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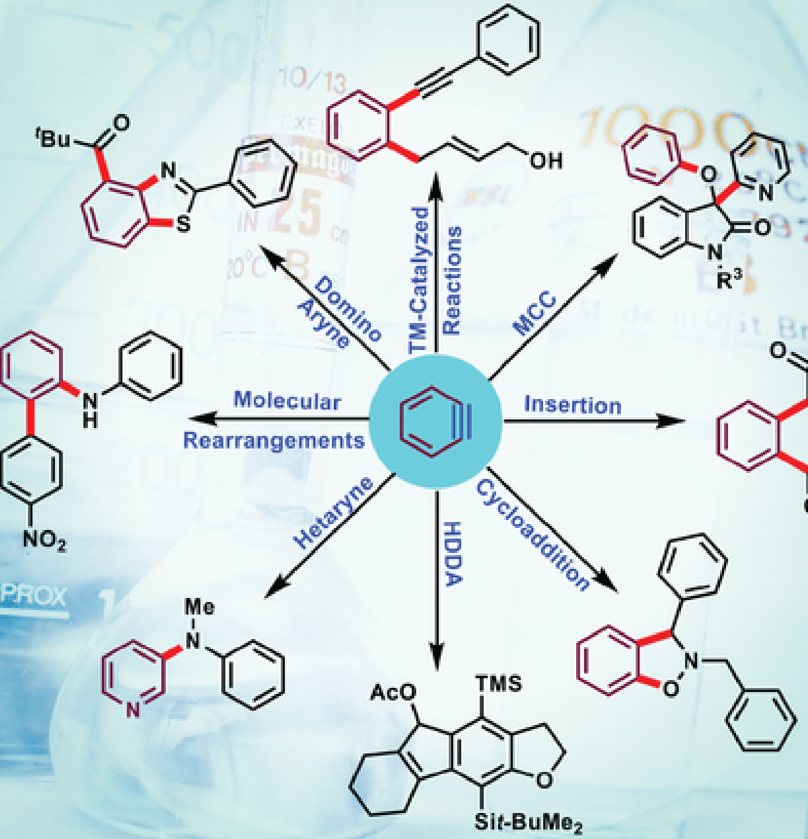
Modern Aryne Chemistry



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Editor

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Foreword

Arynes as fleeting intermediates in organic reactions were first recognized by Stoermer and Kahlert in 1902, but the solid experimental evidence of their (benzyne) involvement came through the seminal ^{14}C tracer studies by J. D. et al. (1953) on the amination of haloarenes, and very recently Pavlićek et al. (2015) have directly observed surface-generated benzyne by atomic force microscopy (AFM). Concurrently, many preparatively useful methods for generating arynes have been devised and their diverse reactivity landscape has been extensively explored and profiled. A breakthrough in the exploitation of arynes in wide range of productive applications in organic synthesis, including total synthesis of natural products, came about through Kobayashi's discovery (1983) that stable 2-(trimethylsilyl)aryl triflates (now commercially available) undergo facile fluoride-mediated 1,2-elimination to generate arynes safely and efficiently. This convenient access to arynes gave a major fillip to mapping the diverse and potentially rich synthetic utility of these highly reactive intermediates in the syntheses of arenes harboring structural complexity and fostering molecular diversity. The next steps in the advance of aryne arena came from the hexadehydro-Diels–Alder reaction developed by Hoye, domino generation of arynes by Li, and the development of heteroarynes by Garg among many other tactical innovations that have immensely enriched the field and amplified the expanse of aryne chemistry. Intramolecular variants, domino and tandem reactions with embellished arynes still offer innovative chemical spaces that await unraveling. While chemical explorations of aryne reactivity cover a vast and varied arena, they can be broadly categorized under lead headings like pericyclic reactions, insertion reactions, multicomponent reactions, transition-metal-catalyzed transformations, and a variety of unforeseen and interesting molecular rearrangements.

The landscape of aryne chemistry has grown by leaps and bounds since the publication of R. W. Hoffmann's seminal monograph *Dehydrobenzene and Cycloalkynes* over half a century ago in 1967. A recent SciFinder search on “benzyne” and “aryne” led to −7500 and −4500 hits, respectively – clearly indicative of a fertile field and the traction it has drawn in the recent decades. These developments in aryne chemistry have been periodically captured in several timely and authoritative accounts and reviews covering diverse facets of this growing field. Nevertheless, there is a much-felt need among students and researchers in the field for an authoritative book that provides a broad, up-to-date coverage of multifaceted advances in aryne chemistry with a nuanced lens on developments that are of topical interest and likely to dominate future directions and activities and also provide a fuller flavor of the field.

Against this background and to fill a widely felt void, Akkattu T. Biju, an accomplished contributor in the arena, has put together an authoritative and timely collection of contributions from leading practitioners in the field of aryne chemistry under the title *Modern Aryne Chemistry*. This book is primarily aimed at highlighting some of the recent advances in carbon–carbon and carbon–heteroatom bond-forming reactions of arynes, as highly reactive and versatile electrophilic species, with numerous, contextual synthetic applications.

The first chapter of the book introduces the chemistry of arynes. This overarching contribution by Akkattu T. Biju (IISc Bangalore) describes the history of arynes, various methods for their generation, characterization techniques, and possible modes of reactivity. A detailed account of the application of arynes in cycloaddition reactions has been presented in the second chapter by E. Guitián from Universidade de Santiago de Compostela, Spain. The synthetic potential of arynes for accessing various polycyclic aromatic hydrocarbons (PAHs) and nanographenes has been highlighted in this chapter. The focal theme of the third chapter of the book compiled by F. Shi (WuXi AppTec Co., Ltd. Wuhan), and P. Li (Henan University) is on dipolar cycloaddition reactions of arynes and provides the interception of arynes with various dipoles for the synthesis of benzo-fused heterocycles. An overview “Recent advances in the insertion reactions of arynes” forms the fourth chapter by S. Yoshida and T. Hosoya from Tokyo Medical and Dental University, Japan. This chapter provides an interesting feature of aryne intermediates to insert into various element-to-element bonds to form 1,2-disubstituted arenes. A variety of nucleophiles can add to arynes and the generated aryl anion can be intercepted with electrophiles to orchestrate multicomponent reactions. A complete coverage of transition-metal-free aryne multicomponent reactions for the synthesis of complex 1,2-disubstituted arenes has been presented by H. Yoshida from Hiroshima University in the fifth chapter.

The sixth chapter of the book by C.-H. Cheng (National Tsing Hua University, Taiwan), M. Jeganmohan (IIT Madras), and K. Parthasarathy (University of Madras) provides a detailed account of the transition-metal-catalyzed reactions involving arynes. Transition-metal-catalyzed cycloisomerization reactions, C—H and N—H bond activations involving arynes leading to annulation reactions, three-component coupling reactions, etc. are described in this chapter. Arynes serve as versatile precursors for a number of molecular rearrangements, resulting in the synthesis of diverse and structurally attractive organic compounds that are otherwise difficult to access. The recent developments in molecular rearrangements triggered through aryne intermediates are summarized in the seventh chapter by S.-K. Tian from University of Science and Technology of China, Hefei. The eighth chapter of the book is dedicated to the new strategies and latest developments in this field and deals with new methods of aryne generation, addresses the regioselectivity and multifunctionalization issues in aryne chemistry, and is authored by Y. Li from Chongqing University. A brief history of hetarynes, cycloalkynes and related potential intermediates, different methods of their generation, various types of reactions and applications in total synthesis are briefly discussed in the ninth chapter by Akkattu T. Biju (IISc Bangalore). The penultimate chapter contributed by T. R Hoye (University of Minnesota) offers the hexadehydro Diels–Alder (HDDA) route to arynes and related chemistry. Although this reaction was first revealed in 1997, it received an expansive growth after a report in 2012 demonstrating its potential as a general strategy for generating reactive benzyne intermediates from simple triyne precursors. The potential applications of arynes in the synthesis of natural products and biologically active molecules have been highlighted by K. Suzuki (Tokyo Institute of Technology) and H. Takikawaa (Kyoto University) in the last chapter of this monograph.

It is expected that in addition to the pedagogic value of the book for the students and the general reader, the simplicity and sophistication of the synthetic strategies using aryne chemistry will also inspire and entice a wide range of organic chemists to explore new reactivity patterns and imaginative applications in total synthesis, material science, and chemical biology. It is reasonable to believe that aryne chemistry will continue to flourish and lead to many interesting/serendipitous observations in the future to enrich organic chemistry. Thus, from a wider perspective, this timely book is expected to serve many purposes to augment and advance organic chemistry and its interfaces.

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4 December 2020

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Preface

Carbon–carbon and carbon–heteroatom bond-forming reactions constitute the backbone of synthetic organic chemistry. When it comes to the utilization of the ring strain in these bond-forming reactions, arynes have always been at the forefront (having low-lying lowest unoccupied molecular orbital [LUMO] with a strain energy of 63 kcal mol^{-1}). Arynes are highly reactive intermediates, which are generated in situ due to their high reactivity. The chemistry of this century-old intermediate, which marked its birth in history with the vague evidence of its existence provided by Stoermer and Kahlert in 1902, has gained outstanding acceleration toward the end of the twentieth century. This unstable intermediate has been characterized using various spectroscopic methods by different research groups. In the course of time, various research groups have developed several methods for the mild generation of arynes. However, the procedure became much simpler since 1983 when Kobayashi uncovered a facile and mild method for generation of arynes from 2-(trimethylsilyl) aryl triflates using simple fluoride sources. Moreover, the reagent-free and metal-free generation and reactivity of arynes generated utilizing the concept of intramolecular hexadehydro Diels–Alder reaction (HDDA) of triynes at elevated temperature has also been studied in detail.

Arynes, being a polarizable intermediate, have a diverse reactivity profile due to their affinity toward charged and uncharged electron donors. Arynes serve as excellent dienophile and dipolarophile in pericyclic reactions such as Diels–Alder reactions, [2+2] cycloadditions and dipolar cycloaddition reactions. Arynes hold the potential to arylate a number of molecules like alcohols, amines, and thiols and to insert into various element–element σ-bonds and π-bonds. Transition-metal-free multicomponent couplings (MCCs) and molecular rearrangements are the emerging class of reactivity of arynes. Moreover, arynes undergo a variety of transition-metal catalyzed reactions. A consecutive double nucleophilic addition realizing the concept of multifunctionalization of aryne using a novel domino aryne precursor was uncovered recently by Li and coworkers. Cycloaddition reactions involving arynes give access to the synthesis of large polycyclic aromatic hydrocarbons (PAHs) that are analogous to nanosized graphene substructures. The applications of arynes are not only limited to developing novel bond-forming reactions but also in natural product synthesis. The synthesis and reactivities of several five- and six-membered hetarynes, and strained cycloalkynes have also been a subject of interest for chemists. A book on arynes is a need of the hour as the area has crossed several milestones ever since the first book on arynes *Dehydrobenzene and Cycloalkynes* by R. W. Hoffmann was published in 1967. The lack of an update to this book incorporating all the developments in the past five decades made us realize this collection of information on arynes. The focus of the present book is on the history, diverse reactivity, and application of arynes in organic synthesis. Moreover, details on hetarynes, domino generation of arynes, and HDDA method of aryne generation have also been included in the book. As the chemistry of arynes has achieved considerable growth and continues expanding further, with the strong support of Wiley-VCH, we decided to bring out a new book under the title *Modern Aryne Chemistry* to highlight the developments occurred in this interesting area. Eleven chapters highlighting the history, different modes of reactivity, and the application of arynes are presented in this book.

The foundation of this book is based on the excellent contributions of all the colleagues working in aryne chemistry, and I am thankful to them. Moreover, I would like to thank all the authors, who have contributed enormously to this project, for their valuable time, efforts as well as the expertise to make this book a source of encouragement for beginners as well as advanced chemists practicing synthetic organic chemistry. It is anticipated that the diverse reactivity and application of arynes will inspire a broad range of organic chemists to explore new opportunities and creative applications of this concept and thereby unraveling some of the remaining challenges in this field. I am also thankful to Dr Lifen Yang (*Program Manager, Books & References*) and Ms Katherine Wong (*Senior Managing Editor*) at Wiley-VCH for their unconditional support and valuable advices in organizing/developing this book.

India
30 November 2020

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1

Introduction to the Chemistry of Arynes

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1.1 Introduction

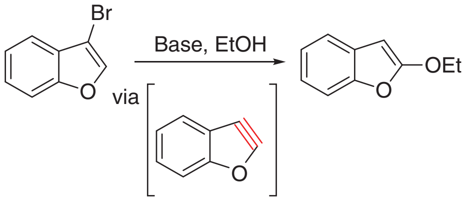
Arynes are highly reactive electrophilic intermediates proposed more than a century ago and have encountered an extraordinary resurgence of interest in the past decades. Chemists have exploited this reactive intermediate for the synthesis of a broad range of 1,2-disubstituted benzene derivatives and 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 Hoye [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 2-ethoxybenzofuran in the reaction of

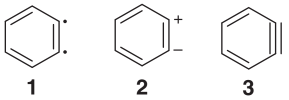
Modern Aryne Chemistry, First Edition. Edited by Akkattu T. Biju.

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].

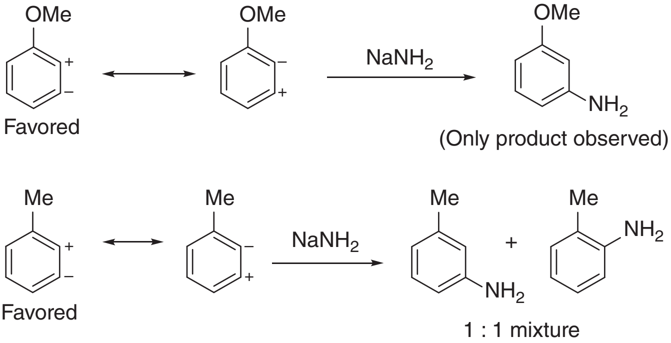
Later in 1927, Bachmann and Clarke at the Eastman Kodak Co. proposed benzyne as a reactive intermediate to explain the formation of triphenylene in a reaction, and it was taken as "decisive in favour of the free radical explanation" (Scheme 1.2) [21]. It was thought that structure **1** was predominant 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].

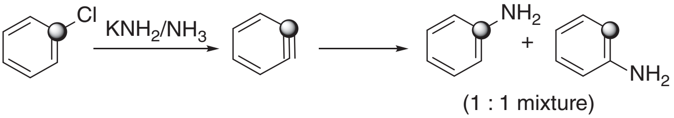
Later, Wittig found that the formation of biphenyl in the reaction of phenyllithium with halobenzenes was fastest with fluorobenzene through nucleophilic substitution reaction via the displacement of fluoride, which was considered as a complicated task to perform [22–25]. Thus, the ylide structure **2** 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].

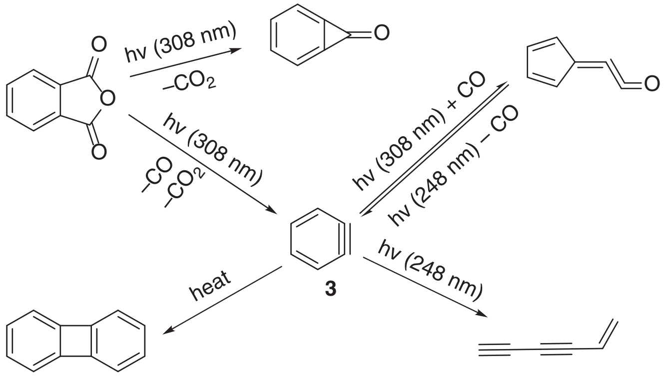


Scheme 1.4 Robert's ^{14}C-labeling experiment. Source: Roberts et al. [27]; Roberts et al. [28].

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 ^{13}C 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 benzynes have been prepared and analyzed by X-ray crystallography for further proof. Crystal structure of metal-bound benzyne shows that C_1—C_2 bond is more ethene-like

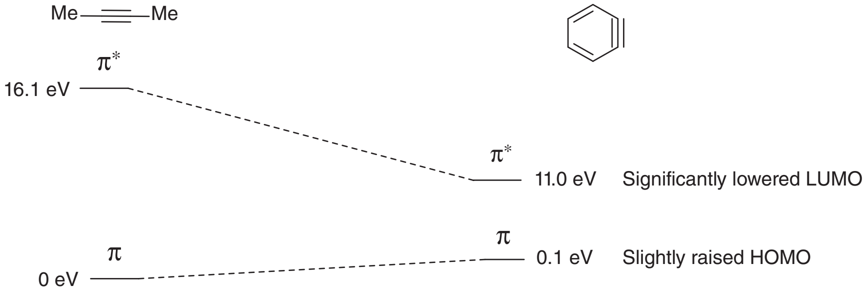
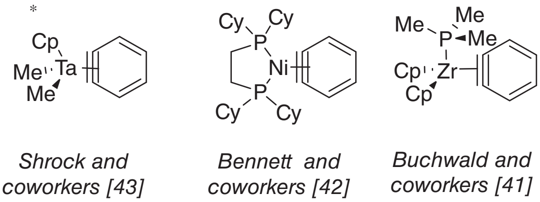


Figure 1.1 Reason for the enhanced electrophilicity of arynes. Source: Based on Hoffmann et al. [40].

(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).



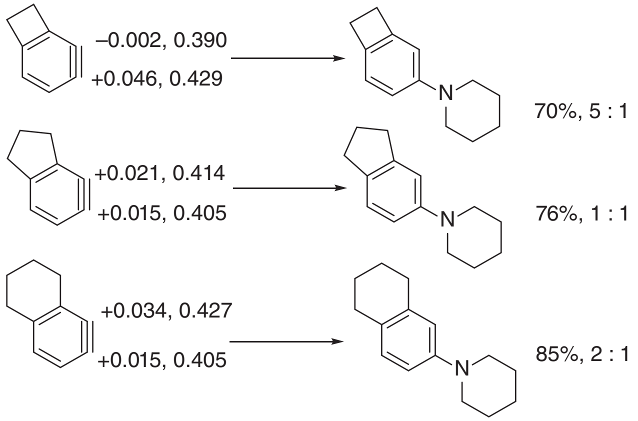
Scheme 1.6 Structures of metal-bound benzyne. Source: Buchwald et al. [41]; Bennett et al. [42]; Mclain et al. [43].

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 (~63 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.

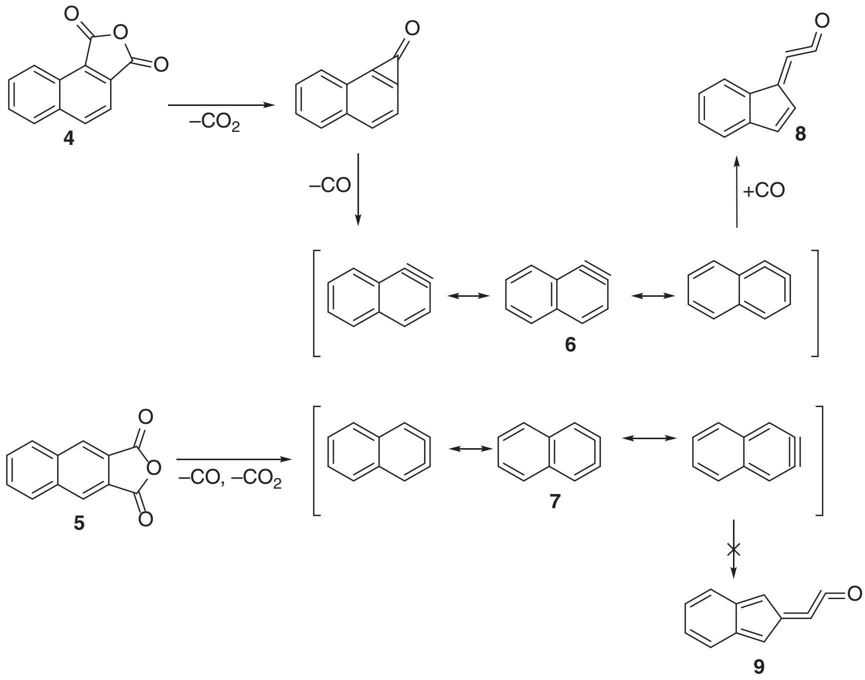
1.4 *Ortho*-Arynes with Substitution

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-positon 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 naphthalyne 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].

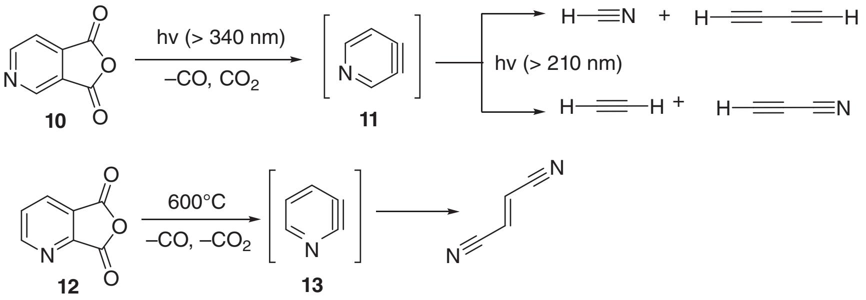


Scheme 1.8 Studies on naphthynes. Source: Lohmann [48].

1.5 *Ortho*-Arynes of Heterocycles

Although hetarynes are much older than benzynes, 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].

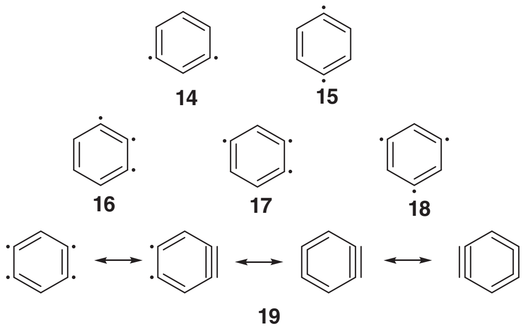


Scheme 1.9 Generation and dissociation of 3,4-pyridyne and 2,3-pyridyne. Source: Cava et al. [58]; Dunkin and MacDonald [59].

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.

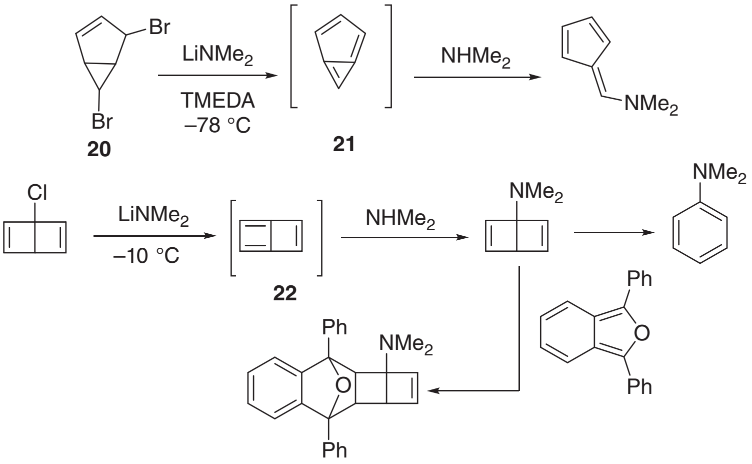
1.6 Other Arynes

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 tetradehydrobenzenes **19** are reported (Scheme 1.10) [61–64]. Tetradehydrobenzene (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 benzynes. 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, butalene **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