



CHEMISTRY & BIOLOGY INTERFACE

An official Journal of ISCB, Journal homepage; www.cbijournal.com

Arynes: important intermediates for synthesis of natural products

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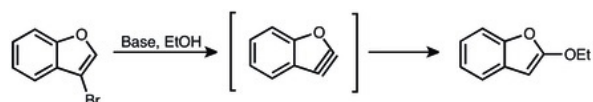
Received 29 May 2017; Accepted 26 July 2017

Abstract: The synthesis of natural products from benzyne intermediates offers an alternative strategy. The concept is as old as benzyne itself, being the basis of Wittig's seminal observations on biphenyl synthesis from phenyl lithium and fluorobenzene in 1940. In the intervening 75 years, the transformation has grown to encompass a remarkable scope of reaction classes, and continues to develop as new benzyne precursors enable inventive natural products syntheses under mild conditions. This review will cover the most aryne methods relevant to biaryl synthesis, drawing together key ideas from the older literature involving halobenzene precursors, with a more comprehensive coverage of modern methods using 2-(trimethylsilyl) phenyl triflates as the source of benzyne.

Keywords: Arynes; Intermediate; Kobayashi method; Benzyne.

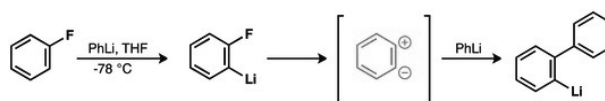
1. Introduction

The first hint of the existence of aryne intermediate came from the work of Stoermer and Kahlert in 1902. They observed that upon treatment of 3-bromobenzofuran with base in ethanol 2-ethoxybenzofuran is formed. Based on this observation they postulated an aryne intermediate [1].



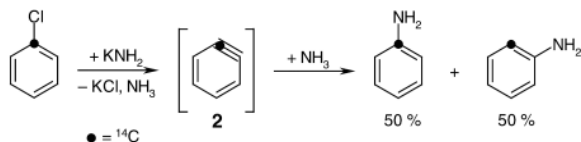
Georg Wittig and coworkers proposed that

the formation of biphenyl via reactions of fluorobenzene and phenyllithium proceeded via a zwitterionic intermediate and experimentally confirmed by John D. Roberts in 1953 [2].

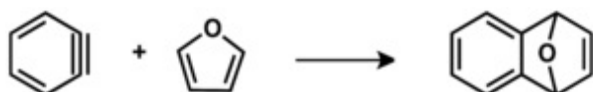


In 1953 John D. Roberts performed the classic ^{14}C labeling experiment, which provided strong support for benzyne. Roberts and his students performed the reaction of chlorobenzene-1- ^{14}C with potassium amide, and analyzed the ^{14}C -label incorporation into the resulting aniline: equal amounts of aniline with ^{14}C

incorporation at C-1 and C-2 were observed. This result necessitated a symmetrical intermediate – now known as benzyne [3].



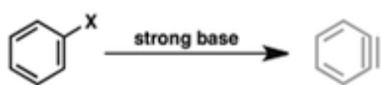
Soon after Roberts' discovery, Wittig and Pohmer found that benzyne can participate in [4+2] cycloaddition reactions [4].



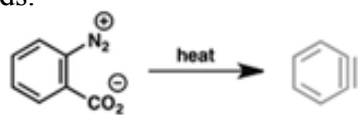
Additional evidence for the existence of benzyne came from spectroscopic studies: IR, UV/Vis, microwave, and NMR spectroscopies.

2. Generation of arynes

Due to extreme reactivity of arynes they must be generated in situ (Figure 1). In the early days of benzyne chemistry, harsh conditions were needed to generate arynes - many of the methods require strong base or high temperatures. Aryl halide can be treated with strong base to remove an aromatic proton and generate benzyne via elimination.



Arenediazonium-2-carboxylates can serve as precursors to benzyne. The main drawback of this method is the explosive nature of diazonium compounds.



Milder methods for benzyne generation have been developed. Aryl triflates have been widely used in synthesis. Fluoride displacement of the trimethylsilyl group, as shown below, allows for generation of benzyne under mild conditions.



A hexadehydro Diels-Alder reaction (HDDA) involves cycloaddition of 1,3-diyne and alkyne. HDDA generates benzyne, which can then be trapped, leading to diverse benzenoid products.

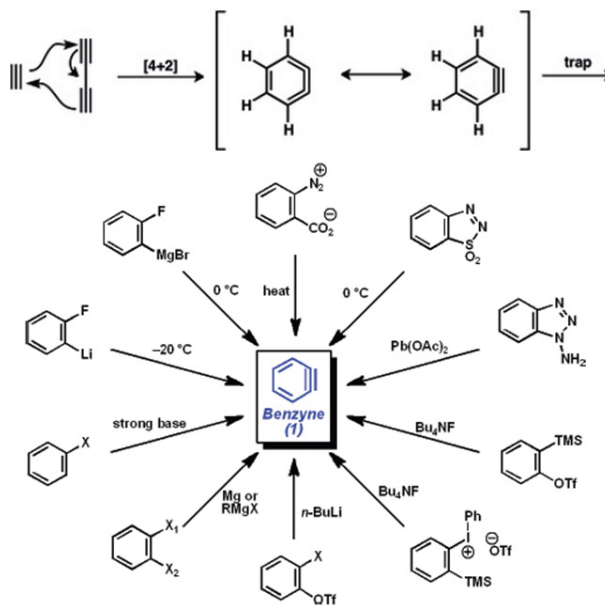


Figure 1. Methods for the generation of benzyne [5]

3. Reactions of arynes

The some reactions of arynes are briefly presented in Figure 2.

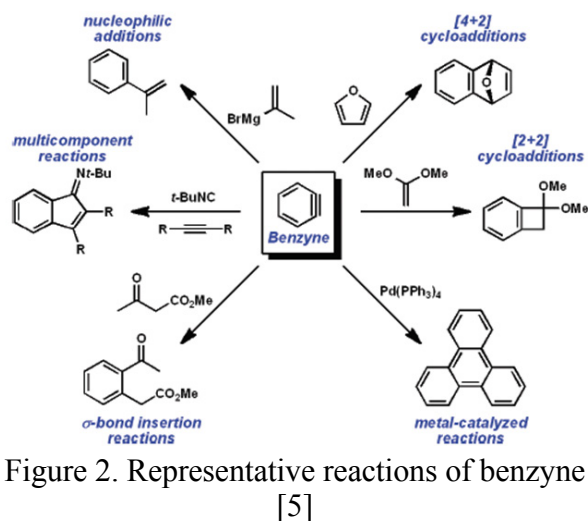
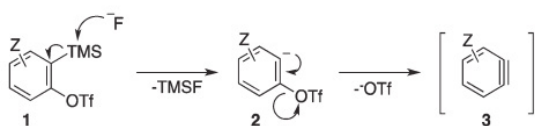


Figure 2. Representative reactions of benzyne [5]

4. Recent applications of aryne chemistry to organic synthesis

4.1. Kobayashi method

The very convenient, mild method for generating arynes from *o*-(trimethylsilyl)aryltriflates developed by Kobayashi in 1983 allows one to conveniently generate a highly reactive benzyne intermediate **3** at reasonable temperatures, using readily accessible solvents and only moderately basic fluoride ion (Figure 3) [6].



Scheme 1 Generation of benzyne using the Kobayashi method.

Figure 3. Generation of benzyne using the Kobayashi method

4.2. Benzotriazoles

Benzynes are well known to participate in cycloaddition reactions with 1,3-dipoles. In 2008, Larock and co-workers reported the so-called “aryne click” reaction, a cycloaddition between azides **4** and arynes generated in situ (Figure 4, 5). The reaction proceeds at room temperature and gives rise to the benzotriazoles **5** in 51–100% yields [7].

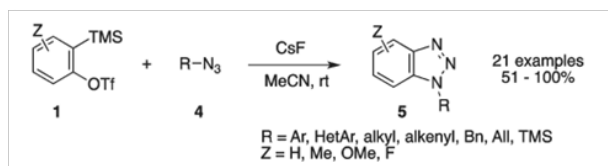


Figure 4. Synthesis of benzotriazoles developed by Larock

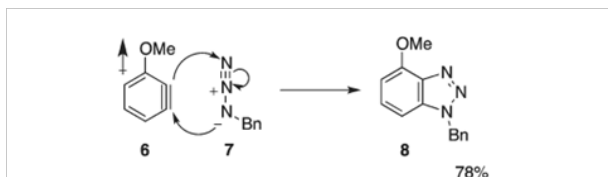


Figure 5. The transition state for coupling with 3-methoxybenzyne

4.3. Isoquinolines

Guan developed yet another set of reaction conditions for the transformation of enamides into isoquinolines. Running the reaction in THF in the presence of CsF/18-crown-6 at 80 °C allows one to obtain the desired products in 60–75% yields (Figure 6). Using this methodology, an interesting tetracyclic product **4o** was obtained in a 75% yield starting from the cyclic enamide **1** (Table 1)[8].

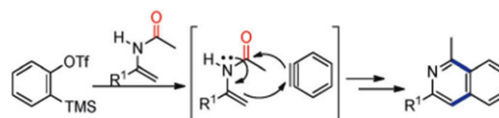
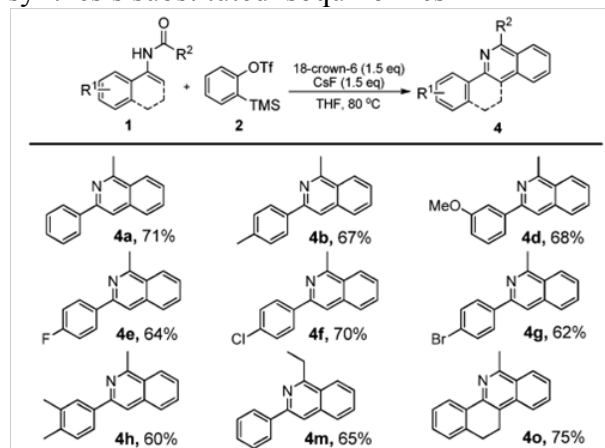


Figure 6. Construction of isoquinolines by amide activation

Table 1. Coupling of enamides and benzyne for synthesis substituted isoquinolines



4.4. Metal Catalyzed Reaction

A silver-catalyzed domino process leading from 2-(1-alkynyl)-benzaloximes to tetracyclic derivatives of the 1,4-dihydroisoquinolines **3a** has been discovered by Wu. As expected, the silver-catalyzed intramolecular cyclization of the starting oximes **1** leads to isoquinoline-N-oxides **A**, which are trapped in situ in a [3 + 2] process by a benzyne intermediate. Unexpectedly, the addition products **C** that are formed are not stable and rearrange to tetracyclic derivatives **3a**, possibly through a radical pathway. The transformation proceeds in the presence of

TBAF (tetra-n-butylammonium fluoride) and catalytic amounts of AgOTf in THF at 50 °C yielding the final products in 41–84% yields (Figure 7) [9].

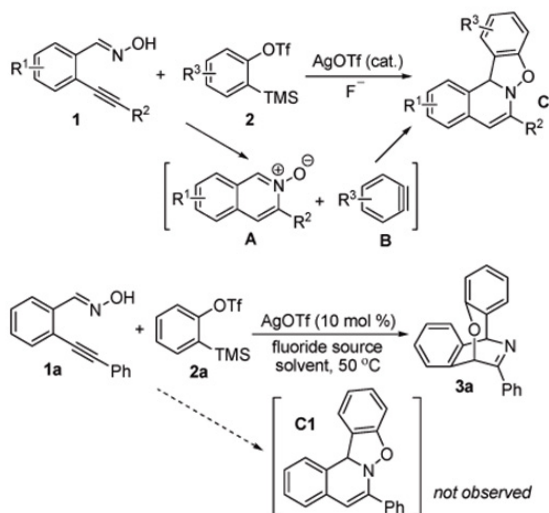


Figure 7. Proposed synthetic route for silver triflate catalyzed reaction of 2-alkynylbenzaloxime with benzyne

Jiang et al. reported an alternative aryne approach to phenanthridinone synthesis through the multicomponent reaction of benzyne, CO, and 1-iodoanilines 381 (Figure 8) [10]. Choice of fluoride proved pivotal in controlling product distribution, with CsF/TBAI in 10% aqueous MeCN generating benzyne relatively quickly and out-competing CO for initial insertion into the aryl–Pd bond. Switching to KF and using a diphosphine ligand created conditions for slow benzyne generation, leading to initial CO insertion and generation of isomeric acridone products.

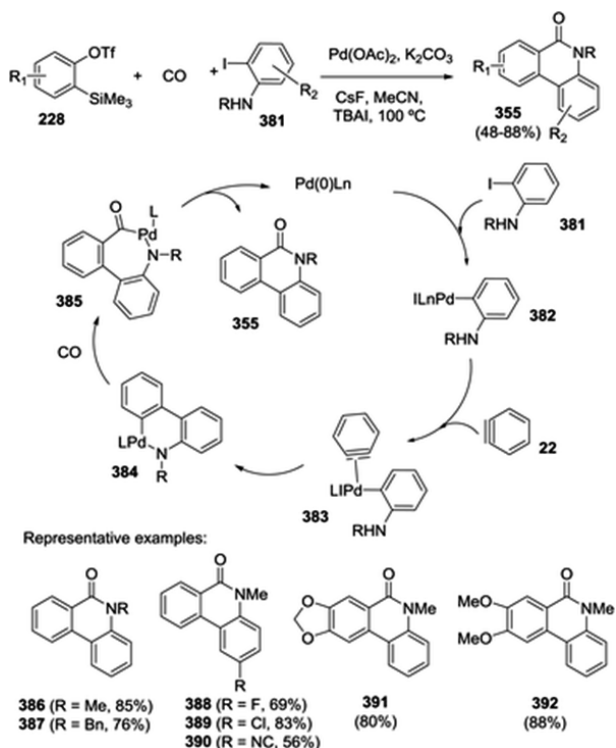


Figure 8. Pd-Catalyzed MCR of arynes, CO and aryl iodides.

4.5. Xanthenes

A route to xanthenes has been developed in the Larock group starting from o-haloarene carboxylic acids 161 (Figure 9). Running the aryne reaction in THF at 125 °C (sealed tube) in the presence of CsF results in an initial insertion of the benzyne into the C–O bond of the acid through a 4-membered ring intermediate 163. The o-hydroxyaryl ketone 164 thus formed apparently undergoes an intramolecular S_NAr process, furnishing the xanthenes 162 in 71–80% yields [11].

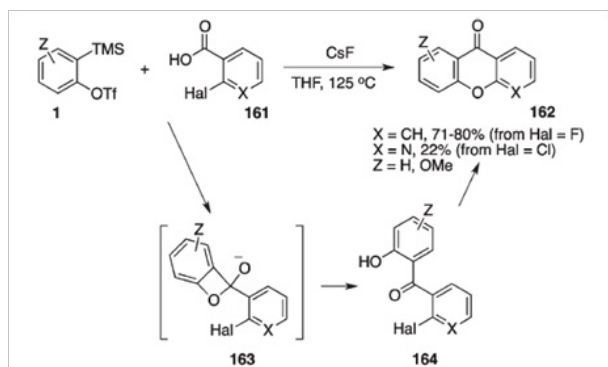


Figure 9. Reaction of o-haloarene carboxylic acids with arynes

4.6. Diels–Alder Reactions of Arynes

Aryne cycloaddition to yield biaryls is possible through Diels–Alder reaction with styrenes. Biju and co-workers recently reported an effective illustration of this idea [12]. Using the silyl precursor 228, a variety of styrenes reacted smoothly to give the 9-aryldihydrophenanthrenes 425 through a cascade Diels–Alder/ene reaction; the initial Diels–Alder adduct 427 is able to react with another aryne molecule in a concerted ene-reaction, as shown by deuterium-labelling experiments. The second ene reaction was found to be suppressed for styrenes containing electron-withdrawing groups in the para-position, yielding the aromatized Diels–Alder adducts 426 (Figure 10).

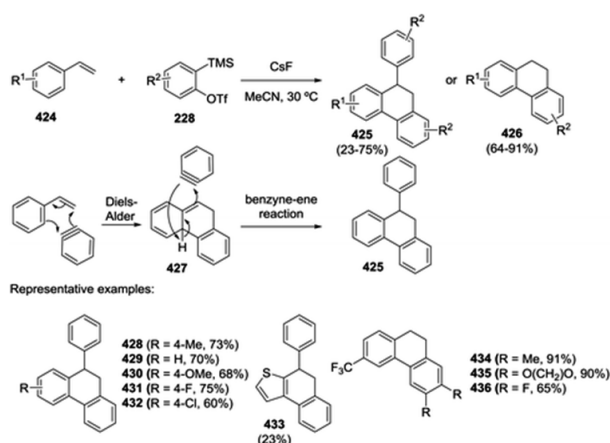


Figure 10. Diels–Alder-ene reactions of arynes and styrenes.

4.7. The Benzyne Fischer-Indole Reaction

A new approach to the Fischer-indole synthesis is reported that uses the reactive intermediate benzyne [13]. The addition of N-tosylhydrazones to arynes, generated through fluoride activation of 2-(trimethylsilyl)phenyl triflate precursors, leads to efficient N-arylation. Addition of a Lewis acid to the same reaction pot then affords N-tosylindole products via Fischer cyclization (Figure 11).

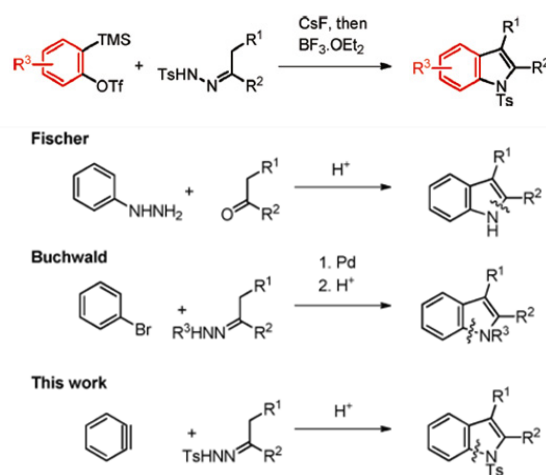


Figure 11. Selected Fischer-indole syntheses

4.8. Alkaloids

Hsung has reported a tandem process involving benzyne and the N-tosylenamides 15 bearing a remote alkene moiety (Figure 12). The process involves a [2 + 2] cycloaddition, followed by ring opening to provide the o-quinodimethane intermediate 18, which undergoes an intramolecular [4 + 2] cycloaddition with the remote C=C bond. Running the reaction in the presence of CsF in 1,4-dioxane at 110 °C provides the tricyclic products in 31–95% yields with excellent stereoselectivity [14].

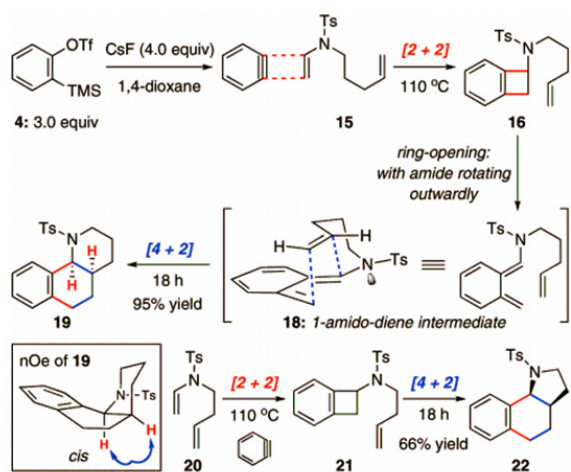


Figure 12. Tandem benzyne-enamide-[2+2]-[4+2]

Later, this methodology was adapted for the synthesis of two alkaloids (Figure 13). Reacting the dioxolane-containing aryne with a remote alkyne-containing enamide under mild reaction conditions lead to formation of the [2+2] cycloaddition product 2. Substituting MeCN with xylene and running the reaction at 120 °C allowed the remaining steps of the tandem process to proceed, providing the common precursor for the two alkaloids in a 65% overall yield [15].

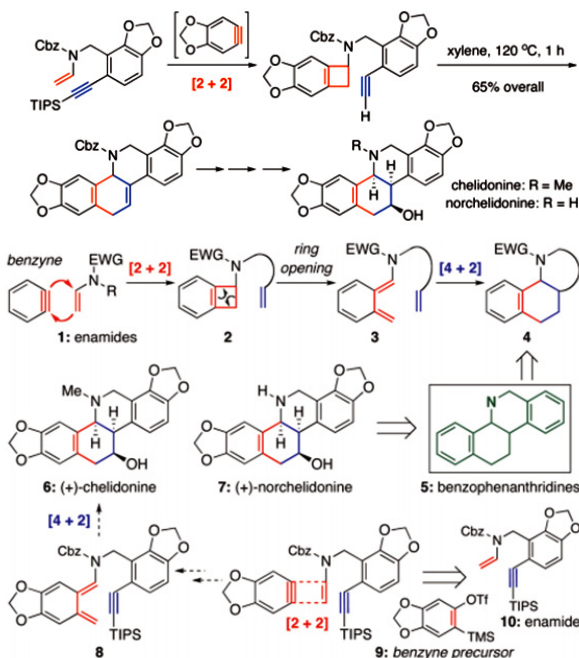


Figure 13. Enamide-benzyne-[2+2] cascade to chelidonine

4.9. Indolactam

Chandrasekhar et al. have recently reported the reaction of 2-sulfonyliminoindolines 627 with arynes to give 3-arylated indole derivatives 630 (Figure 14) [16]. The reaction proceeds through arylation at the 3-position of the indole derivative, then further N-arylation with a second equivalent of the aryne, as confirmed by deuterium labelling experiments in CD_3CN . Performing the reaction in THF, however produced mainly the benzazepine 631 arising from [2+2] cycloaddition/fragmentation reaction.

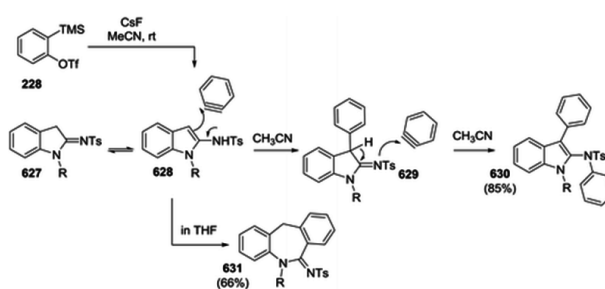


Figure 14. Arylation of 2-sulfonyliminoindolines

4.10. Polymerization

The direct polymerization of arynes was recently achieved by Uchiyama *et al.* for the synthesis of poly(*o*-arylenes) 691, using copper catalysis to control the assembly of *ortho*-linked arene structures (Figure 15) [17]. Their method employed standard conditions of *o*-trimethylsilylphenyltriflates 688, CsF, and 18-crown-6 in THF to generate the monomer arynes, with polymerization taking place in the presence of Cu(I) salts such as CuCN, CuCl, *n*-Bu₂Cu(CN)Li₂ or copper mesitylate. Alternative metal salts such as CuBr₂, KCN, AuCl, or Pd₂(dba)₃ were not successful when used as initiators. The polymeric parameters such as M_n , M_w and PDI depended on the aryne precursor/Cu(I) initiator ratio, with low amounts of the Cu(I) salt forming poly-(*o*-arylenes) with higher average molecular weights.

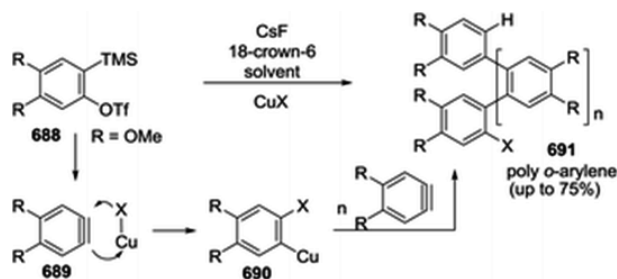


Figure 15. Synthesis of poly(*o*-arylenes) using arynes

5. Conclusion

Benzyne will efficiently react with hard organometallics such as aryllithiums and Grignards, participate in multi-component couplings mediated by transition metals such as copper, palladium and nickel, whilst having a rich pericyclic chemistry on hand that can be exploited in biaryl synthesis. The inherent reactivity of the strained triple bond can also be harnessed in metal-free aryl bond formation, either directly in the intramolecular mode, or through suitably-designed intermolecular heteroatom additions followed by rearrangement. Overall, the recent growth of benzyne chemistry has been driven in large part by the availability of new precursors, including some from quite unexpected sources; further progress in this area promises to open up new reaction regimes for natural products synthesis under mild and operationally-simple conditions.

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