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Introduction to the Chemistry of Arynes

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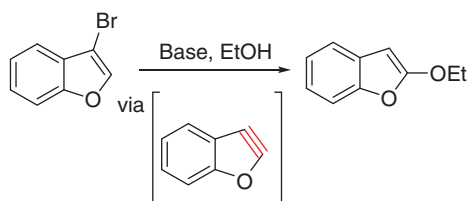
1.1 Introduction

Arynes are highly reactive electrophilic intermediates proposed more than a century ago and have encountered an extraordinary resurgence of interest in the past decades. Chemists have exploited this reactive intermediate for the synthesis of a broad range of 1,2-disubstituted benzene derivatives and also several benzo-fused carbocycles and heterocycles, which are otherwise difficult to achieve by conventional methods [1–14]. With the discovery of mild methods of generation by Kobayashi [15] and Hoyer [16, 17], aryne chemistry has been significantly promoted in recent years in terms of better functional group compatibility as well as accommodation of more reaction modes. The progress in heterocyclic arynes, especially the pyridynes and indolynes, has added extra aroma to the chemistry of this reactive species [18]. The development and applications of the hexadehydro-Diels–Alder (HDDA)-based arynes went parallelly over the last decade and have contributed seminally to the diversification of this field. Moreover, 1,4-benzdiyne equivalents are one of the most dependable components for the synthesis of polycyclic aromatic functional materials at present. A recently exploited domino aryne reagent, the 2-(trimethylsilyl)-1,3-phenylene bis(trifluoromethanesulfonate) (TPBT), is one of the best precursors available for the synthesis of multifunctional aromatic derivatives [19]. A discussion on the brief history of arynes, their characterization, methods of generation, and possible modes of reactivities forms the content of this introductory chapter.

1.2 History of Arynes

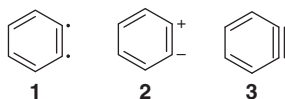
Initial speculation on the existence of aryne intermediate appeared in 1902. Stoermer and Kahlert provided the first evidence for the existence of arynes when they observed the formation of 2-ethoxybenzofuran in the reaction of

3-bromobenzofuran under basic conditions. They postulated the possible intermediacy of a 2,3-didehydrobenzofuran intermediate in this reaction [20]. The unexpected product formation laid the foundation stone for the development of an interesting area based on a highly transient intermediate (Scheme 1.1).



Scheme 1.1 Initial observations by Stoermer and Kahlert. Source: Based on Stoermer and Kahlert [20].

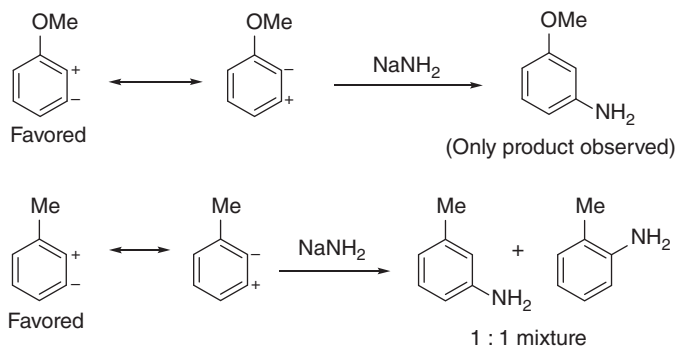
Later in 1927, Bachmann and Clarke at the Eastman Kodak Co. proposed benzyne as a reactive intermediate to explain the formation of triphenylene in a reaction, and it was taken as “decisive in favour of the free radical explanation” (Scheme 1.2) [21]. It was thought that structure **1** was predominant among the three possible structures, where the ylide structure **2** as well as the structure **3** with carbon–carbon triple bond in a six-membered ring were also considered.



Scheme 1.2 Proposed structures of benzyne. Source: Based on Bachmann and Clarke [21].

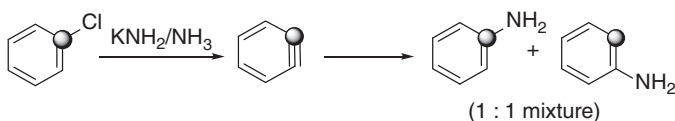
Later, Wittig found that the formation of biphenyl in the reaction of phenyllithium with halobenzenes was fastest with fluorobenzene through nucleophilic substitution reaction via the displacement of fluoride, which was considered as a complicated task to perform [22–25]. Thus, the ylide structure **2** was proposed as a reactive intermediate for the formation of biphenyl. The trimerization of this zwitterion **2** to triphenylene was also noted under certain conditions. At the same time, Morton had also postulated the intermediate **2**, which “cannot be stabilized by double bond formation” in their study of the Wurtz reaction of pentylsodium with chlorobenzene [26]. But the zwitterionic structure failed to explain the observed regioselectivity in the reaction of substituted arynes, and hence its existence was questioned (Scheme 1.3). For instance, the reaction of aryne bearing an OMe group at 3-position with NaNH_2 was regioselective affording a single product, whereas the reaction of arynes having methyl substitution provided a 1 : 1 mixture of regioisomers.

It was also observed that the substitution only occurred in ipso or ortho position to that of halide substitution. Halides having no ortho hydrogen did not undergo any substitution reaction. Robert brought the official introduction of benzyne concept



Scheme 1.3 Regioselectivity in aryne reactions.

[27, 28]. In 1953 at MIT, Robert performed a classical ^{14}C labeling experiment, which confirmed the involvement of a symmetrical, electronically neutral intermediate, benzyne **3** (Scheme 1.4). Later, Wittig performed the Diels–Alder reaction of benzyne with furan to give 76% yield of the [4+2] adduct [29].

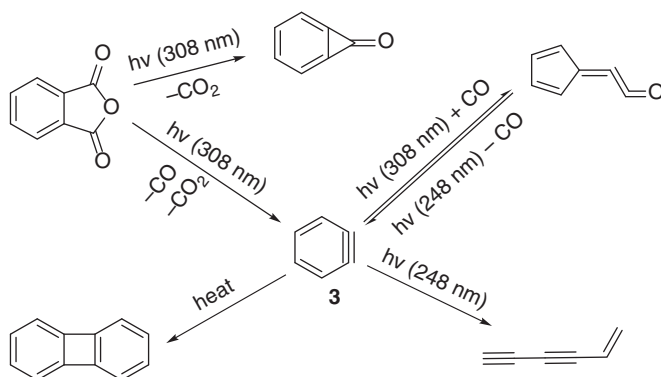


Scheme 1.4 Robert's ^{14}C -labeling experiment. Source: Roberts et al. [27]; Roberts et al. [28].

1.3 Characterization of the Aryne Intermediates

In 1963, Fisher and Lossing provided further insight to the structure **3** using mass spectrometry. They performed the pyrolysis of diiodobenzenes for all three isomers and identified **3** based on the measured ionization potential [30]. Confirmation for structure **3** also came from mass spectra. Berry et al. performed a photoinitiated benzenediazonium carboxylates decomposition in gas phase and identified the mass 76 along with other masses [31]. The same group further explained the structure **3** using UV spectra also. Radziszewsk and coworkers recorded the IR spectra providing a solid proof for the existence of structure **3**. The vibration to absorption peak emerged at 1846 cm^{-1} corresponding to *o*-benzyne, which was confirmed from different isotopomers of phthalic anhydride (Scheme 1.5) [32]. So from the IR data, it is understandable that unlike unstrained alkyne, benzyne triple bond is much weaker, as it has the stretching vibrations usually occurring in the range about 2150 cm^{-1} . IR data resemble cumulene-type structure. However, *o*-benzyne can be better explained by strained alkyne rather than biradical, which can be confirmed by alkyne-like reactivity and large singlet–triplet splitting [33, 34]. Wenthold and Squires determined the enthalpy of formation of structure **3** as

103.6–109.6 kcal mol⁻¹. The C—C triple bond length in acetylene falls at 120.3 pm and C—C double bond in ethylene at 133.9 pm. Experimental C—C triple bond length for benzyne is 122–126 pm, which is closer to that of alkyne triple bond length value, which aims at a cyclic alkyne-like structure rather than a cumulene-type structure [35–38]. Adding strength to all the above evidences, Warmuth was able to measure the nuclear magnetic resonance spectrum in solution in a hemicarcer and as a “molecular container” [39].



Scheme 1.5 Photochemistry of arynes. Source: Based on Berry et al. [32].

The reported ¹³C value of 182 ppm for *o*-benzyne explains the strained alkyne character. Hoffman’s demonstration of extended Hückel theory throws light on the electrophilicity of aryne. The LUMO of aryne is significantly lowered compared to dimethyl acetylene (5.1 eV) and the HOMO is also higher (0.1 eV) in energy, which make the aryne triple bond much more accessible toward different nucleophiles (Figure 1.1) [40].

Because of the high electrophilicity and reactivity of arynes, these intermediates cannot be isolated. However, stable transition metal complexes of benzyne have been prepared and analyzed by X-ray crystallography for further proof. Crystal structure of metal-bound benzyne shows that C₁—C₂ bond is more ethene-like

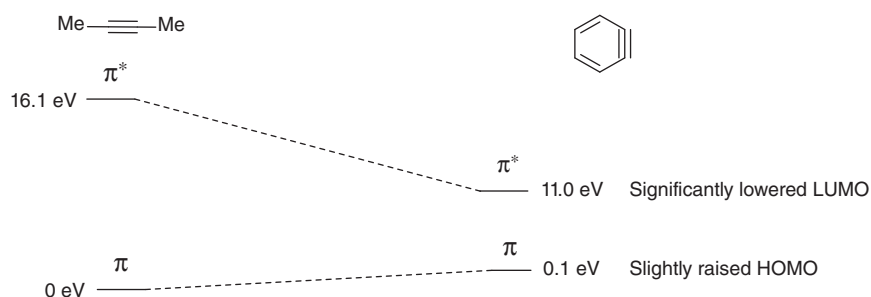
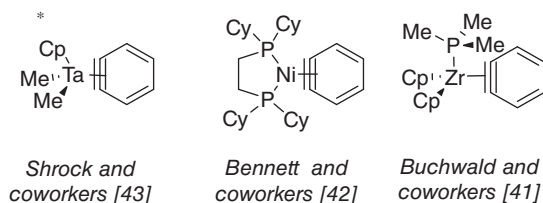


Figure 1.1 Reason for the enhanced electrophilicity of arynes. Source: Based on Hoffmann et al. [40].

(133–136 pm) and all other bond is normal benzene-like (138–140 pm). Thus, these metallocenes can be better described by metallacyclopropenes [41–43] (Scheme 1.6).



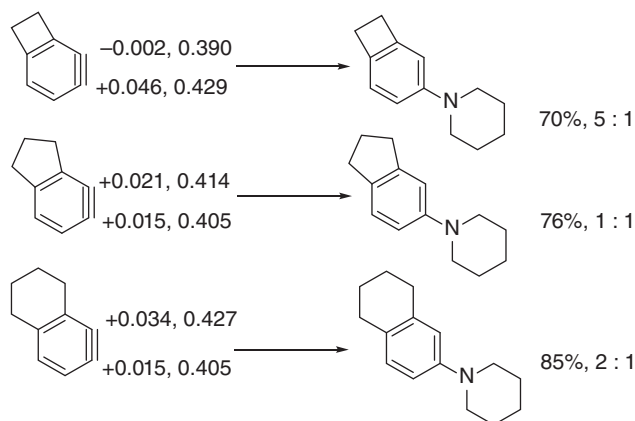
Scheme 1.6 Structures of metal-bound benzyne. Source: Buchwald et al. [41]; Bennett et al. [42]; McClain et al. [43].

Due to the presence of a carbon–carbon triple bond in a six-membered ring, arynes are highly reactive and this also leads to the strained nature of the ring ($\sim 63 \text{ kcal mol}^{-1}$), and consequently, these species have low-lying LUMO, and hence the energy gap between the HOMO and LUMO is smaller than expected. In addition, arynes react as highly reactive alkynes in cycloaddition reactions. Moreover, the low-lying LUMO makes arynes a powerful electrophile for facile addition of nucleophiles.

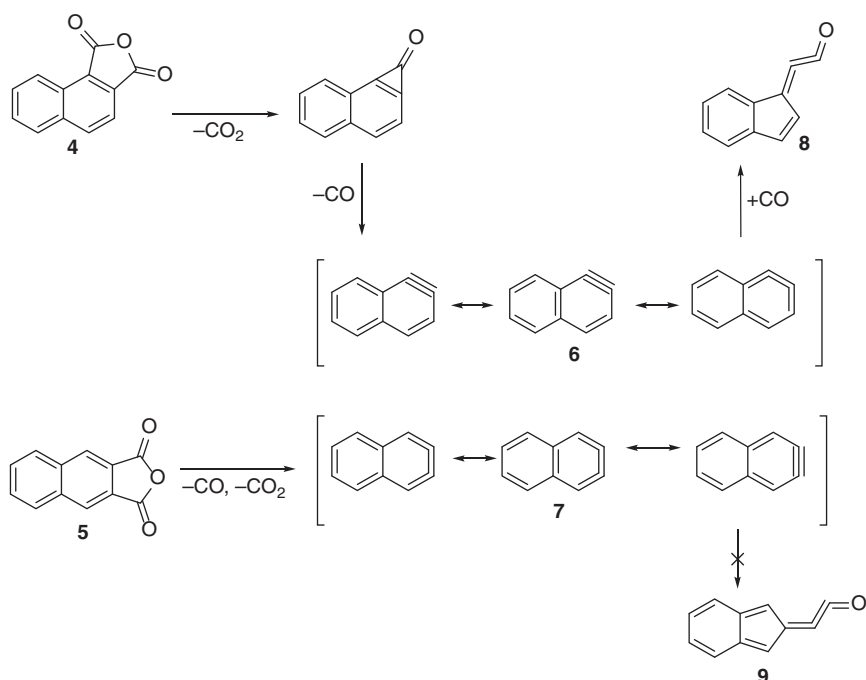
1.4 Ortho-Arynes with Substitution

The effect of substitution on benzyne has game-changing effect on the reactivity of arynes. Numerous reactions go via the formation of benzyne intermediate. Substitution effect can help to understand the observed regioselectivity. Sometimes, experimental reactivity cannot be predicted due to the fact that the attack of the nucleophile is not always charge controlled. Introduction of a polar group at 3-position influences the selectivity to a greater extent. But due to orthogonal nature of bond, classical electron-donating groups are withdrawing. Strain also can induce regioselectivity in benzyne intermediate, demonstrated by Suzuki [44]. Calculation of charge and LUMO coefficient matches prediction of bond angle strain with selectivity trend (Scheme 1.7) [45, 46].

Squires and Cramer theoretically studied naphthalynes [47]. Many naphthalene syntheses were also reported in early 1970s. Lohmann studied the photochemistry of the two isomeric naphthalene dicarboxylic anhydrides **4** and **5**, using laserflash photolysis (LFP) and found that the dimerization of **7** is much faster than **3**; however, intermediate **6** dimerizes rarely (Scheme 1.8) [48]. Intermediates **6** and **7** are accessible when the photolysis conditions are chosen carefully [49]. Intermediate **6** can stay as alkyne but for **7**, it is more like cumulene. Intermediate **6** can be converted easily to **8** via photocarbonylation, but the analogous reaction of intermediate **7** to **9** is not observed experimentally.



Scheme 1.7 Natural atomic charges (above) and atomic populations of LUMO coefficients (below) at C_1 and C_2 calculated with the B3LYP/6-311G(d,p) method. Source: Langenaeker et al. [45]; Johnson and Cramer [46].



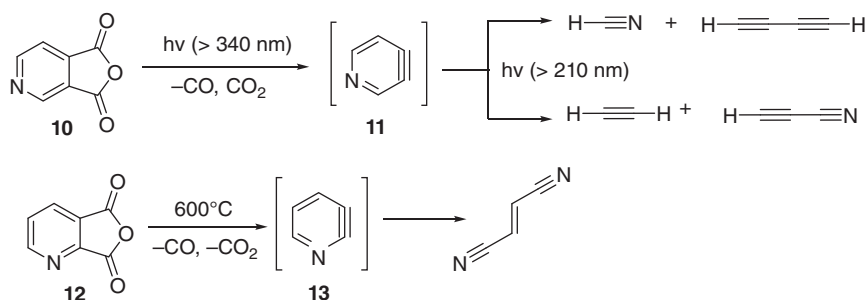
Scheme 1.8 Studies on naphthyne. Source: Lohmann [48].

1.5 *Ortho*-Arynes of Heterocycles

Although hetarynes are much older than benzyne, the physical data on hetarynes were negligible. Different groups reported the generation of five-membered biradicaloid intermediate, but direct spectroscopic evidence for these intermediates was

not known due to the elevated ring strain, which helped these five-membered intermediates go through ring opening [50–53]. Thus, detecting lifetime for five-membered hetarynes by spectroscopic methods is quite less.

Among the six-membered hetarynes, the main focus was on didehydropyridines. Among didehydropyridines, the 3,4-pyridyne **11** generated by the photolysis of the precursor **10** is significantly more stable than the 2,3-isomer **13**. The bond length for the 3,4-pyridyne **11** is comparable with that of benzyne **3** [54]. Berry and coworkers detected 3,4-pyridyne **11** using mass spectrometry [55]. The trapping of the intermediate **11** in a Diels–Alder reaction attempted previously was not successful [56]. In 1988, Leroi and coworkers successfully trapped the pyridyne in nitrogen matrix and characterized it by IR spectroscopy [57]. However, the 2,3-didehydropyridine **13** generated from the precursor **12** by heating is less explored. It was assumed that compound **13** was formed as an intermediate in the gas-phase pyrolysis of 2,3-pyridine dicarboxylic anhydride **12** at 600 °C (Scheme 1.9) [58, 59].

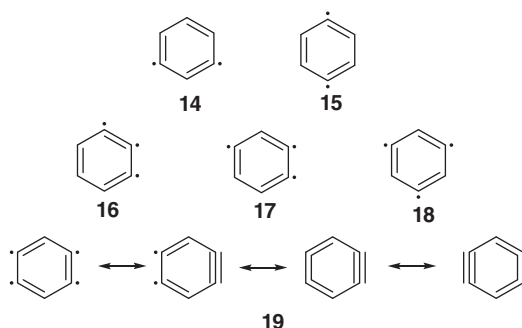


Scheme 1.9 Generation and dissociation of 3,4-pyridyne and 2,3-pyridyne. Source: Cava et al. [58]; Dunkin and MacDonald [59].

Recently, much effort has been put on the development and reactivity studies, including efficient computational model to get insight into the synthetic utility of heterocyclic arynes [60]. Moreover, different types of hetarynes can be generated at desired position of the heterocycles, thus leading to a variety of indolynes, pyridynes, benzofuranynes, and so on, which will be discussed in detail in Chapter 9 of this book.

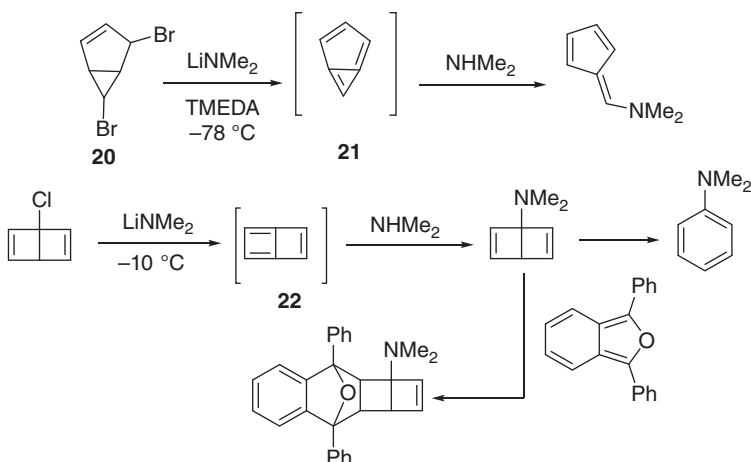
1.6 Other Arynes

Similar to *ortho*-benzyne, arynes can also be generated in other positions of the benzene ring as well. *Meta*- and *para*-benzynes **14** and **15**, tridehydrobenzenes **16–18**, and tetrahydrobenzenes **19** are reported (Scheme 1.10) [61–64]. Tetrahydrobenzene (benzdiynes) can stay in different resonance form as illustrated in Scheme 1.10. Multireference methods are preferable for a proper quantum mechanical description [65, 66]. Due to high reactivity of 1,4-benzdiynes, it can form complex with transition metals and these complexes can be isolated in many cases [67–69].



Scheme 1.10 Possibility of uncommon benzyne. Source: Wenthold [61].

The existence of *m*-benzyne has been a matter of discussion, partly due to experimental proof for the existence of an isomer, bicycle[3.1.0]hexatriene **21**, as a reactive intermediate formed by the base treatment of the bicyclohexene **20** (Scheme 1.11) [72]. Likewise, butadiene **22** also denotes the existence of *p*-benzyne (Scheme 1.11) [70, 71]. However, both reactions are not fully understood due to complex nature of the reactions.

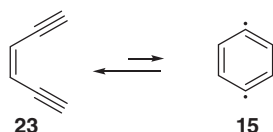


Scheme 1.11 Possible formation of *m*-benzyne and *p*-benzyne intermediates. Source: Breslow et al. [70]; Breslow and Khanna [71].

Early Hückel theory indicates that **21**, being a nonalternant “azulenoid” 6π electron system, maintains benzenoid resonance energy [73, 74]. Although it is a high-energy intermediate, it is resonance stabilized. On the other hand, iscyclobutadiene derivative **22** possesses antiaromatic character, and hence it is a high-energy species. General valence bond calculations estimated that the lowest energy forms of the 1,3- and 1,4-dehydrobenzenes are monocyclic structures having considerable biradical character [75]. In general, *m*-benzyne has much less biradical character and a larger singlet–triplet splitting than *p*-benzyne [76]. Gas-phase experimental

studies and matrix isolation IR spectra are also consistent with monocyclic structure, and they do not correspond with **21** and **22**. Thus, the intermediate generated from the reactions shown in Scheme 1.11 is not clarified completely.

The Bergman cyclization (Scheme 1.12) is biologically a very important reaction because various natural products with antitumor and/or antibiotic properties contain such enediyne moieties **23** and their biological activity can be rationalized in terms of formation of transient *p*-benzynes. If *p*-benzyne abstracts hydrogen, it will generate phenyl radical, which can abstract hydrogen from DNA leading to the DNA cleavage [77–81]. The feasible interconversion of the *o*-, *m*-, and *p*-benzynes has been investigated theoretically. The experiments also indicated that the *o*- and *m*-isomers may rearrange to the *p*-isomer by H-atom tunneling and then the *p*-isomer undergoes the Bergman ring opening.



Scheme 1.12 The Bergman cyclization.

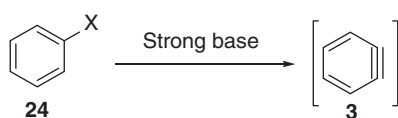
1.7 Methods of Aryne Generation

Due to the highly elevated reactivity, arynes are generated *in situ* in solution and cannot be isolated. However, ever since realizing the potential of this intermediate, different research groups have developed a number of methods for the mild aryne generation in solution. Selected methods are discussed as follows.

1.7.1 Selected Methods of Aryne Generation

1.7.1.1 Deprotonation of Aryl Halides

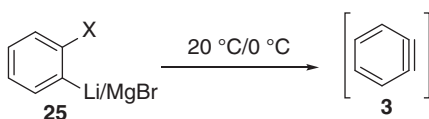
Deprotonation of aryl halides **24** followed by the dehalogenation of the anionic intermediate generated arynes in solution. However, the use of strong bases such as sodamide or *n*-BuLi limits the practical utility of this method [82]. Many base-sensitive functional groups were not compatible under the reaction conditions. Hence, this protocol is considered as a harsh method for the generation of arynes although this is traditionally important (Scheme 1.13).



Scheme 1.13 Aryne generation from halobenzene. Source: Based on Kitamura [82].

1.7.1.2 Metal–Halogen Exchange/Elimination

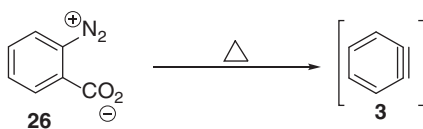
Another approach involves the metal–halogen exchange/elimination of 1,2-disubstituted haloarenes **25** or haloaryl triflates mediated by metals (Mg or Li) or organometallic reagents derived from Cu, Li, and Mg [83, 84]. Many side products formed via the nucleophilic addition of the organometallic reagents itself made this route less practical (Scheme 1.14).



Scheme 1.14 Metal–halogen exchange/elimination route to arynes. Source: Ebert et al. [83]; Matsumoto et al. [84].

1.7.1.3 From Anthranilic Acids

The zwitterionic benzenediazonium 2-carboxylates **26** generated from anthranilic acid derivatives form arynes in the reaction course. Benzenediazonium 2-carboxylate decomposes upon heating, generating aryne with the liberation of nitrogen and carbon dioxide [85, 86]. Although the method has advantages, e.g. the side products are gases, the explosive nature of diazonium compounds limits the practical application of the method (Scheme 1.15).



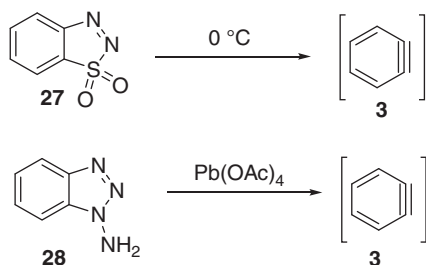
Scheme 1.15 Arynes from anthranilic acid derivatives. Source: Stiles and Miller [85]; Friedman and Logullo [86].

1.7.1.4 Fragmentation of Amino Benzotriazoles

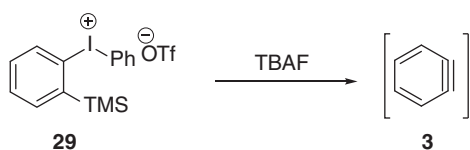
Benzo[*d*][1,2,3]thiadiazole 1,1-dioxide **27** and amino benzotriazoles **28**, upon fragmentation, produce arynes with the evolution of nitrogen gas. The use of explosive precursor and the requirement of lead tetraacetate as oxidant appear to be the demerits of this method. Moreover, the method suffers from less functional group tolerance and hence is not widely used (Scheme 1.16) [87].

1.7.1.5 From Phenyl(2-(trimethylsilyl)phenyl)iodonium Triflate

Fluoride-induced elimination of the aryne precursor phenyl(2-(trimethylsilyl)phenyl)iodonium triflate **29** is an additional process for the generation of aryne. However, the preparation of starting material involves a complex process (Scheme 1.17) [88].



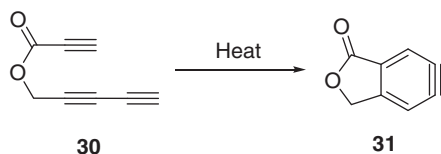
Scheme 1.16 Arynes from benzothiadiazole dioxide and amino benzotriazole. Source: Based on Campbell and Rees [87].



Scheme 1.17 Arynes from phenyl(2-(trimethylsilyl)phenyl)iodonium triflates. Source: Based on Kitamura and Yamane [88].

1.7.1.6 Using Hexadehydro Diels–Alder (HDDA) Reaction

Recently, Hoyer and coworkers developed a new metal-free method for aryne generation using the concept of intramolecular HDDA reaction of triynes **30**, which diversified the reactivity profile of the aryne intermediate. This method allows reagent-free and metal-free thermal generation of arynes **31**; however, in some cases, it requires elevated temperature for the formation of arynes (Scheme 1.18) [16, 17].



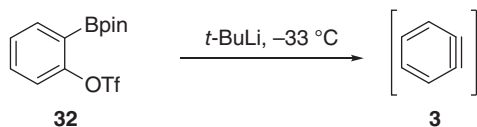
Scheme 1.18 Arynes using HDDA strategy. Source: Hoyer et al. [16]; Yun et al. [17].

1.7.1.7 From *ortho*-Borylaryl Triflates

In 2013, Hosoya and coworkers developed the generation of aryne intermediates from *ortho*-borylaryl triflate **32** mediated by *sec*- or *tert*-BuLi at low temperature. However, the use of strong base limits its potential applications (Scheme 1.19) [89].

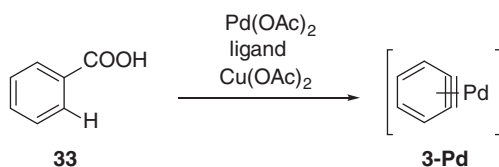
1.7.1.8 Pd(II)-Catalyzed C–H Activation Strategy Starting from Benzoic Acids

Greaney and coworkers developed a Pd(II)-catalyzed C–H activation strategy for the formation of Pd-aryne intermediate, and applied this strategy for the synthesis



Scheme 1.19 Arynes from *ortho*-borylaryl triflates. Source: Based on Sumida et al. [89].

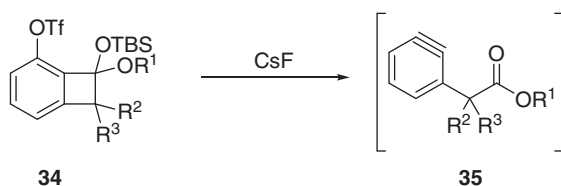
of triphenylenes starting from benzoic acids **33** (Scheme 1.20). The intermediate is formed via an *ortho*-C–H activation of benzoic acid, followed by the decarboxylation from the palladacycle [90].



Scheme 1.20 Arynes via Pd(II)-catalyzed C–H activation. Source: Based on Cant et al. [90].

1.7.1.9 via Grob Fragmentation

The [2+2] cycloadducts of 3-triflyloxy arynes **34** can undergo a chemoselective ring opening to generate 2,3-aryne intermediate **35** via Grob fragmentation, which could be derivatized to trisubstituted arenes (Scheme 1.21) [91].



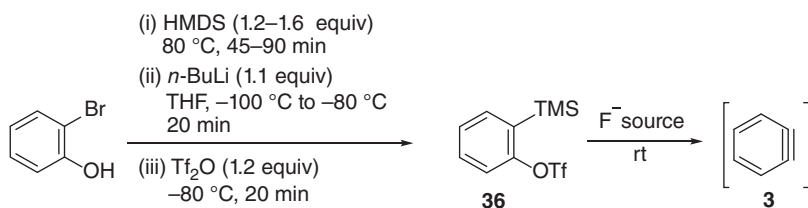
Scheme 1.21 Arynes via Grob fragmentation. Source: Based on Shi et al. [91].

All the methods outlined above require either metals or stoutly basic or harsh reaction conditions. The use of metals, strongly basic conditions, and high temperature are not compatible with a large number of functional groups, which considerably restricted the scope of arynes reactions in organic synthesis. The breakthrough for a mild method of arynes generation came in 1983 when Kobayashi and coworkers demonstrated a practical method for the generation of arynes intermediates.

1.7.2 Kobayashi's Fluoride-Induced Aryne Generation

In 1983, Kobayashi and coworkers, through a pioneering work, uncovered a route for the generation of arynes, which is base-free and could be carried out under mild reaction conditions. The strategy involves a fluoride-induced 1,2-elimination of 2-(trimethylsilyl)aryl triflates **36** to generate arynes in solution. This influential discovery led to a swift development in the field of arynes chemistry (Scheme 1.22)

[15]. This precursor could easily be synthesized from 2-bromophenol in three steps. Moreover, a one-pot method also could be employed for the synthesis of the precursor.



Scheme 1.22 Kobayashi's method of aryne generation. Source: Based on Himeshima et al. [15].

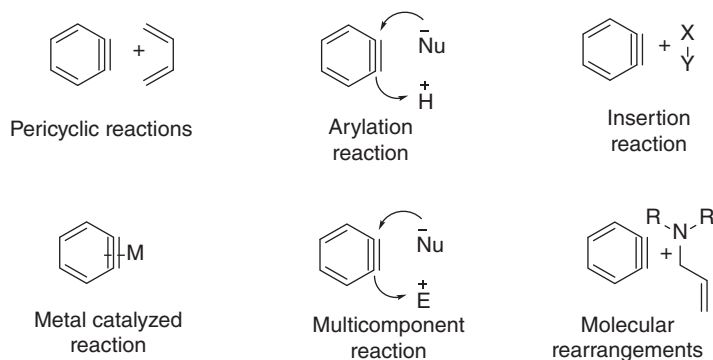
Kobayashi's method, unlike conventional routes, was compatible with a range of functional groups and reagents. KF (with 18-crown-6 as additive) in THF, CsF in CH₃CN, TBAT in THF, and tetrabutyl ammonium fluoride (TBAF) in THF are generally used as fluoride sources for the generation of aryne from the silyl triflate **36**. The kinetic control in the aryne reaction can be attained with cautious selection of fluoride source and solvent combination. This selection of the fluoride sources controls not only the rate of aryne generation but also the regioselectivity in the product formation. Kobayashi's method is highly preferred by synthetic chemists over traditional methods for aryne generation in recent decades. Many traditional aryne reactions were revisited to enhance the scope and yield after the establishment of mild and efficient Kobayashi's procedure of aryne generation.

1.8 Possible Reactivity Modes of Arynes

Due to their low-lying LUMO, arynes have been widely used as electrophiles in various reactions (Scheme 1.23). Arynes are well explored by synthetic organic chemists as they found that the intermediate is capable for unparallel transformations. The diverse reactivity profile of this transient intermediate is noteworthy. Aryne reactivity can be classified into:

- Pericyclic reactions
- Arylation reactions
- Insertion reactions
- Transition-metal-catalyzed reactions
- Multicomponent couplings (MCCs)
- Molecular rearrangements

Owing to their well-defined electrophilic nature, arynes are excellent dienophile and dipolarophile in pericyclic reactions such as Diels–Alder reactions, [2+2] cycloaddition, and dipolar cycloaddition reactions. Arynes hold the ability to arylate a number of molecules like alcohols, amines, and thiols leading to efficient

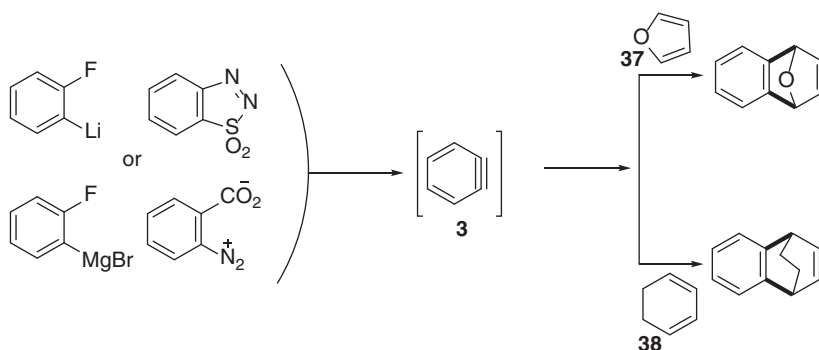


Scheme 1.23 Possible modes of reactivity of arynes.

X-H (X = O, S, and NH) insertion reactions. Arynes are well known to insert into various element–element σ -bonds and π -bonds, resulting in the formation of a library of functionalized 1,2-disubstituted arenes. Arynes have also been efficiently utilized as the electrophilic component in various transition-metal-free multicomponent couplings (MCCs). Molecular rearrangements are the emerging class of reactivity of arynes, where initial aryne addition is followed by unique molecular rearrangements (Scheme 1.23).

1.8.1 Pericyclic Reactions

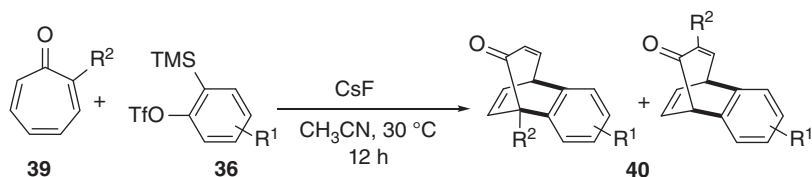
Due to high electrophilicity of the carbon–carbon triple bond in arynes, they are excellent dienophiles in pericyclic reactions. Many times, pericyclic reactions of arynes are utilized for the detection of the aryne generation in solution. Moreover, these reactions could result in the formation of complex arenes in one step under mild conditions. The Diels–Alder reaction of arynes began with the successful trapping of the in situ-generated aryne intermediate **3** by Wittig and Pohmer with furan **37** via a [4+2] cycloaddition reaction furnishing epoxynaphthalene derivative in good yields (Scheme 1.24) [29]. Independently, Huisgen and Knorr



Scheme 1.24 Wittig and Huisgen's aryne cycloaddition experiment. Source: Wittig and Pohmer [29]; Huisgen and Knorr [92].

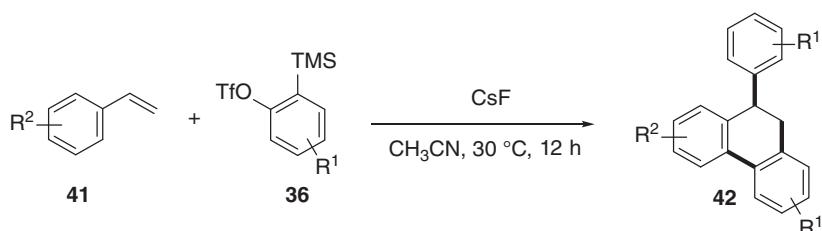
have utilized aryne as an electrophilic dienophile when they demonstrated the reaction of aryne generated from different precursors with furan **37** or cyclohexadiene **38** [92].

The Diels–Alder reaction of tropones **39** with arynes generated from the Kobayashi precursor **36** using CsF resulted in the convenient method for the synthesis of benzobicyclo[3.2.2]nonatrienones **40** in good yield and broad scope (Scheme 1.25) [93]. Although tropones can react as 4π , 6π , or 8π components in cycloaddition reactions, the reactivity in this case as diene (4π component) is noteworthy.



Scheme 1.25 Diels–Alder reactions of tropones with arynes. Source: Thangaraj et al. [93].

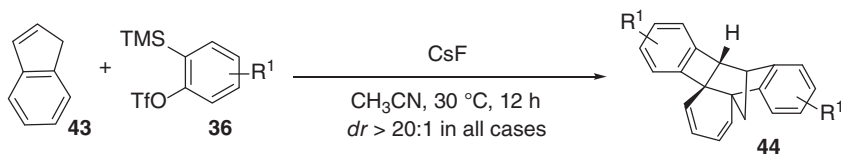
The poor yield and limited scope in the Diels–Alder reaction of styrene with arynes, known as early as 1966, has been revisited recently in a reaction of styrenes **41** with arynes generated from **36** using CsF in CH₃CN affording the 9-aryl dihydrophenanthrene derivatives **42** (Scheme 1.26) [94]. Electronics decided the products in this transformation as electron-rich and neutral styrenes reacted with arynes to form 9-aryldihydrophenanthrenes, whereas electron-poor styrenes afforded the dihydrophenanthrenes (1,1 adducts).



Scheme 1.26 Reaction of styrenes with arynes. Source: Bhojgude et al. [94].

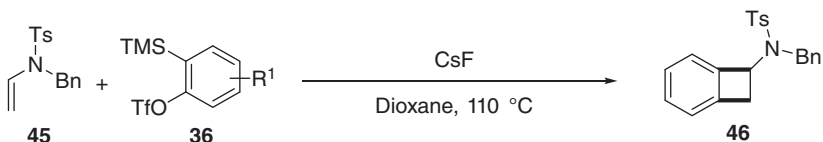
However, similar reactivity was not observed when indene/benzofuran was treated with arynes under identical conditions. Using indene **43** as the diene component, reaction afforded the dihydrobenzocyclobutaphenanthrenes **44** in moderate-to-good yields (Scheme 1.27) [95]. The reaction features a unique [4+2] cycloaddition followed by a diastereoselective [2+2] cycloaddition to afford the desired product.

Due to their high electrophilicity and strong dienophilic nature, arynes are well known to participate in [2+2] cycloaddition reactions with electron-rich carbon–carbon double bonds. For instance, a tandem stereoselective aryne [2+2]



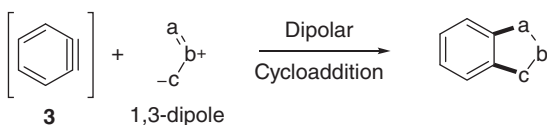
Scheme 1.27 Tandem [4+2]/[2+2] cycloaddition involving arynes and indene. Source: Bhojgude et al. [95].

cycloaddition reaction with enamides **45** for the synthesis of benzocyclobutanes **46** has been uncovered by Hsung and coworkers (Scheme 1.28) [96].



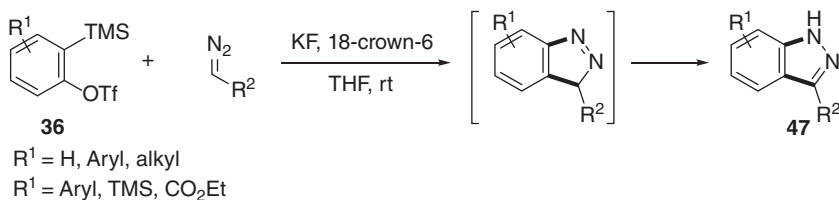
Scheme 1.28 [2+2] Cycloaddition involving arynes and enamides. Source: Based on Feltenberger et al. [96].

Apart from [4+2] and [2+2] cycloaddition reactions, arynes are well known to participate in dipolar cycloaddition reactions. Arynes are excellent dipolarophiles and can add to various 1,3-dipoles for the synthesis of benzo-fused five-membered rings. The commonly used 1,3-dipoles that can conveniently add to arynes are nitrones, nitrile oxides, nitrile imines, azomethine imines, azides, diazo compounds, etc. (Scheme 1.29).



Scheme 1.29 1,3-Dipolar cycloaddition of arynes.

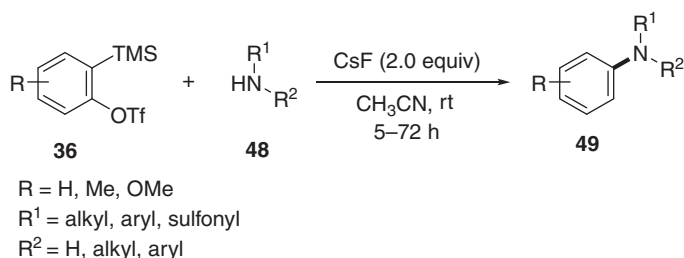
For example, the 1,3-dipolar cycloaddition of arynes with diazomethane derivatives for the synthesis of *N*-unsubstituted indazoles **47** has been reported by Larock and coworkers (Scheme 1.30) [97].



Scheme 1.30 [3+2] Cycloaddition reaction of diazo compounds with arynes. Source: Based on Liu et al. [97].

1.8.2 Arylation Reactions

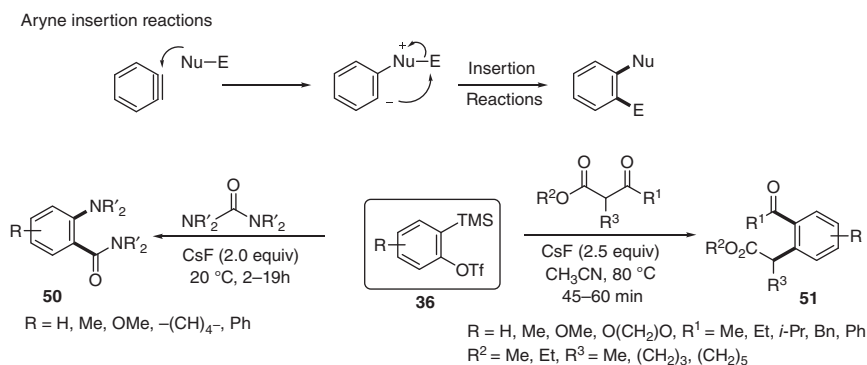
Arynes are highly electrophilic species; hence, they react with a number of charged as well as uncharged nucleophiles, resulting in the in situ generation of aryl anions, which can be protonated, thus leading to efficient arylation reactions. Thus, arynes can be used as the aryl source for the arylation of OH, SH, and NH bonds under transition-metal-free conditions. In 2003, Larock and coworkers developed a mild strategy for the *N*-arylation of primary and secondary amines **48** by making use of the arylating property of arynes generated from the precursor **36** (Scheme 1.31) [98].



Scheme 1.31 *N*-Arylation of amines. Source: Based on Liu and Larock [98].

1.8.3 Insertion Reactions

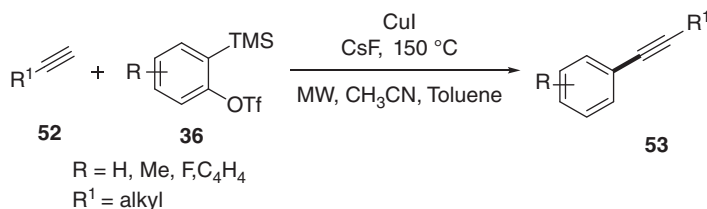
Arynes have the exceptional ability to insert into various element–element σ -bonds and π -bonds. This insertion phenomenon of arynes has been extensively employed for the synthesis of functionalized 1,2-disubstituted arenes. For example, Shirakawa, Hiyama and coworkers utilized the benzyne insertion strategy for the synthesis of 2-aminobenzamides **50** via a N—CO bond insertion of ureas (Scheme 1.32) [99]. Also, the insertion of arynes into a carbon–carbon σ -bond of acyclic and cyclic β -ketoesters led to the one-step synthesis of 1,2-disubstituted arenes **51** as demonstrated by Stoltz and coworkers in 2005 (Scheme 1.32) [100].



Scheme 1.32 Insertion of arynes to amides and β -keto esters. Source: Yoshida et al. [99]; Tamber and Stoltz [100].

1.8.4 Transition-Metal-Catalyzed Reactions

The development of *o*-(trimethylsilyl)aryl triflate by Kobayashi and coworkers helped to discover many novel transition-metal-catalyzed reactions involving arynes [101]. Metal-catalyzed aryne-based insertion, annulations, cycloadditions, and multicomponent reactions are well known. In 2009, Biehl and coworkers reported the coupling of a terminal alkyne **52** and aryne in the presence of CuI for the synthesis of phenyl acetylene derivatives **53** (Scheme 1.33) [102].



Scheme 1.33 Metal-catalyzed coupling reaction of arynes. Source: Based on Akubathini and Biehl [102].

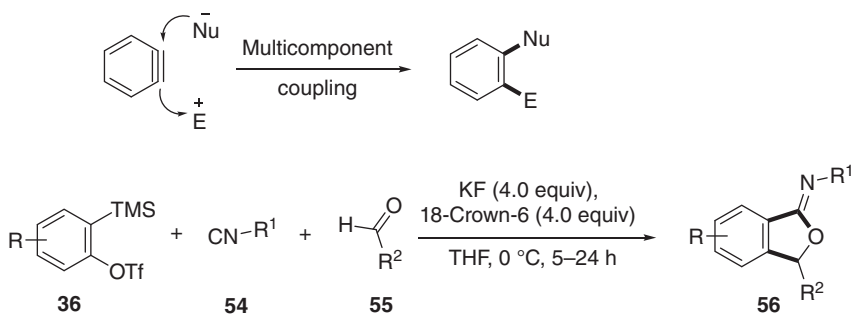
1.8.5 Multicomponent Couplings (MCCs)

Transition-metal-free MCCs involving arynes have received considerable attention in the past two decades. A number of 1,2-disubstituted arenes are synthesized using the MCCs involving arynes in one step. In a typical aryne MCC, the nucleophiles having no acidic proton are added to the in situ-generated arynes forming the aryl anion intermediate, which is subsequently intercepted by an electrophilic third component to form complex 1,2-disubstituted arenes. If the nucleophile and the electrophile do not belong to the same molecule, these reactions result in unique MCCs. For instance, Yoshida, Kunai, and coworkers reported a facile three-component reaction of arynes with isocyanides **54** and aldehydes **55** under mild reaction conditions for the efficient synthesis of iminoisobenzofurans **56** in good yields (Scheme 1.34) [103]. The variation on all the three components is well tolerated, and the use of other third components such as activated imines and electron-poor olefins is also possible.

1.8.6 Molecular Rearrangements

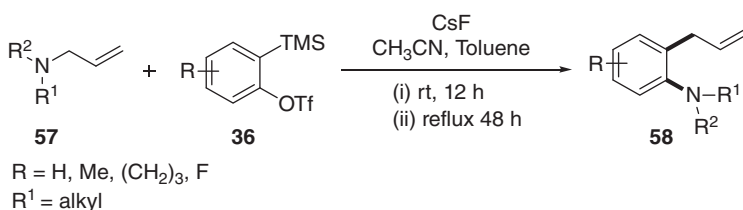
Molecular rearrangements involving arynes are of high interest in recent years. These rearrangement reactions have provided a number of structurally important motifs, which is otherwise complicated to synthesize. Many well-known conventional molecular rearrangements were applied in aryne chemistry to make the aryne version of the same. Using arynes as the aryl source, many of these rearrangements proceed under mild conditions in broad scope. For example, Greaney and coworkers developed an aza-Claisen rearrangement to synthesize functionalized anilines **57** using various piperidine and morpholine-derived tertiary allylic amines **58** (Scheme 1.35) [104].

Multicomponent coupling employing arynes



$R = \text{H, Me, (CH}_2\text{)}_3, \text{OMe, F}$
 $R^1 = \text{CMe}_2\text{-CH}_2\text{-CMe}_3, t\text{-Bu, 1-Ad}$
 $R^2 = \text{Et, } t\text{-Bu, Ph, Ar}$

Scheme 1.34 MCCs involving arynes, isocyanides, and aldehydes or activated imines. Source: Based on Yoshida et al. [103].



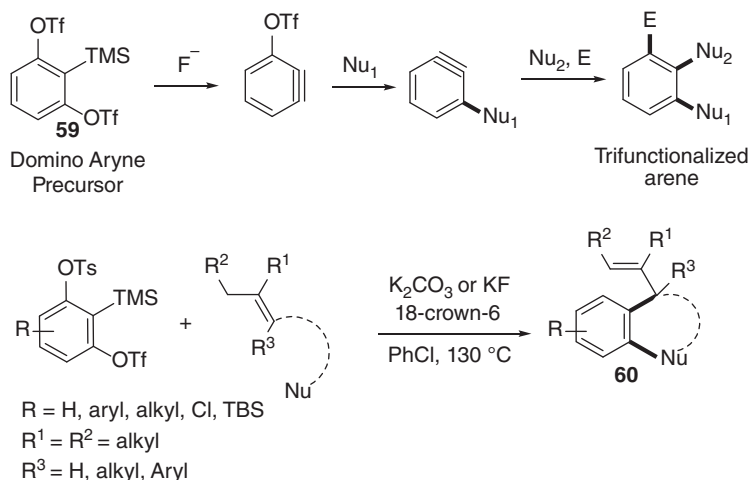
Scheme 1.35 Aryne aza-Claisen rearrangement. Source: Based on Cant et al. [104].

1.9 Domino Aryne Generation

The concept of multifunctionalization of aryne materialized with the realization of the concept of domino aryne generation by Li and coworkers [105]. A novel domino aryne precursor **59** has been developed (Scheme 1.36), which has vicinal electrophilic centers, capable of receiving consecutive double nucleophilic addition onto it. Utilizing this concept, a methodology for the nucleophilic addition-ene reaction end for the construction of indoline scaffolds **60** was developed by the same group [106]. A detailed discussion on the domino aryne strategy is provided in Chapter 8 of this book.

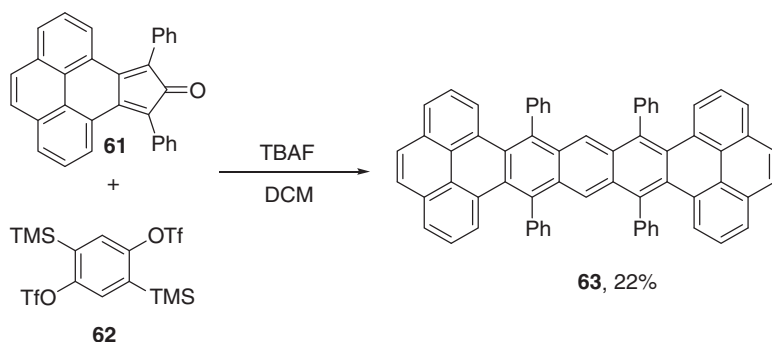
1.10 Arynes for the Synthesis of Large Polycyclic Aromatic Compounds

Cycloaddition reactions involving arynes give access to the synthesis of large polycyclic aromatic hydrocarbons (PAHs) containing five or more fused benzene rings. This strategy is of high value since the products find applications in the



Scheme 1.36 Domino aryne strategy and the indoline synthesis. Source: Shi et al. [105]; Xu et al. [106].

field of materials science. Moreover, several PAHs are analogous to nanosized graphene substructures. The benzodiyne precursor has been efficiently utilized for the synthesis of a number of symmetrical and unsymmetrical PAHs. For example, Wudl and coworkers reported the synthesis of the stable large PAH **63**, in a reaction of cyclopentadienone **61** with benzodiyne precursor **62** (Scheme 1.37) [107]. The two-fold Diels–Alder reaction of aryne generated from **62** with the diene **61** is followed by the elimination of two molecules of CO resulting in the formation of the PAH **63** in one step.

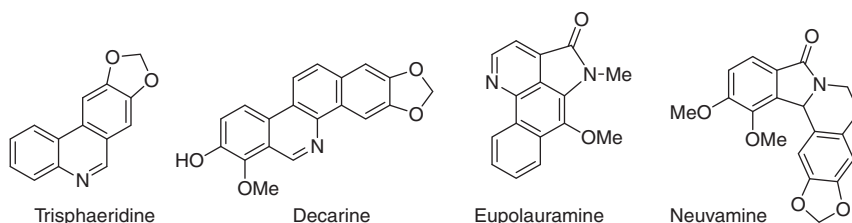


Scheme 1.37 Polycyclic aromatic hydrocarbons (PAHs) synthesis using arynes. Source: Based on Duong et al. [107].

1.11 Arynes in Natural Product Synthesis

Arynes are not only exploited in developing novel carbon–carbon and carbon–heteroatom bond-forming reactions but also in natural product synthesis

(Scheme 1.38). The motifs with new carbon–carbon or carbon–heteroatom bonds formed on the aromatic rings in the aryne reactions form the backbone for several biologically important molecules. For example, biologically important molecules such as trisphaeridine, dacarine, eupolauramine, and neuvamine could be easily synthesized using the aryne strategy. More details on application of arynes in natural products synthesis have been provided in Chapter 11 of the book.



Scheme 1.38 Selected examples of natural product synthesized using the aryne concept.

1.12 Concluding Remarks

Arynes are century-old transient intermediates, which can now be accessed using simple precursors in mild and convenient ways. This has considerably broadened the diverse range of applications using this reactive intermediate. Ever since the development of Kobayashi's mild protocol for aryne generation, the field has revolutionized significantly. The reactivity of arynes can be classified into cycloaddition reactions, insertion reactions, multicomponent reactions, transition-metal-catalyzed transformations, and aryne-induced molecular rearrangements. Recent developments in the area have shown rapid emergence of a new class of reactions under molecular rearrangement employing arynes as aryl source. The potential synthetic utility of a variety of heterocyclic arynes has also been uncovered recently by synthesizing various heterocycle-fused ring systems. The generation of benzyne through the HDDA reaction has allowed this intermediate to explore new modes of intrinsic reactivities. The trifunctionalization of arynes and the domino aryne strategies are new concepts emerging recently in this field. Moreover, aryne methodologies have widely been employed for the synthesis of several natural products. It is expected that the mild and transition-metal-free method for the generation of arynes will inspire synthetic chemists to explore new reactions and potential applications using the concept of arynes.

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