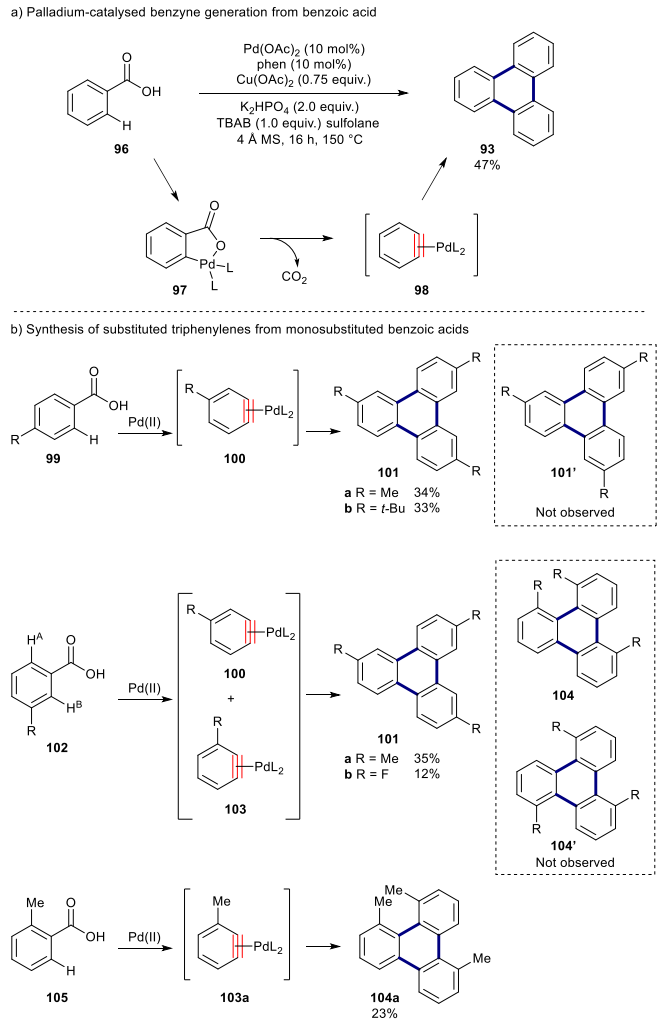
In 2008, Kim and co-workers established that certain *ortho*-bromobenzoates generate triphenylenes under Pd catalysis, with an aryne intermediate suggested to account for the products.[36] Oxidative addition into the C-X bond of *ortho*-halobenzoate **90** is believed to be followed by *δ*-carbon elimination and loss of CO_2 from arylpalladium 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**,[3a] 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 trinaphthylene **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).[37] 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 aryne regioisomer **100**, which could lead to a pair of regioisomeric triphenylenes **101** and **101'**. However, the unsymmetrical isomer **101** was

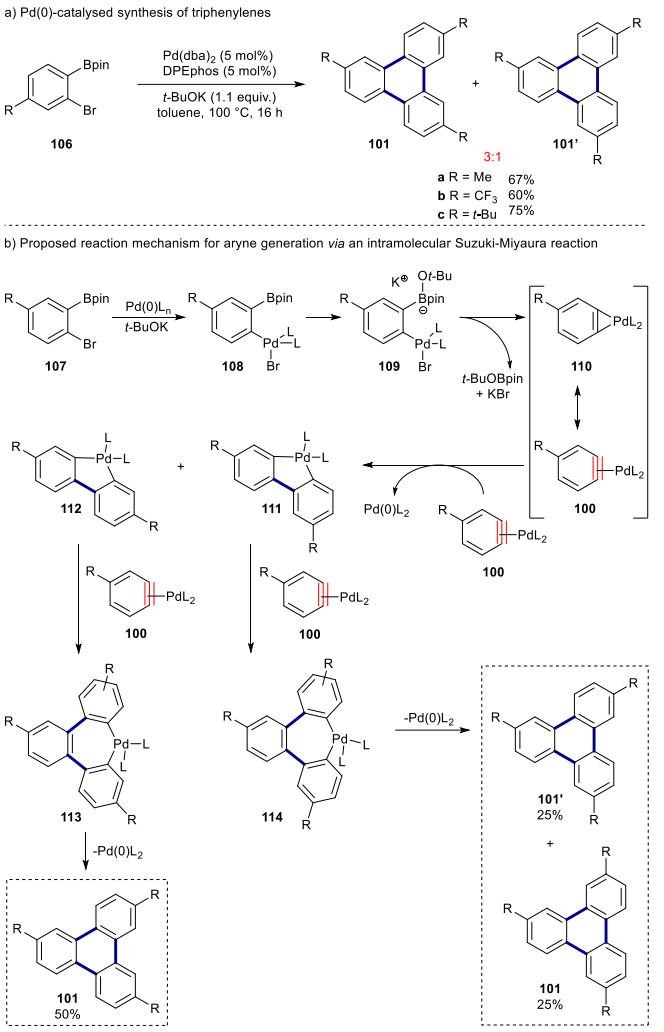


Scheme 14 Pd(0)-catalysed aryne generation from *o*-halobenzoates.[36]

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 triphenylenes (**101**, **104** and **104'**). Nonetheless, only one isomer (**101**) was observed, which indicated activation of the distal C-H bond (H^A) to the *meta* substituent



Scheme 15 Palladium-catalysed C-H activation strategy for the generation of arynes from benzoic acid.[37]



Scheme 16 Palladium-catalysed intramolecular Suzuki-Miyaura reaction for the generation of arynes from *ortho*-bromoarylboronic esters.[38]

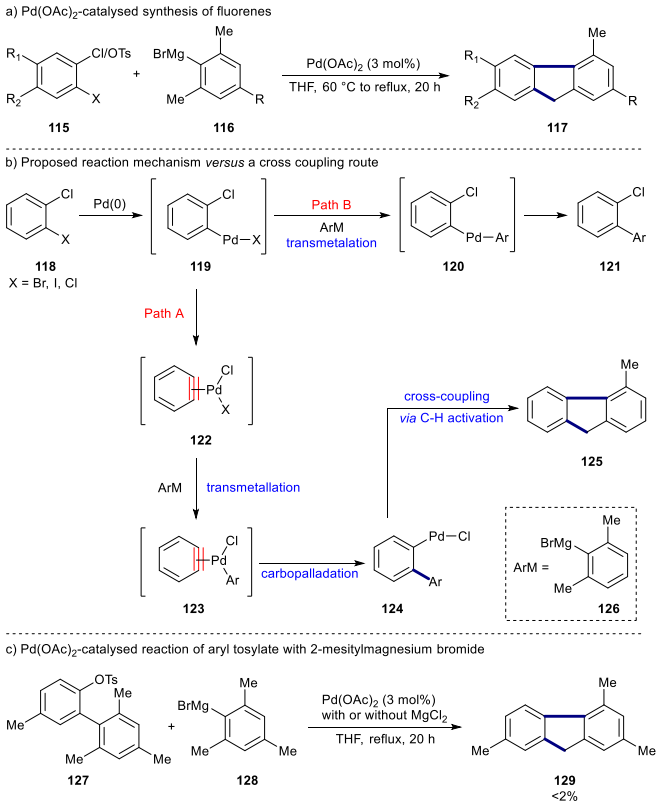
in **102**. Therefore, it was reasoned that both the *meta*- and *para*-substituted benzoic acids **99** and **102** proceeded *via* aryne intermediate **100**. Finally, the authors noted that a limitation of the methodology was that *ortho*-substituted precursors were generally ineffective at aryne generation. However, one example was obtained with *ortho*-toluic acid **105**, yielding 23% of the unsymmetrical triphenylene **104a**. Although the yields were generally moderate, this report demonstrates the exciting principle of catalytic aryne generation utilising a cheap monofunctionalised starting material.

More recently, in 2014, Greaney and co-workers introduced 2-bromoarylboronic esters **106** as alternative catalytic aryne precursors (Scheme 16a).[38] 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 aryne 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 benzynes from *ortho*-metalated phenyl boronic esters,[39] a mechanism involving a Pd-coordinated aryne was proposed to account for the regiochemical outcome (Scheme 16b).[38] Oxidative addition into the aryl bromide **107** is followed by a base-mediated intramolecular transmetalation step, involving boron-*ate* complex **109**, to form Pd-associated aryne **100**. Ligand exchange between two equivalents of **100** and subsequent cyclopalladation results in the formation of the isomeric palladacycles **111** and **112**. Here the authors assume a 1:1 ratio of isomers given that *meta*-substituents typically do not exert any regiocontrol in aryne chemistry. Palladacycle **112**, which contains a C_2-symmetry axis, can only lead to the unsymmetrical triphenylene **101**, *via* reductive elimination of palladated intermediate **113**, regardless of the orientation of the final aryne insertion. In contrast, palladacycle **114** can form the C_3-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

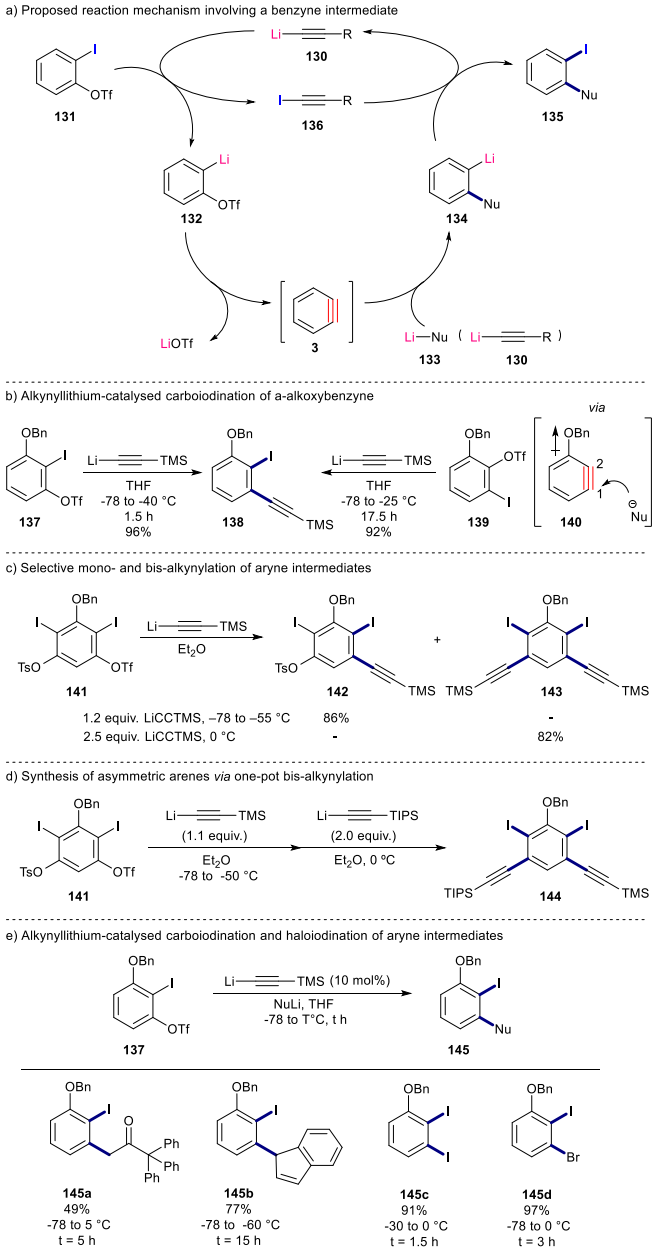
catalytic $Pd(PPh_3)_4$, providing empirical support that a Pd-associated aryne intermediate is operative in this method.

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).[40] In the presence of hindered aryl Grignard reagents **116**, a palladium-catalysed domino reaction of the 1,2-difunctionalised 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* β-halogen elimination from an aryl Pd intermediate **119** to generate Pd-associated aryne **122**. Transmetalation with aryl Grignard **126**, followed by carbopalladation of aryne **123** yields the aryl 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 aryl Pd 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 **122** and **123**.

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).[41] 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 °C; the electron-withdrawing triflates and tosylates are thought to facilitate initial lithium-halogen exchange.[8,42] In their most



Scheme 17 Palladium-catalysed domino reaction for the synthesis of fluorenes.[40]



Scheme 18 Transition metal-free catalytic aryne generation.[41]

recent work, the authors rationalised that the rate of aryne formation could be moderated by slowing the iodine-lithium exchange.[41] This was achieved using poorer nucleophiles, such as alkynyllithium reagents **130**, with subsequent elimination of the triflate group from **132** generating benzyne **3** (Scheme 18a). Next, if the alkynyllithium **130** was present in a stoichiometric amount then it would intercept the electrophilic benzyne **3** (i.e. 'Nu' would be 'C≡CR'). 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 aryne 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 $LiC{\equiv}CSiMe_3$ 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-alkynylation 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 aryne 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 aryne 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 aryne generation from mono-substituted arenes and an interest in the potential for catalytic generation of arynes, 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 arynes remain an indispensable tool for synthetic chemists.

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

We are grateful to the EPSRC (EP/M026221/1, C.R.J.) and QMUL (studentship, F.I.M.I.) for financial support.

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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.