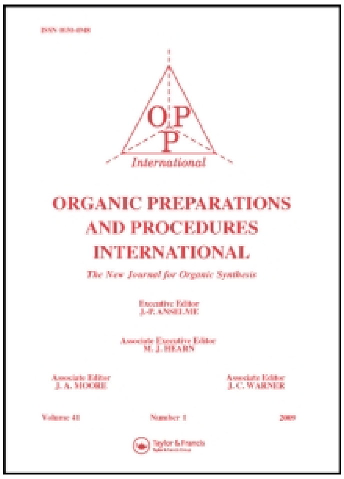

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RECENT APPLICATIONS OF ARYNE CHEMISTRY TO ORGANIC SYNTHESIS. A REVIEW

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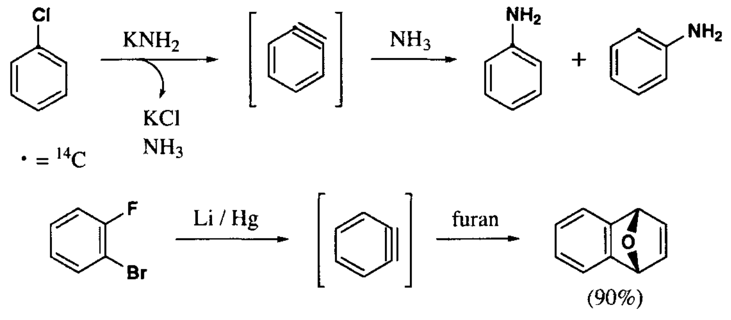
INTRODUCTION

Arynes are neutral intermediates in which two adjacent atoms of an aromatic ring lack substituents, thus leaving two atomic orbitals (perpendicular to the aromatic π system) to form a weakly bonding molecular orbital occupied by two electrons. This review is intended to be an update of *ortho*-benzyne (1,2-di-dehydrobenzene) chemistry and of its derivatives (referred as arynes) published in the last five years (2002-2007), since early work has already been reviewed extensively.[1] The focus of this review is on the application of arynes in organic synthesis, but not on other related aspects such as their generation and capture through the deployment of organometallic complexes,[2] their structures, or the related systems *meta*-, and *para*-arynes.[3] Nevertheless, the review will give an overview of general aspects about the structure, reactivity, and the main methods for the generation of arynes. The rest of the article will be devoted to the more recent advances in the synthetic applications of these intermediates.

I. STRUCTURE AND REACTIVITY

o-Benzyne was first suggested as a reactive intermediate in 1927.[4] In the 1950's, the classic isotopic labelling experiments of Roberts and co-workers in the reaction of ^{14}C-labeled chlorobenzene with potassium amide,[5] and the Diels-Alder trapping with furan by Wittig,[6] gave strong support to the existence of benzyne (*Scheme 1*). This triple bond is not that of a normal



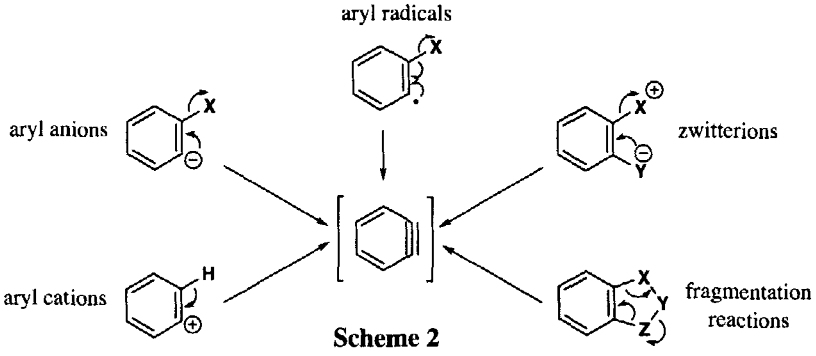
Scheme 1

alkyne as these are linear. In fact one π-bond is normal as it is just part of the aromatic system, but the other π-bond is abnormal, formed by lateral overlap of the two sp^2 orbitals in the plane of the ring. As expected, the formal C–C triple bond in benzyne is significantly weaker than in unstrained alkynes as shown by the C≡C stretching vibration (1846 cm^{-1} for benzyne,[7] whereas this band for normal alkynes usually occurs in the range about 2150 cm^{-1}). While the IR stretching frequency is a good indication that the third bond between the two dehydrogenated carbons is intermediate between a double and triple bond, a direct measurement of the bond length of 1.24 Å by Radziszewski and co-workers[8] is in good agreement with that predicted by theoretical calculations.[9] All these findings support that *o*-benzyne is better described as a strained alkyne than as a biradical. Moreover, the alkyne-type character of *o*-benzyne is also demonstrated by its reactivity patterns.

A direct consequence of the strained nature of the ring (ca. 63 kcal mol^{-1})[10] is that arynes have low lying LUMOs and hence the energy gap between the HOMO and LUMO is small. Accordingly, *o*-benzyne shows the properties of a highly reactive alkyne participating in a range of cycloaddition and *ene* reactions with alkenes. A second consequence of its low lying LUMO is that *o*-benzyne behaves as a powerful electrophile. Also, the triple bond in *o*-benzyne can be stabilized by complexation to transition metals and these aryne complexes undergo a range of fascinating reactions. The applications of arynes in organic synthesis have been classified in these three categories.

II. GENERATION OF ARYNES

Even at low temperatures, arynes are extraordinarily reactive and they must be generated *in situ*. As shown in *Scheme 2*, arynes can be generated from aryl anions, aryl cations, zwitterions, aryl radicals, and by fragmentation reactions.



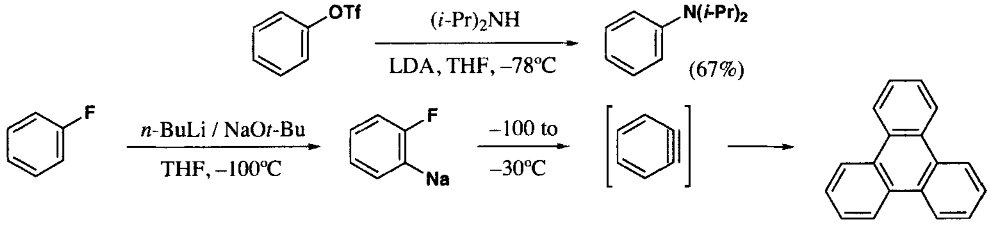
Scheme 2

1. Aryl Anions

The elimination of a leaving group such as halide, tosylate, triflate, diazonium, trialkylammonium, etc. from the *ortho*-position of a metallated aromatic ring is one of the most important classical routes to arynes.

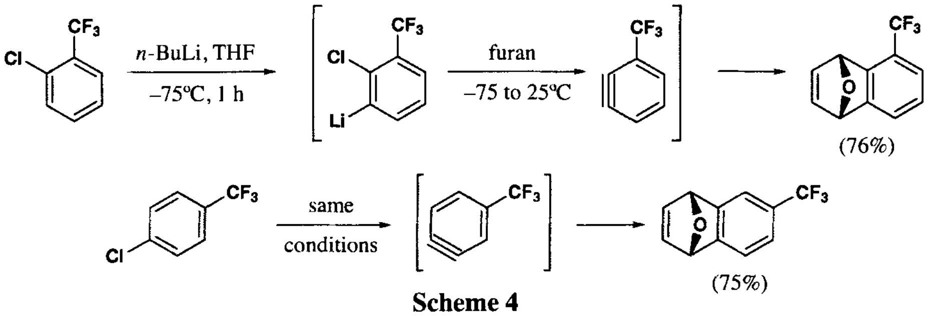
a) Aryl Halides and Related Systems

The *ortho*-metallation of aromatic halides[5] and aryl triflates[11] with strong bases such as alkali metal amides, alkyllithiums, etc. is a firmly established route to *o*-arynes. For example, phenyl triflate reacts with LDA at -78°C to generate benzyne, which then adds with diisopropylamine to generate *N,N*-diisopropylaniline (*Scheme 3*). Fluorobenzene is also easily *ortho*-metallated with equimolar mixtures of *n*-BuLi and NaO*t*-Bu in THF to generate benzyne, which decomposes rapidly at ca. -30°C to give a relatively good yield of triphenylene (*Scheme 3*).[12]



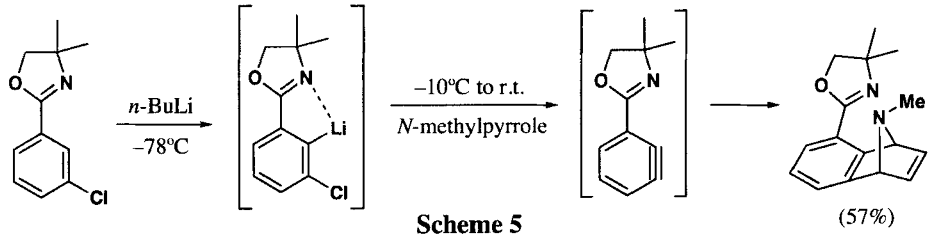
Scheme 3

Using this approach, Schlosser and co-workers have generated trifloromethyl-functionalized benzynes and applied them to the synthesis of functionalized derivatives of 1- and 2-(trifluoromethyl)naphthalenes (*Scheme 4*).[13]



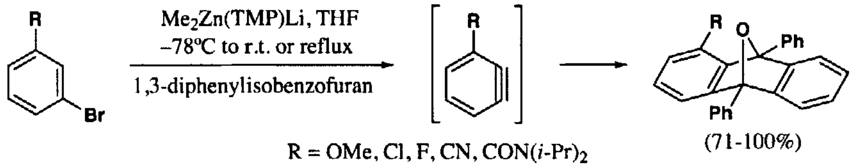
Scheme 4

In aromatic systems where two possible arynes could be formed from a single precursor, the regioselectivity depends on the nature of the *m*-substituent and the relative ease of elimination from the two anions. With *m*-substituents that are electron-withdrawing or *ortho*-directing metallating groups (DMG), the formation of the anion is rate-determining, and, provided that loss of halide is rapid, a single aryne will result (*Scheme 5*).[14] In this context,



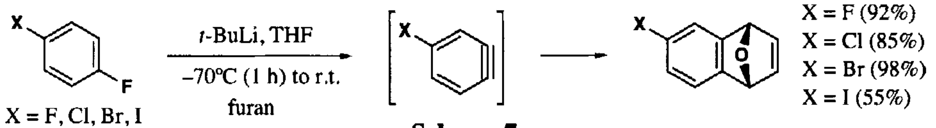
Scheme 5

Uchiyama and co-workers have described a versatile generation of 3-substituted benzynes *via* deprotonative zincation of *meta*-functionalized haloaromatics using dimethyltetramethylpiperidino-zincate ($Me_2Zn(TMP)Li$) as metallating agent. Intermediate functionalized arynes were trapped through Diels-Alder reactions with 1,3-diphenylisobenzofuran (*Scheme 6*).[15]



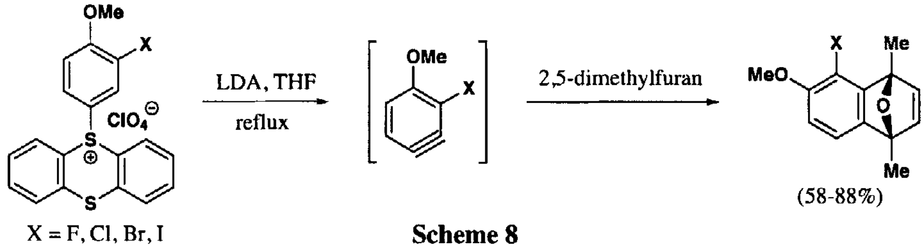
Scheme 6

Interestingly, Biehl and co-workers have found that 4-halobenzynes could be efficiently obtained and trapped with furan, by addition of *t*-BuLi to the corresponding 4-halofluorobenzene at −70°C and maintained at that temperature for 1 h before allowing the reaction mixture to warm to room temperature (*Scheme 7*).[16] The use of other conditions or LDA as base led to different results.



Scheme 7

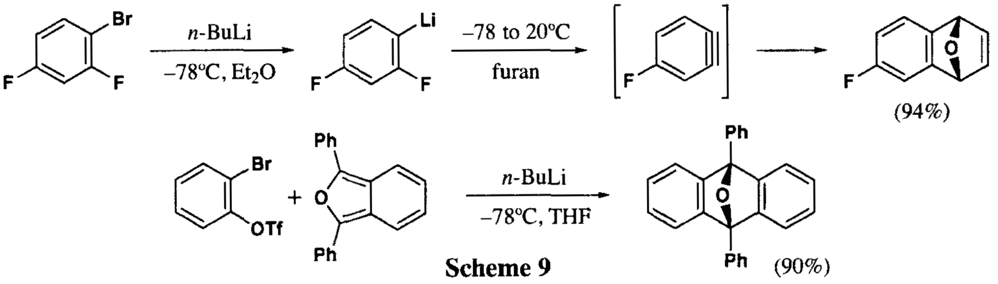
A unique generation of 3-halo-4-methoxybenzynes has been described from 5-(3-halo-4-methoxyphenyl)thianthrenium perchlorates, because in these cases a thianthrene molecule acts as a leaving group instead of a halogen atom (*Scheme 8*).[17]



Scheme 8

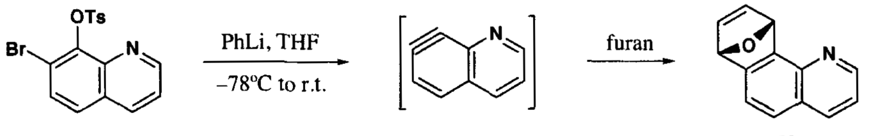
b) Aryl 1,2-Dihalides and Related 1,2-Disubstituted Systems

Metallation of 1,2-dihalobenzenes and related systems either through Grignard or aryllithium formation is a useful method to generate arynes. For *o*-dihalides[18] and *o*-halotriflates[19] the initial metal–halogen exchange occurs at lower temperature in the case of lithium and is followed by elimination of a lithium salt (*Scheme 9*). This strategy achieves total regiocontrol in the elimination step and in general, when different halogens are present on the ring, the more electropositive halogen exchanges first. The relative stability of the intermediate *o*-substituted aryllithium toward elimination is highly dependent on the nature of the group being eliminated and on the overall electronic effects in the aromatic ring induced by other substituents.



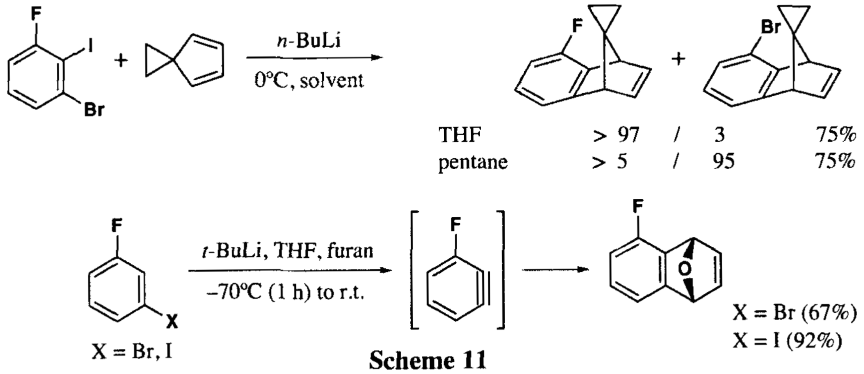
Scheme 9

Arynes have also been generated *via* the reaction of *ortho*-halo aryltosylates with organolithium reagents as shown in the generation of 7,8-quinolyne which can be trapped with furan in moderate yield (*Scheme 10*).[20]



Scheme 10

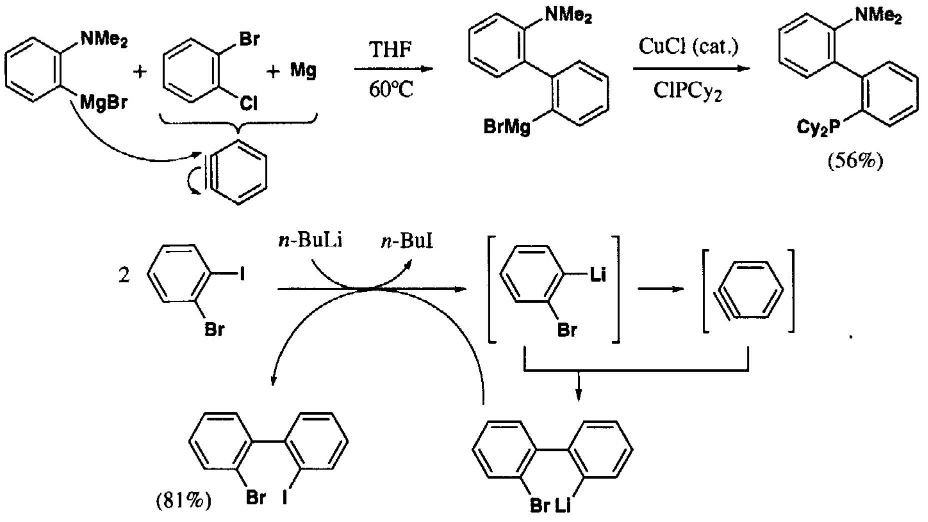
In this context, studies with mixed halide precursors and non-acidic Diels-Alder diene traps reveal that ether and hydrocarbon solvents influence the nucleofugic ability of the halide, resulting in a reversal of 3-halobenzyne regioselectivity.[21] A similar result, *i. e.* formation of 3-fluorobenzyne, was also obtained when 3-fluoro-1-bromobenzene or 3-fluoro-1-iodobenzene were deprotonated with *t*-BuLi in THF (*Scheme 11*).[16]



THF	> 97	/	3	75%
pentane	> 5	/	95	75%

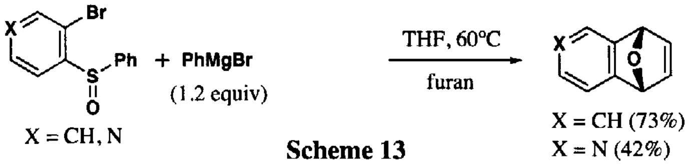
Scheme 11

Related approaches to the synthesis of asymmetric biaryls *via* benzynes, generated from *o*-dihalides, have been developed independently by Buchwald[22] and Schlosser.[23] In this way, functionalized dialkylphosphinobiphenyl ligands were prepared by the addition of arylmagnesium halides to benzyne prepared *in situ* from 1-bromo-2-chlorobenzene and magnesium (*Scheme 12*). Symmetrical and unsymmetrical biaryls can be constructed by this "aryne route" starting from *o*-dihalides as shown in the reaction of 1-bromo-2-iodobenzene with half a molar equivalent of *n*-BuLi (*Scheme 12*).



Scheme 12

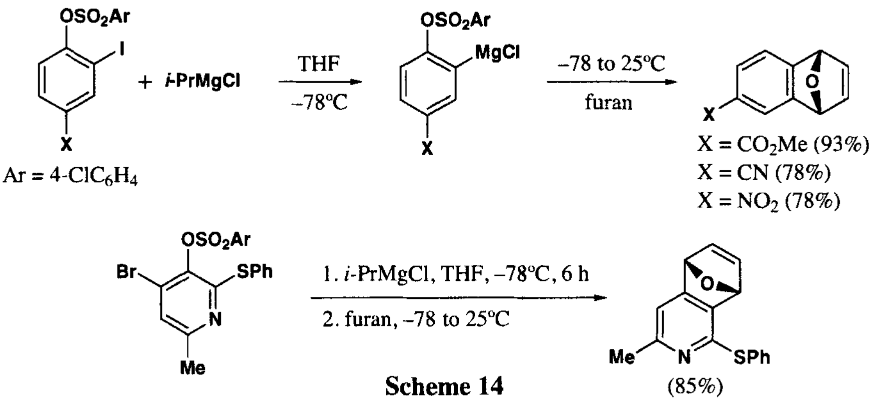
On the other hand, *o*-bromophenyl phenylsulfoxides or 3-bromo-4-pyridyl phenylsulfoxides also generate benzyne (or 3,4-pyridyne) on treatment with Grignard reagents.[24] However, this route has not been exploited further probably due to the difficult access to the starting materials compared with the corresponding *o*-dihalides (*Scheme 13*).



Scheme 13

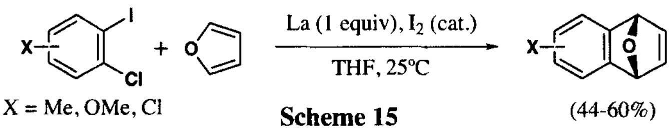
Using the halogen-metal exchange methodology to generate benzyne, the preparation of functionalized arynes is often incompatible with the basic conditions employed. Knochel and co-workers have developed a general method for the preparation of arynes which possess a variety of functionalities (ester, nitrile, iodine, nitro, etc.) by the elimination of the Grignard derivative of aryl sulfonates.[25] These functionalized aryl Grignard reagents are readily available through iodine-magnesium exchange, but the nucleofugic ability of the sulfonate group was found to be essential for the optimization of the reaction conditions and yields. The best results were obtained using the 4-chlorobenzenesulfonate derivatives shown in *Scheme 14*. More recently, this methodology has also been applied to the preparation of functionalized 3,4-pyridines (*Scheme 14*).[26]

The reaction of 1,2-dihalogen substituted arenes with lanthanum metal in the presence of dienes gives rise to the Diels-Alder products showing the generation of the corresponding



Scheme 14

arynes through efficient transfer of electrons from the metal (*Scheme 15*).[27] However, *o*-chlorophenylcopper turned out to be stable at room temperature when it was generated by oxidative addition of activated copper to *o*-chloroiodobenzene allowing its use in nucleophilic displacements.[28]

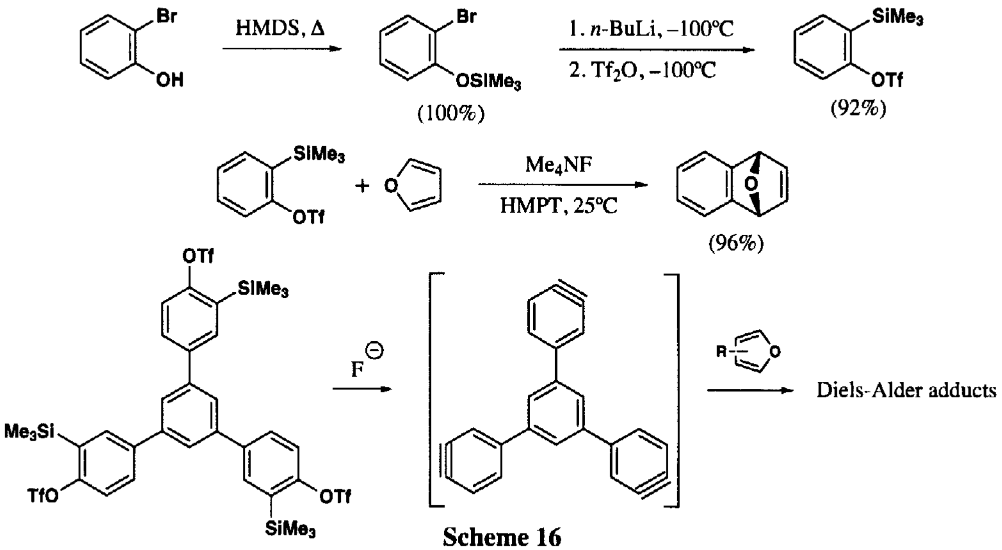


Scheme 15

The introduction of 2-(trimethylsilyl)phenyl triflate, first reported by Hobayashi in 1993 and now commercially available,[29] as a benzyne precursor under mild conditions (room temperature without the use of strong bases or oxidants) has enabled the development of a variety of transition metal-catalyzed reactions with arynes in the last years, which will be discussed in the last part of this review. The starting materials are also easily obtained from *o*-bromophenols and the generation of benzyne takes place by fluoride displacement of the trimethylsilyl group (*Scheme 16*). More recently, a trisaryne equivalent has been synthesized and used for assembling diverse polycyclic aromatic hydrocarbons (*Scheme 16*).[30]

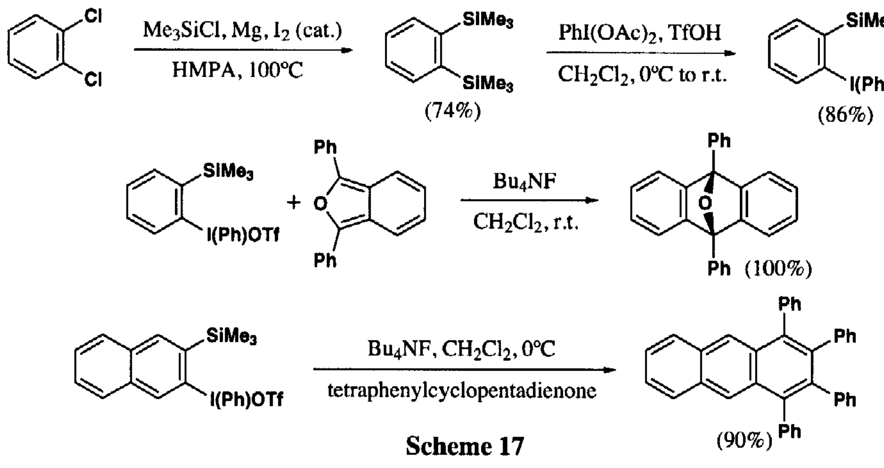
In an analogous way, Kitamura and co-workers have developed (phenyl)[2-(trimethylsilyl)phenyl]iodonium triflate as an efficient benzyne precursor, due to the high leaving ability of the hypervalent iodine group and to the facile cleavage of the trimethylsilyl group by fluoride ion.[31] This reagent was prepared by treatment of *o*-*bis*(trimethylsilyl)benzene with iodobenzene diacetate activated with TfOH. Remarkably, this benzyne precursor afforded Diels-Alder adducts with furans, anthracene, tetraphenylcyclopentanedienone, and 1,3-diphenylisobenzofuran in nearly quantitative yield upon treatment with a THF solution of Bu_4NF in CH_2Cl_2 (*Scheme 17*). In the same way, (phenyl)[3-(trimethylsilyl)-2-naphthyl]iodonium triflate acts as a highly efficient 2,3-dihydronaphthalene precursor (*Scheme 17*).[32]

This hypervalent iodine approach to benzyne generation has attracted the attention of other research groups and various applications, particularly in the syntheses of theoretically interesting molecules and functional materials, have been reported.[33] Later on, the same team



Scheme 16

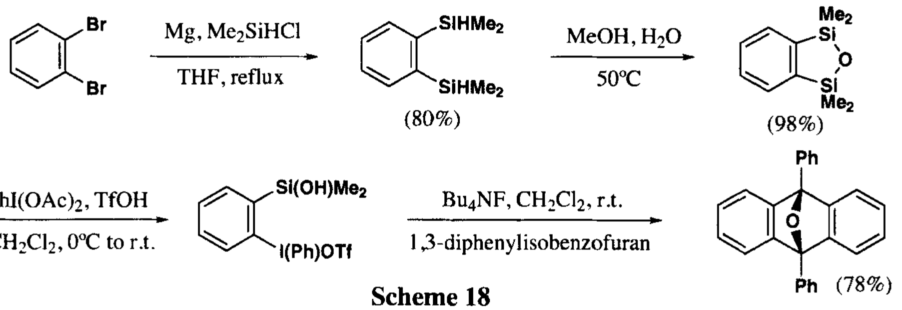
reported another related new benzyne precursor, [2-(hydroxydimethylsilyl)-phenyl](phenyl)iodonium triflate, which was prepared from 1,2-dibromobenzene in good yield thus avoiding the use



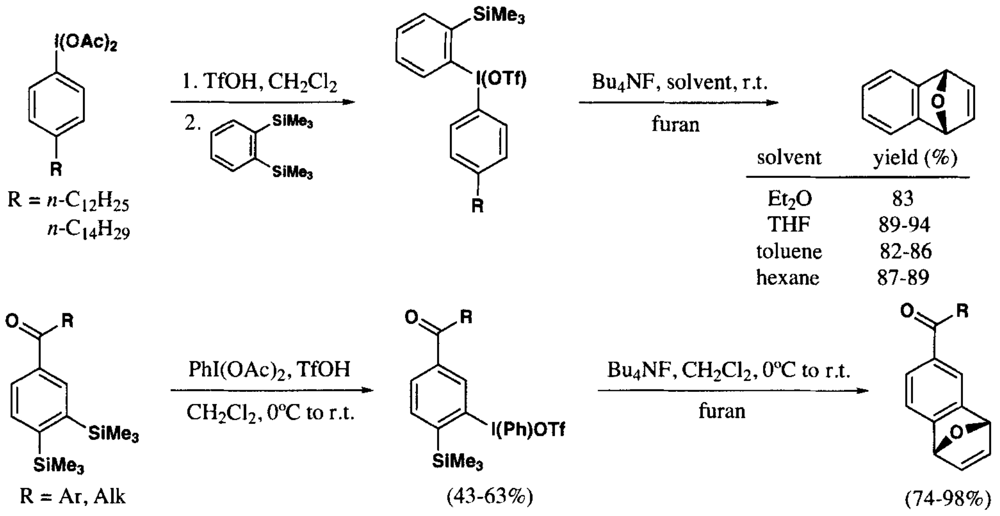
Scheme 17

of carcinogenic HMPA. The generation and trapping reaction of benzyne could be conducted by simply mixing the precursor triflate with a fluoride source in the presence of trapping agents (*Scheme 18*).[34]

New hypervalent iodine-benzyne precursors bearing long alkyl chains have been prepared by Kitamura and co-workers in order to improve their solubility in other organic solvents such as diethyl ether, THF, and toluene (*Scheme 19*).[35] Moreover, with this approach, ketone-functionalized benzynes are easily generated from the corresponding iodonium triflates, giving high yields of Diels-Alder cycloadducts (*Scheme 19*).[36]



Scheme 18

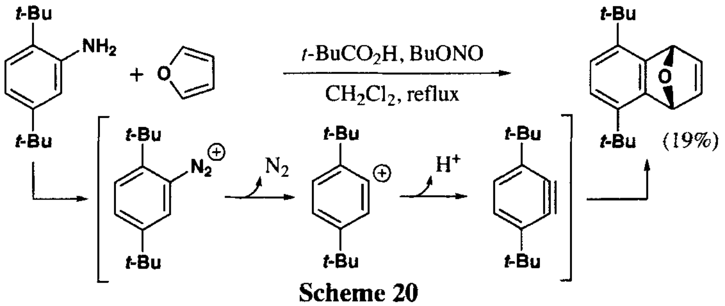


solvent	yield (%)
Et_2O	83
THF	89-94
toluene	82-86
hexane	87-89

Scheme 19

2. *Aryl Cations*

An aryne pathway in the decomposition of diazotized 2,5-di-*t*-butylaniline was postulated to account for the generation of the Diels-Alder adduct, albeit in very low yield, when the diazotation of this hindered aniline was conducted in the presence of furan (*Scheme 20*).[37]

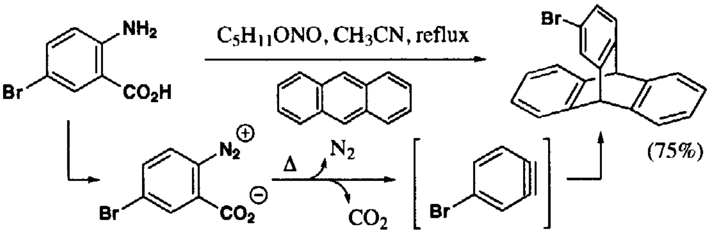


Scheme 20

Provided that a large *ortho*-substituent is present, loss of a proton becomes competitive with the normal nucleophilic addition to the cation.

3. Zwitterions

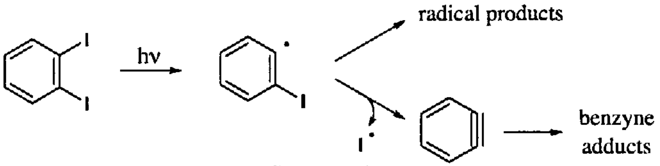
Arynes may also be obtained from anthranilic acids, which are readily diazotated by alkyl nitrites in aprotic media to give presumably a benzenediazonium-2-carboxylate. This intermediate undergoes fragmentation to the corresponding aryne, nitrogen, and carbon dioxide (*Scheme 21*).[38]



Scheme 21

4. Aryl Radicals

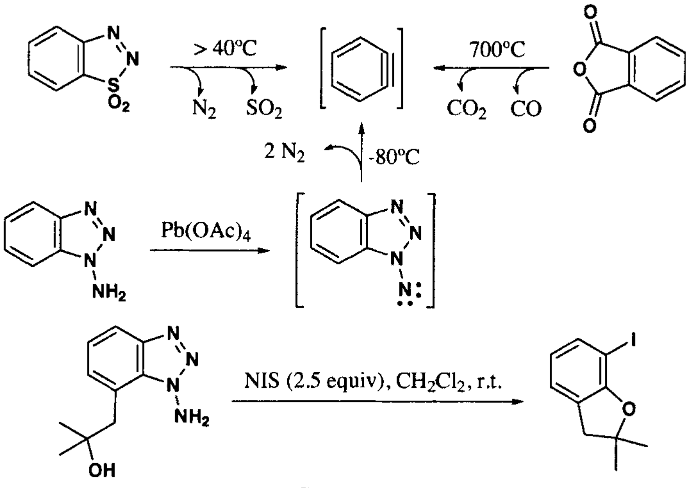
Irradiation of 1,2-diiodobenzene can lead to benzyne derived products, probably *via* an aryl radical intermediate resulting from cleavage of the weak C–I bond (*Scheme 22*).[39]



Scheme 22

5. Fragmentation Reactions

Arynes can also be generated by fragmentation of cyclic systems by electronic rearrangements. However, this type of processes is only favorable if the other fragments so formed are extremely thermodynamically stable molecules. Even so the thermal energy required to initiate the fragmentation is often considerable. Two examples of these benzyne precursors are shown in *Scheme 23*.[40] Nevertheless, 1-aminobenzotriazole, firstly reported by Rees,[41] gives rise to benzyne under mild oxidative conditions probably through generation of an aminonitrene followed by fragmentation with loss of two molecules of nitrogen. *N*-Iodosuccinimide was later shown to be a superior reagent for the generation of arynes from 1-aminobenzotriazoles containing *ortho*-hydroxyethyl groups. Intramolecular trapping afforded good yields of iodo-functionalized dihydrobenzofurans (*Scheme 23*).[42]



Scheme 23

IV. PERICYCLIC REACTIONS OF ARYNES

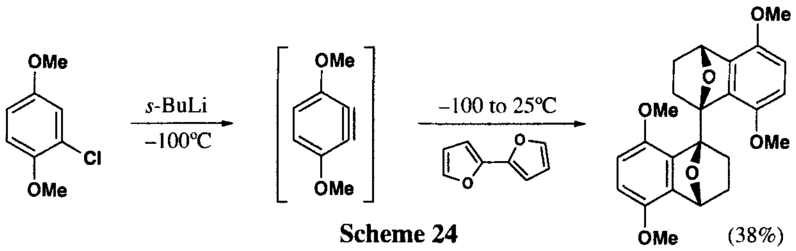
Due to their highly electrophilic character, arynes readily participate in pericyclic reactions. However, since the addition of nucleophiles is also extremely facile, reactions with non-nucleophilic reagents such as dienes and alkenes cannot usually take place unless the aryne is generated in the absence of nucleophiles. In this section, the most significant contributions from the last few years will be presented.

1. Diels-Alder Cycloaddition Reactions

The first cycloaddition reaction of benzyne (from 1-bromo-2-fluorobenzene) was observed in 1955 by Wittig[6] (see *Scheme 1*). Since then, the Diels-Alder reaction is one of the most important reactions of arynes and is usually used both as a means of detecting arynes and as a synthetic tool. The examples are organized according to the type of the diene partner and the method of generation the intermediate aryne.

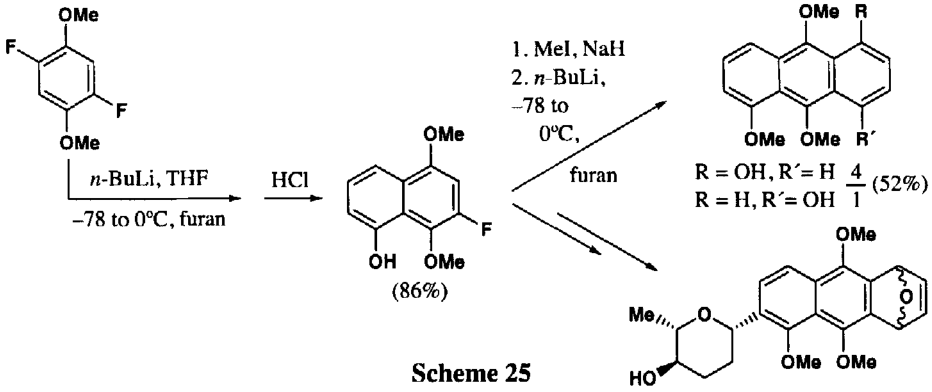
a) Cyclic Dienes: Furans and Related Species

Diels-Alder reactions of arynes with *cisoid* dienes such as furan or related species have been especially well-studied. A double benzyne-furan cycloaddition has been described to take place in moderate yield using 2,2'-bifuryl as a "double diene" and 2-chloro-1,4-dimethoxybenzene as the aryne precursor (*Scheme 24*).[43]



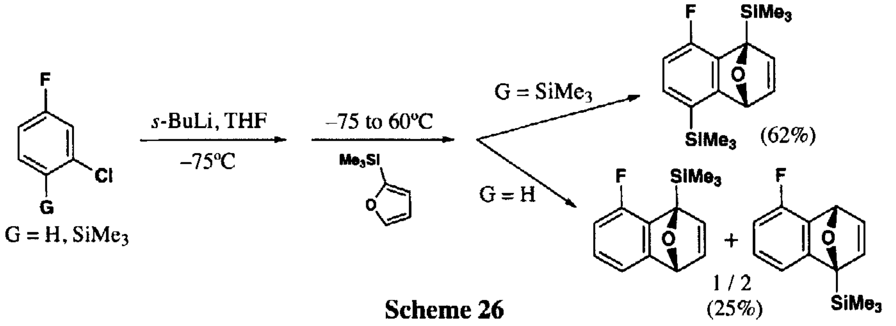
Scheme 24

1,4-Difluoro-2,5-dimethoxybenzene has been reported as a novel precursor for iterative two-directional benzyne-furan Diels-Alder reaction. Highly substituted anthracenols were finally generated after acid-catalyzed isomerization of the cycloadducts although usually as a mixtures of regioisomers, mainly when substituted furans are used.[44] The same authors have applied this concept in the preparation of an oxa-bridged 1,4-dihydroanthracenyl *C,O*-disaccharide (*Scheme 25*), a model compound relevant to the total synthesis of the *angucycline* antibiotic *Sch 47555*.[45]



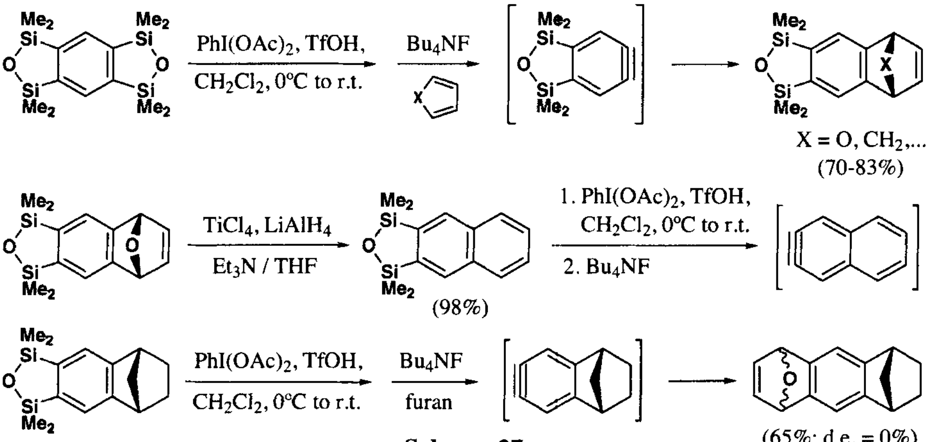
Scheme 25

A partial solution to the problem of positional selectivity in the Diels-Alder reaction between arynes and substituted furans has been provided by Schlosser and co-workers who observed that if bulky trialkylsilyl groups are present in both components, the cycloaddition reaction proceeds regioselectively (*Scheme 26*).[46]



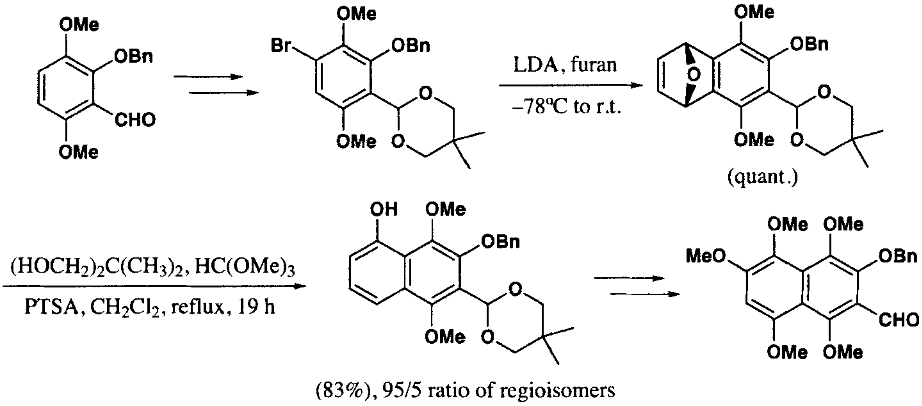
Scheme 26

Since the introduction of [2-(hydroxydimethylsilyl)phenyl](phenyl)iodonium triflate by Kitamura and co-workers (see *Scheme 18*), this hypervalent iodine approach to benzyne generation has attracted the attention of several research groups. Lee and co-workers have reported various applications, particularly in the syntheses of theoretically interesting molecules and functional materials. For instance, they have synthesized linear and angular benzobisoxadisiloles, which can serve as the precursors for the stepwise generation of the synthetic equivalents of 1,4- and 1,3-benzdiynes. The benzyne derivatives, generated *via* the corresponding iodonium triflates intermediates, were trapped as [4 + 2] cycloaddition products. A new precursor of 2,3-naphthalyne has been prepared by removing the oxygen bridge from the furan adduct (*Scheme 27*).[47] These authors have applied this methodology to the synthesis of *mono-* and *bis*-oxadisilole-fused isobenzofurans, which have been used as the building blocks for the preparation of oxadisilole fused linear acenes.[48]



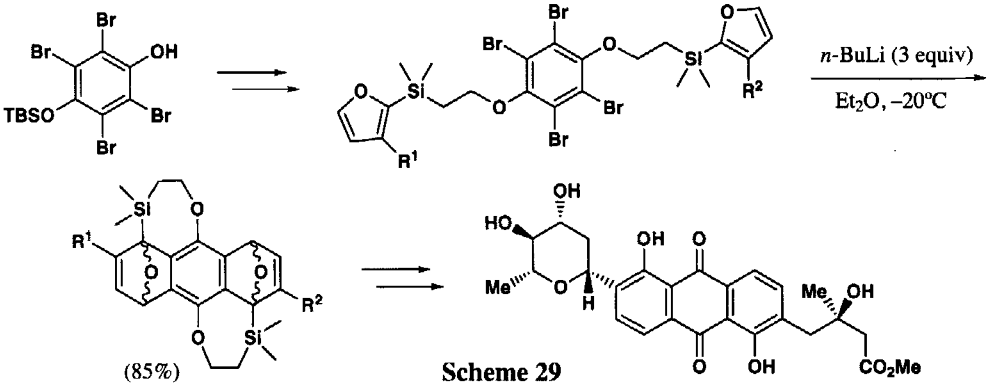
Scheme 27

An efficient synthesis of a highly substituted naphthaldehyde has been developed for the planned preparation of compounds of the rubromycin family. The synthesis of this aldehyde could be achieved in a 12-step sequence in an overall yield of 9% involving, as the key step, an aryne cycloaddition and a subsequent regioselective ring-opening, under fine-tuned reaction conditions, of the obtained tricyclic adduct (*Scheme 28*).[49]



Scheme 28

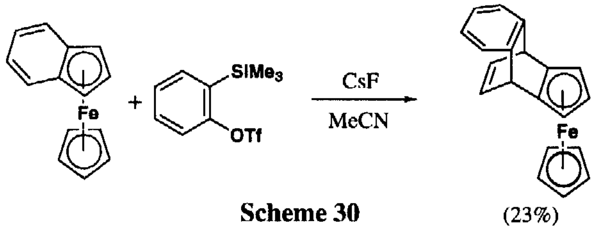
An intramolecular Diels-Alder reaction of substituted benzynes and furans, using silicon tethers as disposable linkers to control the regiochemistry, has been used by Martin and co-workers in a novel and highly convergent synthesis of vineomycinone B_2 methyl ester. In this example, the bis-aryne intermediate was generated by the treatment of an aromatic tetrabromide with *n*-BuLi, affording the biscycloaddition product in high yields as a mixture of diastereoisomers (*Scheme 29*).[50]



Scheme 29

b) Other Cyclic Dienes

Indenyl iron complexes were found to react with benzyne, generated from Kobayashi's benzyne-precursor *o*-trimethylsilylphenyl triflate, to afford the corresponding Diels-Alder adducts (*Scheme 30*).[51]

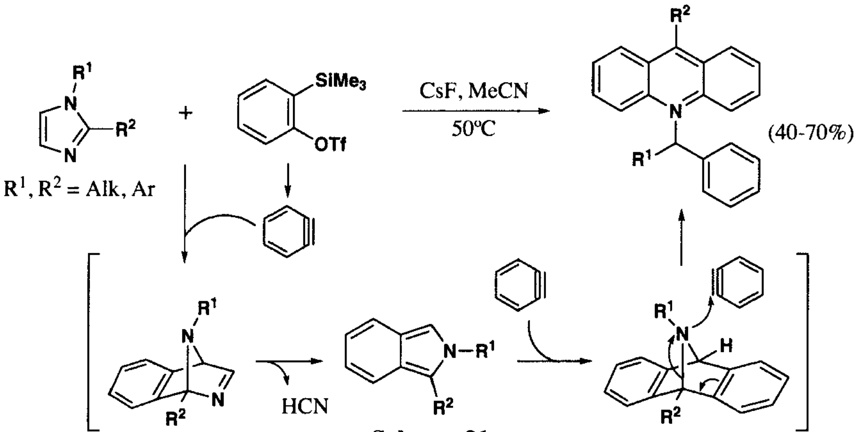


Scheme 30

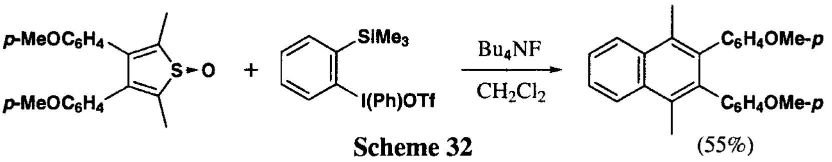
The reaction of benzyne with *N*-substituted imidazoles affords a novel way to prepare arylamines containing anthracene under mild conditions. The use of benzyne and imidazole in a 1:1 ratio was crucial for the outcome of the reaction. This transformation is assumed to proceed *via* a Diels-Alder cycloaddition that affords a nitrogen-bridged isoquinoline intermediate. Subsequent retro Diels-Alder reaction generates a new intermediate, which undergoes the second Diels-Alder reaction with benzyne. A final intermolecular nucleophilic addition to benzyne gives rise to the isolated arylamine (*Scheme 31*).[52]

Thiophene *S*-oxides, prepared by oxidation from thiophenes, have been subjected to cycloaddition reactions with benzyne, generated from Kitamura's precursor *o*-(trimethylsilyl)phenyl(phenyl)iodonium triflate, affording a cycloadduct that further extrudes sulfur oxide (*Scheme 32*).[53]

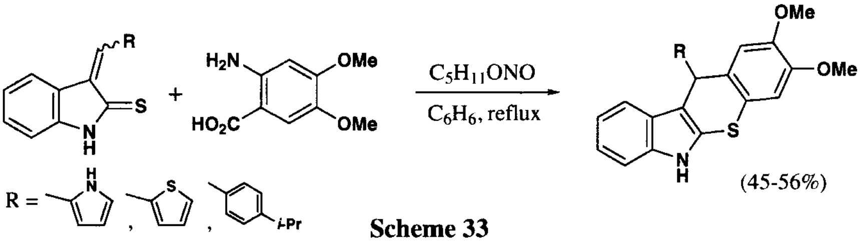
Multi-substituted heterocycles such as benzothiopyrano[2,3-*b*]indoles have been prepared in modest yields by the cyclization of 1,3-dihydroindole-2-thiones with methoxybenzynes, generated from the thermal decomposition of the corresponding diazonium carboxylate (*Scheme 33*).[54]



Scheme 31

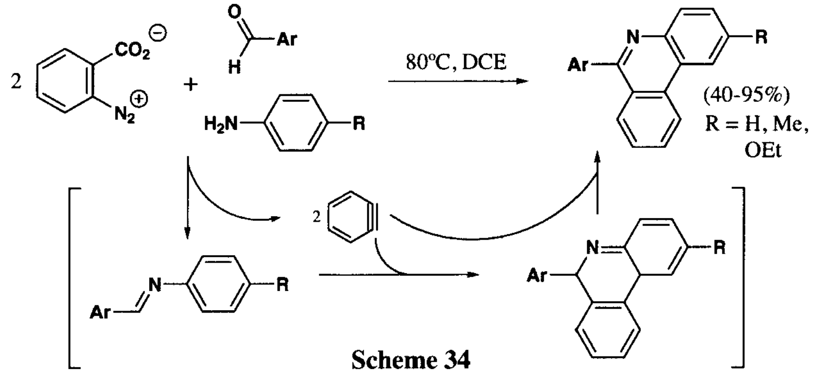


Scheme 32



Scheme 33

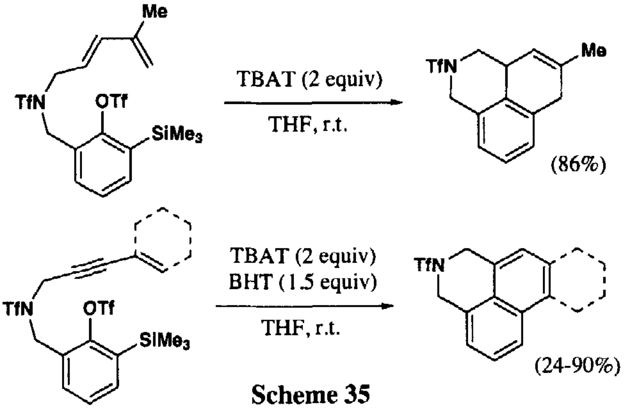
Furthermore, *in situ* generated benzyne from benzenediazonium-2-carboxylate reacts with aromatic aldehydes and aniline to afford 6-arylphenanthridine derivatives through a three component cascade reaction (*Scheme 34*).[55] Noteworthy, 1,2-diarylbenzazetidenes, the major products of [2 + 2] cycloaddition reactions of *N*-arylimines with benzyne were not isolated.



Scheme 34

c) Acyclic Dienes

Whereas aryne Diels-Alder reactions with cyclic dienes are frequently utilized, reactions with functionalized acyclic dienes are much less common, probably due to the fact that they are often complicated by competing [2+2] cycloaddition and *ene* reaction pathways. Danheiser and co-workers have achieved the first example of an efficient intramolecular Diels-Alder reaction of an aryne, generated by the reaction of *o*-(trimetylsilyl)aryl triflates with tetrabutylammonium triphenyldifluorosilicate (TBAT), with an acyclic diene. Moreover, these arynes also participate in intramolecular [4+2] cycloadditions with conjugated enynes and arenynes to furnish highly condensed polycyclic aromatic compounds (*Scheme 35*).[56] The TBAT-promoted generation of the intermediates arynes resulted to be crucial for the success of these reactions.

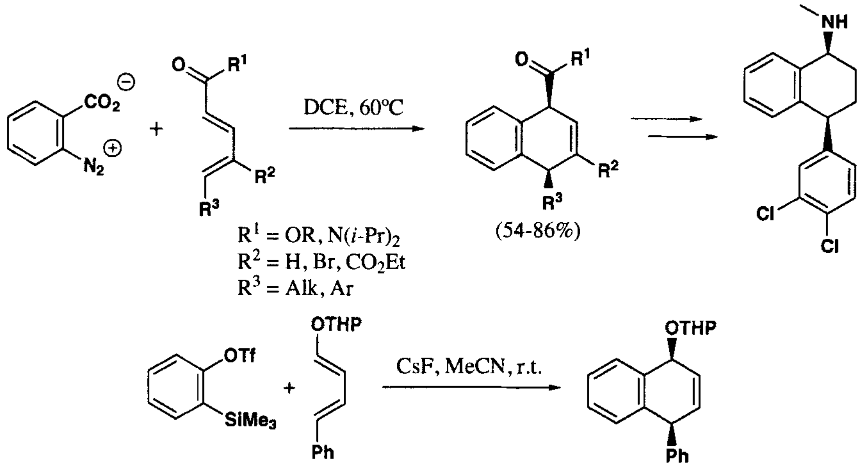


Scheme 35

Lautens and co-workers have studied the scope and diastereoselectivity of the aryne Diels-Alder reaction with acyclic dienes and demonstrated its usefulness as a method for the synthesis of functionalized 1,4-dihydronaphthalenes. Reactions take place with electron-releasing and electron-withdrawing substituents on the diene, indicating that an inverse electron-demand Diels-Alder pathway might be operating in these cases. These authors have applied this methodology to the synthesis of *sertraline* (*Scheme 36*).[57]

2. [2+2] Cycloaddition Reactions

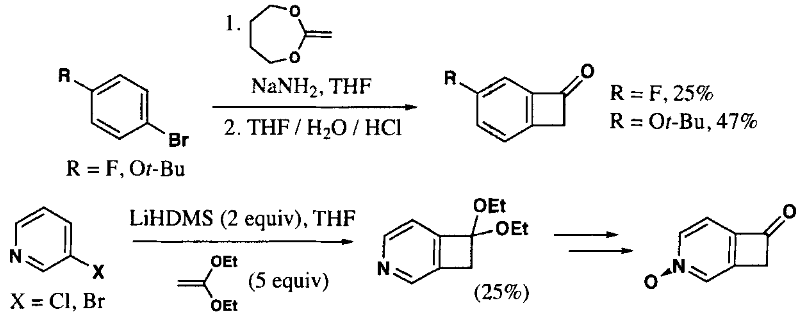
The [2+2] cycloadditions of arynes with alkenes or carbon-heteroatom double bonds have attracted considerable attention as an efficient method for construction of benzocyclobutenes, which are valence isomers of synthetically useful *o*-quinoid species. Because of the electrophilic nature of benzyne, the reactions proceed better with electron-rich alkenes, including vinyl ethers, ketene acetals, and enamines. Moreover, some examples using carbon-heteroatom double bonds have also been described, although sometimes these reactions may involve heteroatom addition to benzyne *via* a single-electron transfer process.



Scheme 36

a) [2+2] Cycloadditions with Alkenes

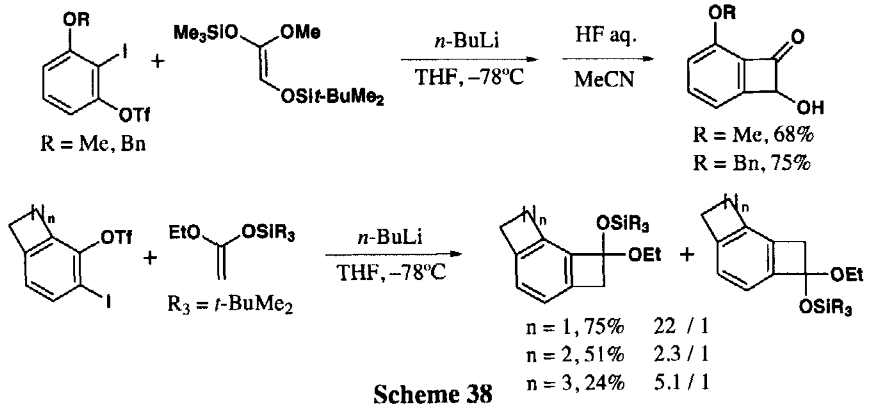
Ketene dialkyl acetals are shown to be useful partners for arynes[58] and heterarynes[59] in the preparation of benzocyclobutenone derivatives. Sometimes, high regioselectivity was observed with substituted arynes (*Scheme 37*).



Scheme 37

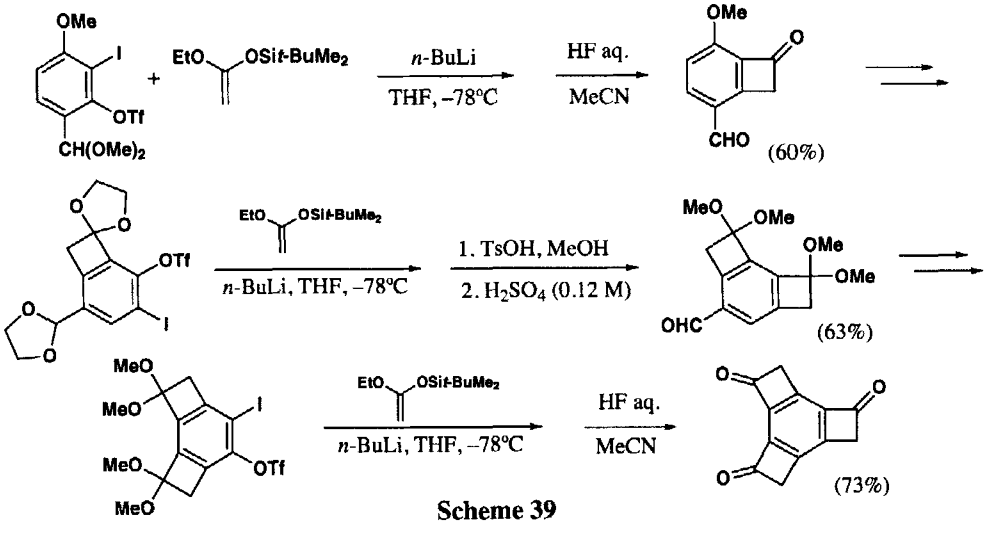
In addition, it was probed that ketene silyl acetals (KSAs) are efficient counterparts for arynes, generated from *o*-haloaryltriflates by halogen-lithium exchange, in the regioselective synthesis of benzocyclobutenone derivatives. Suzuki and co-workers have studied the directing ability of *o*-substituents, such as alkoxy groups[60] and fused four-membered rings[61] within aryne intermediates, in effecting regioselective [2+2] cycloaddition reactions (*Scheme 38*).

The origin of excellent reactivities and yields observed for these reaction partners can be ascribed to the high HOMO level of KSAs and the low-lying LUMO of benzynes that is made even lower by the inductively electron-withdrawing alkoxy group. The enhanced electrophilicity at the *m*-position relative to the *o*-position due to the alkoxy group accounts for the observed regioselectivity in the alkoxybenzynes. For arynes possessing fused rings, the crucial factor for determining the regioselectivity resides in the four-membered ring itself rather than the steric bulkiness. According to Streitwieser *et al.* and Finnegan,[62] the bridgehead carbon rehybridizes to use orbitals of higher *p* character in bonding to the strained ring and hence, the proximal C is bound to an orbital of higher electronegativity, rendering the distal C more electron-deficient.



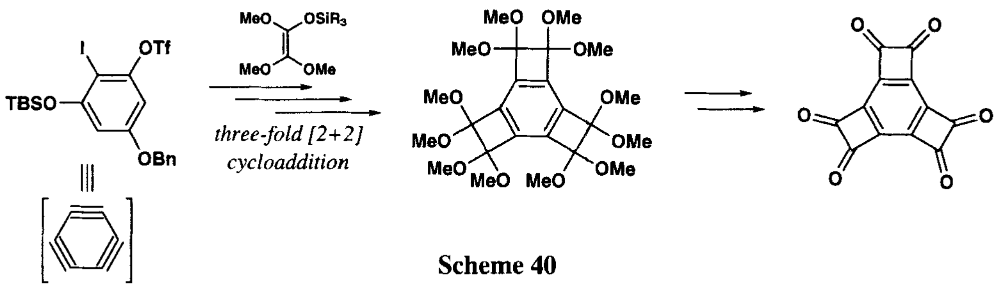
Scheme 38

The ring strain resulted to be the origin of the regioselectivities observed for the reactions of cyclobuta-annulated benzynes with alkenes, dienes or nucleophiles. Based on their previous findings, the same authors have developed an elegant synthetic route to highly oxygenated tricyclobutabenzenes, which relied on the repeated regioselective [2+2] cycloaddition of benzyne and KSAs (*Scheme 39*).[63]



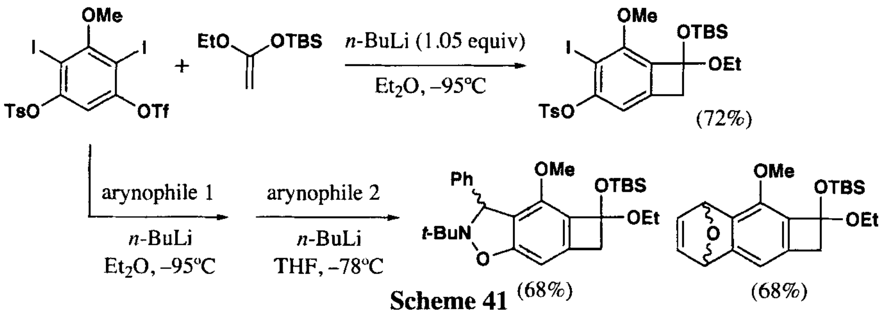
Scheme 39

In the same context, they have reported the synthesis of dodecamethoxytetracyclobutabenzene and hexaoxotricyclobutabenzene, *via* 3-fold [2+2] cycloadditions of benzyne and KSAs, using a selectively protected 2-iodophloroglucinol derivative as a novel synthetic equivalent of benztriyne (*Scheme 40*).[64] The synthesis of this hexaketone is remarkable because all of the carbon atoms are sp^2 hybridized without the stabilization of annulated aromatic rings as in [4]phenylene.



Scheme 40

Moreover, Suzuki and co-workers have disclosed dual cycloadditions of benzynes successively generated in one pot from a *bis*(sulfonyloxy)diiodobenzene, which can be viewed as a synthetic equivalent of 3-alkoxy-1,4-benzdiyne. Selective halogen-lithium exchange by careful control of the reaction temperature enables the tandem generation of benzynes and dual cycloadditions with two identical or different arynophiles (*Scheme 41*).[65] All these results clearly show the methodology developed by Suzuki and co-workers as a powerful tool in the synthesis of polycyclic compounds.

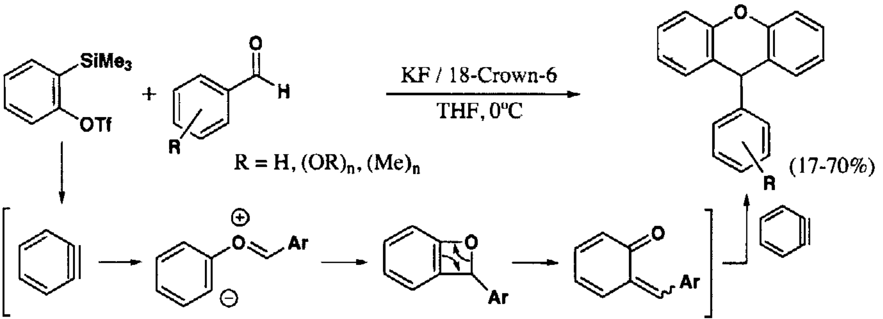


Scheme 41

b) [2+2] Cycloadditions with Carbon-Heteroatom Double Bonds

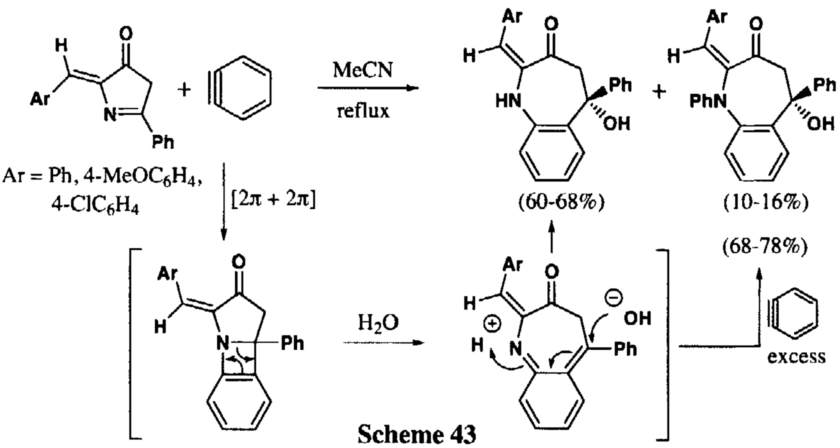
A straightforward method for the construction of diverse xanthene derivatives has been accomplished based upon a 2:1 coupling reaction of arynes with aryl aldehydes. *o*-Quinone methide arising from a [2+2] cycloaddition of an aldehyde with an aryne and subsequent isomerization was postulated as a transient intermediate. A final [4+2] cycloaddition with a second aryne provides a xanthene (*Scheme 42*).[66]

Aly have reported that 4-arylidene-2-phenyl-5(4*H*)-1,3-oxazolones behave as an ene system in [2+2] cycloaddition during the reaction with benzyne, which was generated by diazotization of 1,2-anthranilic acid. The reaction between one mole of benzyne and the azomethine group initially forms a benzazetidine, which was converted by ring opening into its valence



Scheme 42

tautomer. Further addition of moisture afforded the *N*-H benzoxazepine derivative, which on nucleophilic attack to another mole of benzyne leads to the formation of the *N*-phenyl-1,4-benzoxazepines (*Scheme 43*).[67]

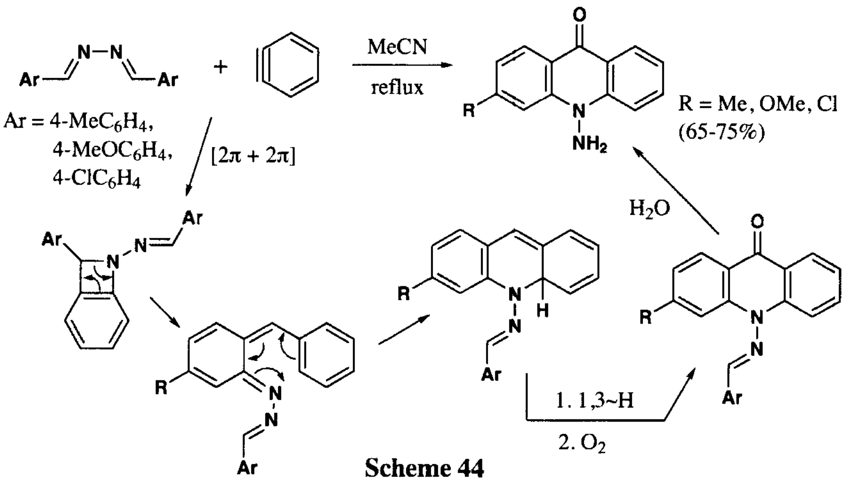


Scheme 43

In this context, the same author has reported that diarylazines react with benzyne to give 10-amino-3-substituted-9(10*H*)-acridinones through benzazetidines derived from a [2+2] cycloaddition between benzyne and one azomethine group of the azine (*Scheme 44*).[68]

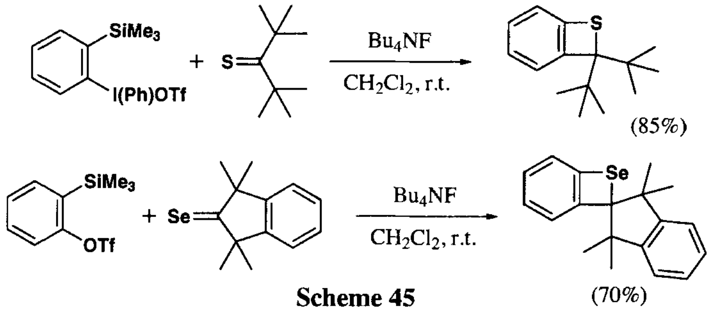
Okuma and co-workers have reported that the reaction of sterically congested aliphatic thiones with benzyne afforded a [2+2] cycloadduct,[69] and, in the same way they have synthesized the first isolable 2*H*-benzoselenete by the reaction of 1,1,3,3-tetramethylindane-2-selone with Kobayashi's precursor of benzyne (*Scheme 45*).[70]

A convenient method for the preparation of sulphur- and nitrogen-containing tricyclic and tetracyclic heterocyles *via* the reaction of Barton esters and benzynes has been described. Although no direct evidence for free-radical addition of Barton esters to benzyne was found,



Scheme 44

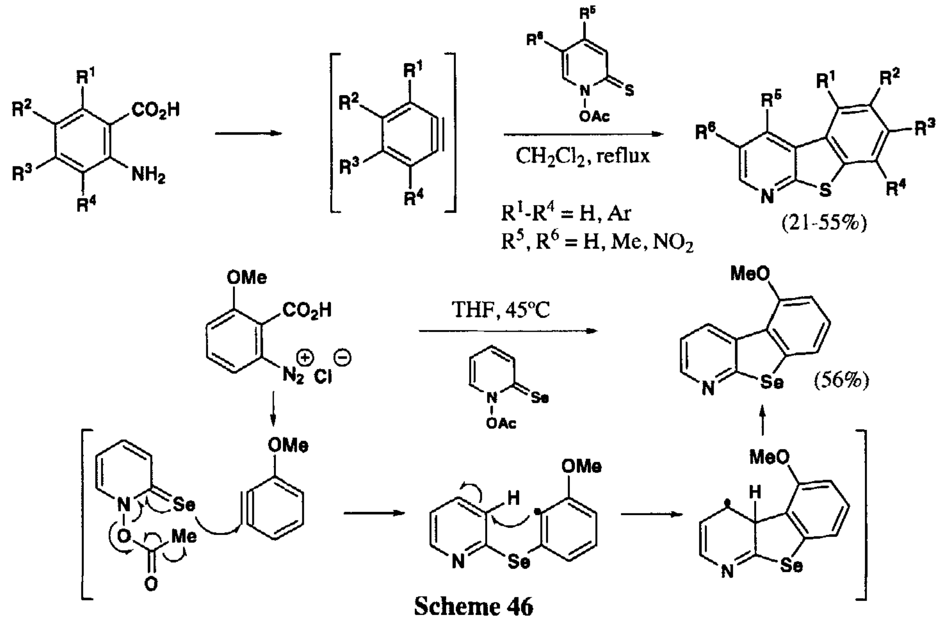
these esters could react with benzynes by SET (single electron transfer) to give a radical intermediate, which could subsequently undergo intramolecular cyclization to give the final product



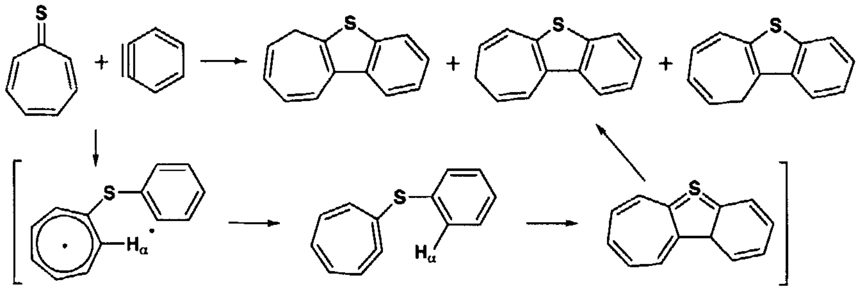
Scheme 45

(*Scheme 46*).[71] In the same way, the reaction of related acetic acid 2-selenoxo-2*H*-pyridin-1-yl esters with benzynes offers a convenient route to benzo[*b*]seleno[2,3-*b*]pyridines (*Scheme 46*).[72]

Interestingly, whereas the reaction between benzyne and tropothione was expected to be a typical cycloaddition, the experimental and computational study has revealed that benzyne must be regarded as a phenyl biradical reactant rather than as an electrophile toward this thioketone. The benzyne is, first, added to the tropothione *via* one center C–S bond formation. Then, a singlet biradical intermediate is formed, in which an α hydrogen atom of the tropothione moiety is moved to the benzyne moiety. The generated allene-type intermediate is further isomerized, and final proton shifts lead to the products (*Scheme 47*).[73]



Scheme 46

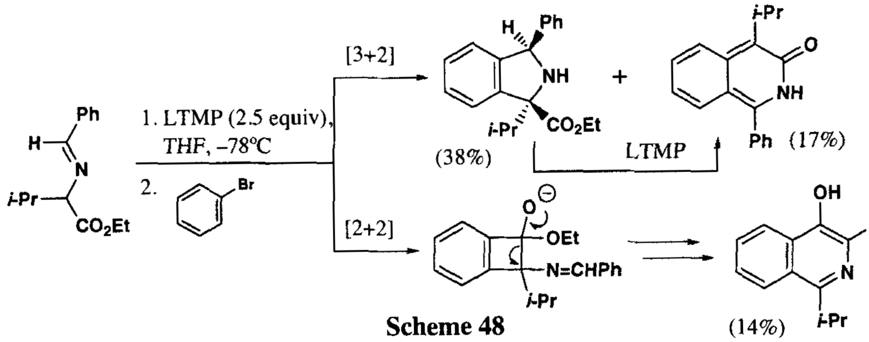


Scheme 47

3. [3+2] Cycloaddition Reactions

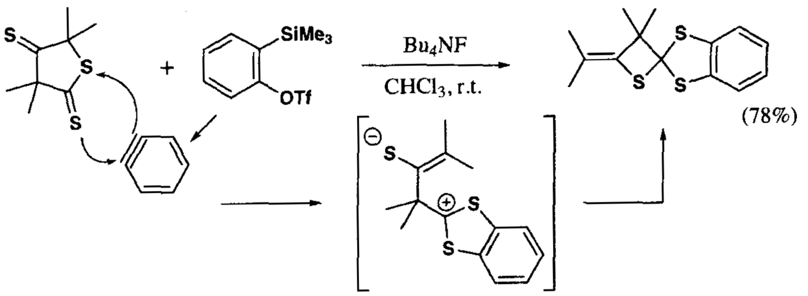
A wide variety of stable 1,3-dipolar compounds undergo cycloadditions with arynes. Reaction of the azaallyllithiums derived from imines of α-amino esters with benzynes resulted in the formation of 1,3-dihydroisoindoles and 4-hydroxyisoquinolines *via* [3+2] and [2+2] cycloadditions, respectively. The isoindole derivatives further rearrange to form 3-(2*H*)-isoquinolinones under the basic reaction conditions (*Scheme 48*).[74]

Reaction of 3,3,5,5-tetramethylthiolane-2,4-thione with benzyne gave a new type of benzodithiole. Probably, the dithioester thiocarbonyl group initially attacks benzyne through a formal 1,3-dipolar cycloaddition to afford a betaine, which finally rearranged to give benzodithiole (*Scheme 49*).[75]



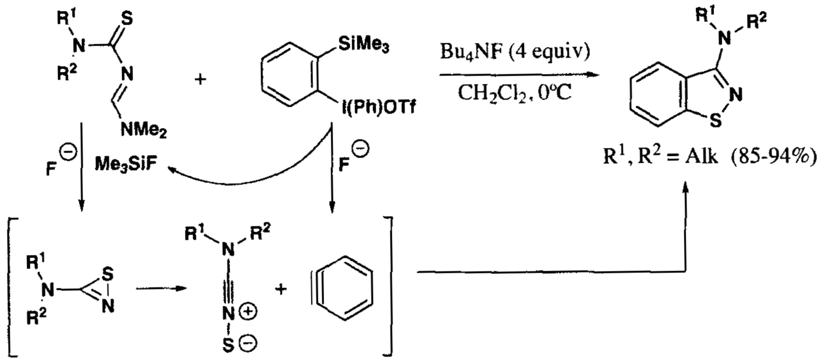
Scheme 48

A novel approach to 3-aminobenzoisothiazoles was successfully achieved by the reaction of benzyne, generated from Kitamura's precursor, with aminothiazadienes. Excellent yields



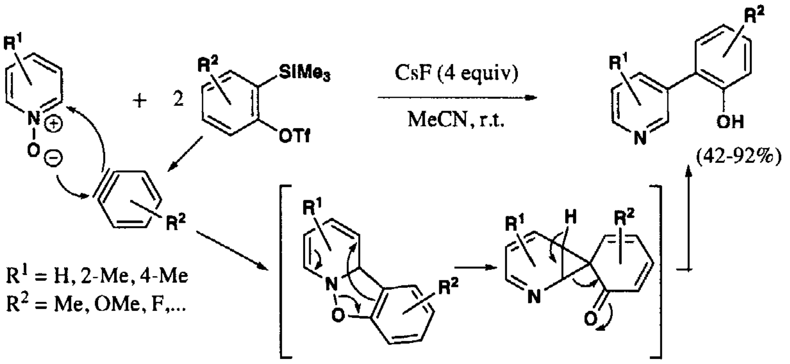
Scheme 49

were obtained by using excess of Bu_4NF, and the authors postulate a fluoride-induced formation of a nitrile sulfide that undergoes cycloaddition to benzyne (*Scheme 50*).[76]



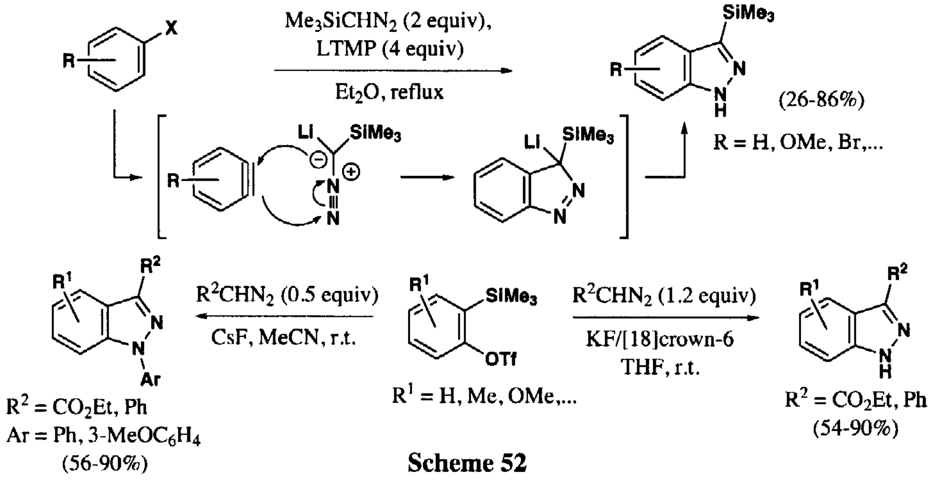
Scheme 50

A regioselective coupling reaction between pyridine *N*-oxides and arynes has been developed, which provides 3-(2-hydroxyphenyl)pyridines in high yields. The proposed mechanism involves a first [3+2] cycloaddition reaction followed by a series of rearrangements (*Scheme 51*).[77]



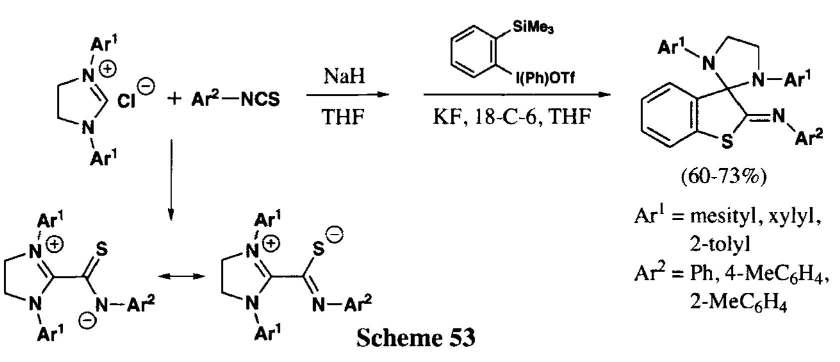
Scheme 51

Two different approaches have been reported for the synthesis of 1*H*-indazoles based on 1,3-dipolar cycloadditions of arynes with diazomethane derivatives. First, [3+2] cycloaddition reaction of lithium trimethylsilyldiazomethane with benzynes, generated from halobenzenes, gave the corresponding 3-trimethylsilylindazoles in good to moderate yields (*Scheme 52*).[78] More recently, Yamamoto has reported that the reaction between arynes generated from Kobayashi's precursor, and various diazomethane derivatives proceeded smoothly under very mild conditions to give, depending on the reaction conditions, 1*H*-indazoles or 1-aryl indazoles in good to high yields (*Scheme 52*).[79]



Scheme 52

The first reaction of carbon-centered 1,3-dipoles with arynes has been recently reported by using 2-arylthiocarbamoylimidazolium inner salts as a unique type of stable ambident C–C–S and C–C–N 1,3-dipolar systems. The one-pot reaction of arynes, aryl isothiocyanates and *N*-heterocyclic carbenes proceeds in the C–C–S fashion affording spiro(imidazolidine-2,3'-benzo[*b*]thiophenes) (*Scheme 53*).[80]



(60-73%)

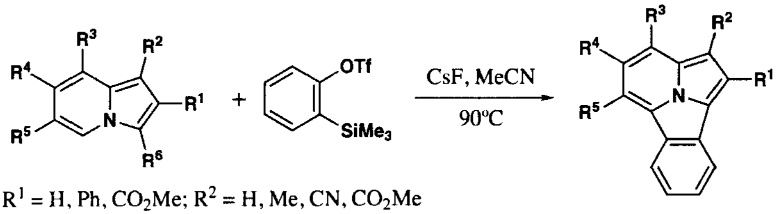
Ar^1 = mesityl, xylyl, 2-tolyl

Ar^2 = Ph, 4-MeC_6H_4, 2-MeC_6H_4

Scheme 53

4. Other Cycloaddition Reactions

Indolizino[3,4,5-*ab*]isoindoles and their annulated derivatives have been synthesized by [8+2] cycloaddition reactions of the corresponding indolizines with benzyne, generated from the Kobayashi's precursor, in moderate yields (*Scheme 54*).[81] Interestingly, some of these compounds fluoresce in the blue region with high quantum yields.



R^1 = H, Ph, CO_2Me; R^2 = H, Me, CN, CO_2Me

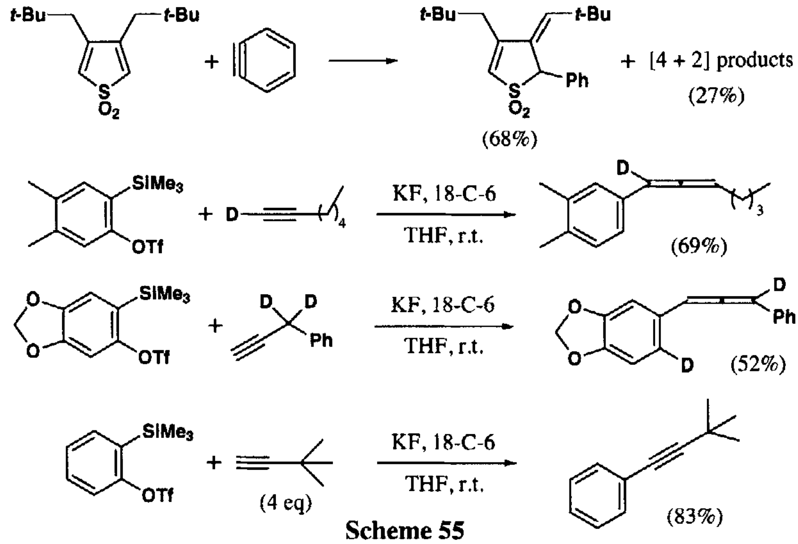
R^3, R^4, R^5 = H, Me; R^6 = H, CN

Scheme 54

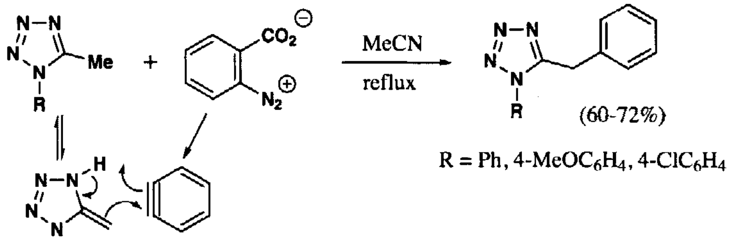
5. Ene Reactions

Few synthetically useful reports have appeared for the *ene* reaction of arynes with olefins or alkynes bearing allylic or propargylic hydrogen atoms, respectively, since Nakayama and co-workers reported an unexpected *ene* reaction of 3,4-dineopentylthiophene-1,1-dioxide with benzyne (*Scheme 55*).[82] Interestingly, Cheng and co-workers have recently described the first *ene* reaction of arynes with alkynes, which was supported by deuterium-labelling experiments. This process leads to phenylallene derivatives in usually good yields. These authors have also observed the first addition of an acetylenic C–H across benzyne when an alkyne without propargylic hydrogens was used (*Scheme 55*).[83]

An *ene*-addition of an intermediate enamine with benzyne has been postulated to account for the formation of 1-aryl-5-benzyl-1*H*-tetrazoles from the reaction of 1-aryl-5-methyl-1*H*-tetrazoles with benzyne (*Scheme 56*).[84]



Scheme 55

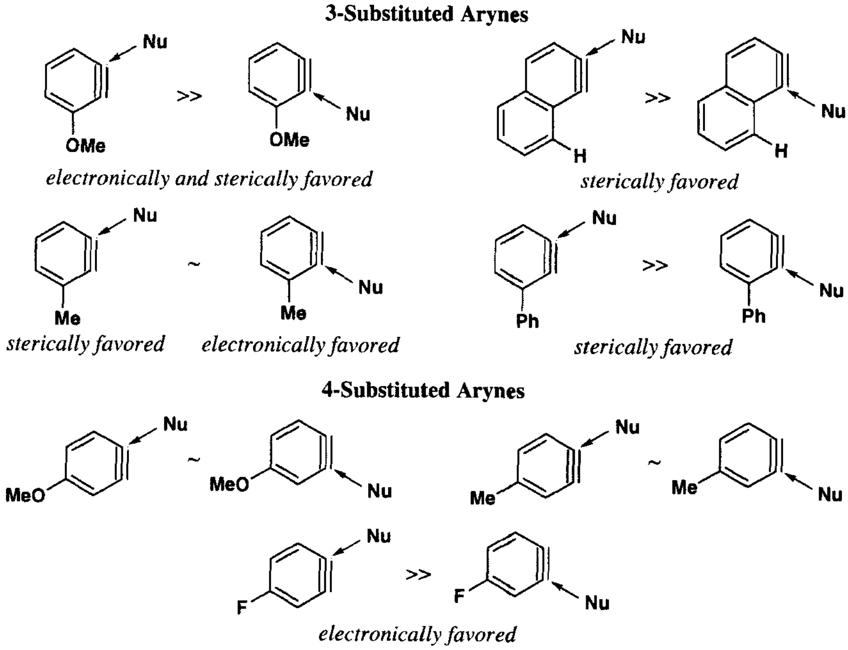


Scheme 56

IV. NUCLEOPHILIC ADDITION REACTIONS TO ARYNES

Owing to their low-lying LUMO, arynes are powerful electrophiles, and even neutral nucleophiles, which are inert toward alkynes, readily add to arynes. Considerable attention has been paid to nucleophilic coupling reactions with arynes, and these reactions have been exploited in the construction of complex organic molecules.[85] The addition of a nucleophile Nu to benzyne leads to the formation of an aryl carbanion or a zwitterion, depending on the anionic or neutral character of the nucleophile, that can be trapped with an electrophile, including a proton. This section will be further divided depending on the character (anionic or neutral) of the nucleophile and on its nature (heteroatomic nucleophiles, stabilized carbanions, and organometallics).

Whereas the addition reactions to unsubstituted or symmetrically substituted benzynes have not regiochemical problems, the use of substituted-benzynes would, at first, lead to regioisomers. The observed regioselectivities in the reaction of unsymmetrical arynes should be due to electronic and/or steric effects of the substituent on the arynes. The reactions of 3-methoxybenzyne usually occurred with high regioselectivity, which can be rationalized in terms of steric and/or electronic effects, both of which favor nucleophilic attack at the *meta* position of the methoxy group (*Scheme 57*). With other 3-substituted-benzynes such as 1,2-naphthalyne and 3-phenylbenzyne, high regioselectivities are also usually observed, which would be attributable to unfavorable steric repulsion between the substituent in the aryne and the nucleophile. However, for 3-methylbenzyne, the steric effect would be in conflict with an electron-donating inductive effect of the methyl moiety (*Scheme 57*). In contrast, 4-substituted arynes such as 4-methoxybenzyne and 4-methylbenzyne usually give almost equal amounts of regioisomeric products, showing that the steric and electronic effects are very similar in the *meta* and *para* positions to the substituent of the aryne (*Scheme 57*). Owing to the strong electron-withdrawing effect of a fluorine atom in 4-fluorobenzyne, the developing negative charge at the *meta* position (*vs. para*) would be stabilized to a greater extent in the transition state for a nucleophilic addition *para* to the fluorine atom (*Scheme 57*).

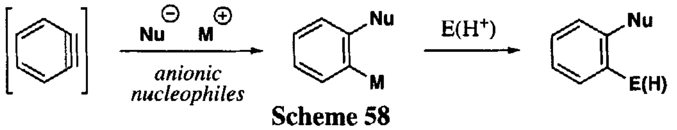


Scheme 57

1. *Anionic Nucleophiles*

In a formal sense, the addition of anionic reagents with strongly polarized carbon–metal bonds or heteroatom–metal bond can be considered formally as the insertion of the aryne into the carbon– or heteroatom–metal bond (*Scheme 58*).

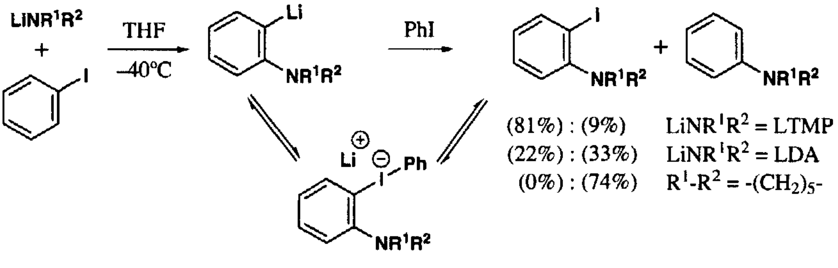
Most anions having negative charge on carbon, nitrogen, or sulphur are effective nucleophiles *versus* arynes. In this section we will describe the addition reactions to arynes that really involve anionic nucleophiles, previously or *in situ* generated with highly basic reagents. Moreover, the addition of a nucleophile that is part of an aryne side chain to the benzyne intermediate to form a new ring has provided a simple synthetic route to a variety of benzo-fused carbocycles and heterocycles. This strategy, often called benzyne cyclization and introduced independently by Huisgen and Bunnett,[86] has been successfully applied to the synthesis of natural products and of a variety of heterocyclic and homocyclic systems.



Scheme 58

a) Heteroatomic Nucleophiles

The intermolecular reaction of arynes with primary and secondary lithium amides provides a convenient route to alkylated anilines. Interestingly, benzyne generation from iodobenzene with LTMP afforded the 2-iodoaniline derivative in high yield by iodine transfer from iodobenzene to the intermediate 2-lithioaniline (*Scheme 59*).[87] Significant lower yields of the iodo-functionalized anilines are obtained for sterically less hindered amines.

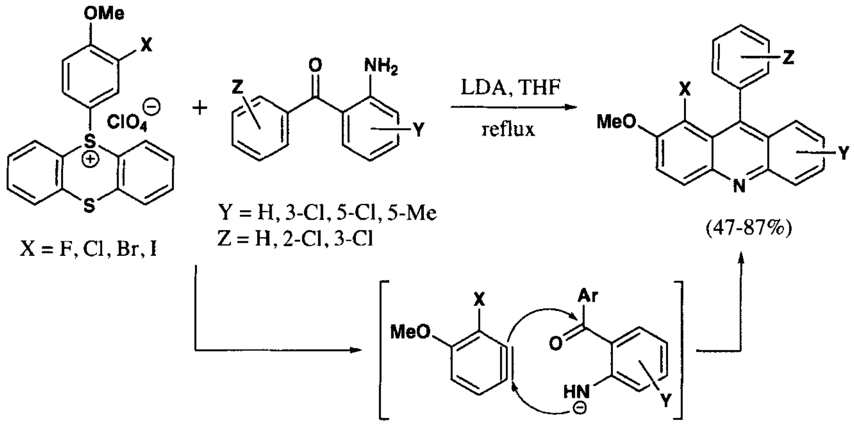


Scheme 59

Although the addition of various nitrogen nucleophiles to arynes has been reported, the successful trapping of the intermediates with electrophiles has been reported in only a few cases. One of them is based on the use of aminocarbonyl derivatives as nucleophiles. Thus, 3-halo-4-methoxybenzynes, generated from 5-(3-halo-4-methoxyphenyl)thianthrenium perchlorates and LDA, react with 2-aminobenzophenones to give regiospecifically 9-aryl-1-halo-2-methoxy-acridines (*Scheme 60*).[17]

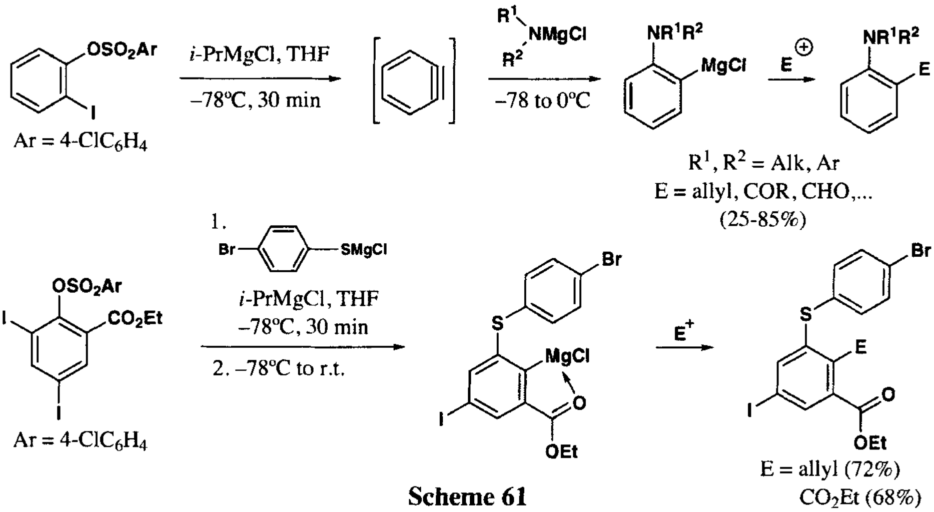
In a more general approach, Knochel and co-workers found that polyfunctional arynes, generated by the elimination of 2-magnesiated diaryl sulfonates prepared from the corresponding iodides,[25] react with magnesiated thiols and amines providing 2-thio- and 2-amino-substituted arylmagnesium species. Interestingly, these arylmagnesium reagents can be trapped by a range of electrophiles giving rise to *o*-functionalized thioethers and arylamines (*Scheme 61*).[88]

The rate of addition to the aryne depends on the nucleophilicity of the magnesium reagent. Thus, whereas magnesium amides are basic reagents, magnesium thiolates are more nucleophilic and therefore add more readily. Other highly nucleophilic reagents, such as

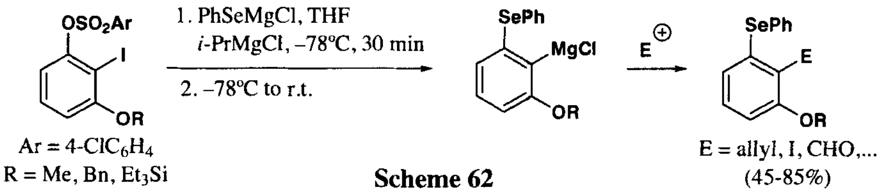


Scheme 60

phenylselenylmagnesium chloride also reacts with benzyne and the resulting polyfunctional arylmagnesium reagents can be trapped with electrophiles, yielding polyfunctional selenoethers (*Scheme 62*).[89]



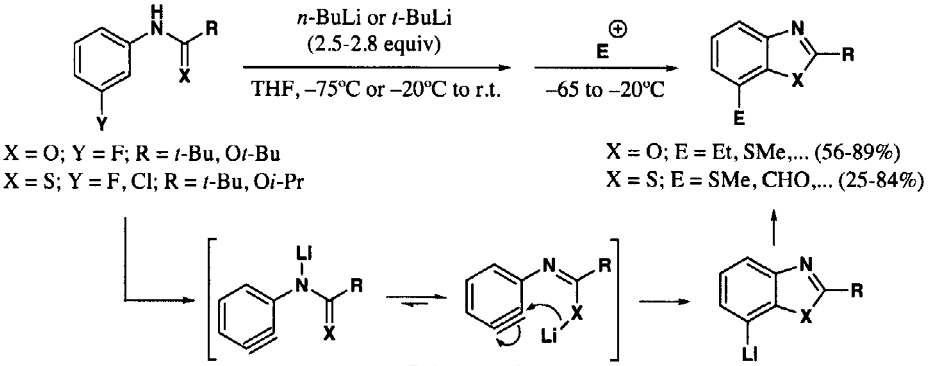
Scheme 61



Scheme 62

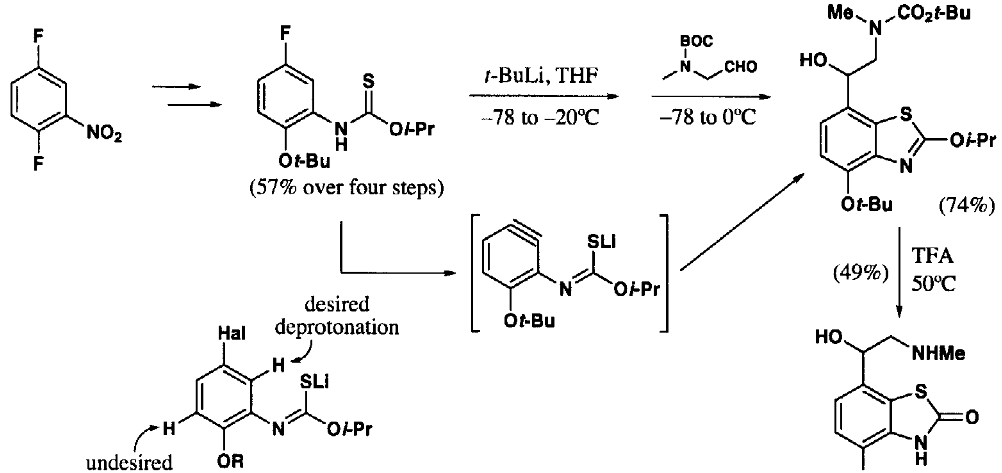
The strategy of intramolecular trapping of benzyne intermediates with adjacent side-chain nucleophiles has proved to be very useful for the synthesis of benzo-fused heterocycles. In

1982 Clark and Caroon reported a novel synthesis of 7-substituted benzoxazole derivatives by intramolecular trapping of the benzyne intermediate derived from *N-t*-BOC-3-fluoroaniline, and subsequent quenching of the generated organolithium compound with various electrophiles (*Scheme 63*).[90] Several years later, Stanetty reported a similar approach to benzothiazole derivatives selectively functionalized at position 7 by intramolecular nucleophilic cyclization of lithiated benzyne thioamides and thiocarbamates (*Scheme 63*).[91]



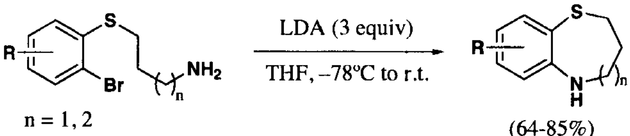
Scheme 63

More recently, Fairhurst and co-workers have synthesized the marine sponge derived β_2-adrenoceptor agonist S1319 employing a 7-lithiated-2,4-dialkoxybenzothiazole as a key intermediate (*Scheme 64*).[92] This organolithium derivative was obtained *via* a directed lithiation/benzyne cyclization reaction following the approach reported by Stanetty and described above. To significantly increase the efficiency of the pivotal cyclization, a *t*-butyl aryl ether residue was used in order to sterically suppress a competing directed *o*-lithiation reaction.



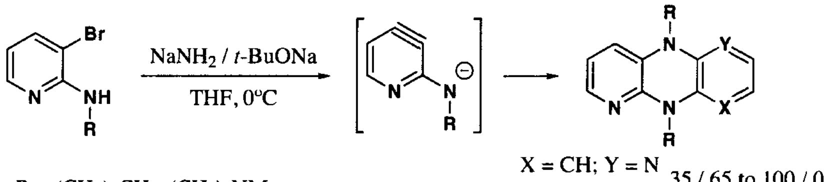
Scheme 64

Biehl and co-workers have prepared new five- and six-membered heterocycles by nucleophilic addition to arynes possessing charged substituents[1c] and, more recently, they have found that benzyne ring closure reactions are also a valuable method for the preparation of seven- and eight-membered rings possessing nitrogen and sulfur atoms. 2,3,4,5-Tetrahydro[*b*][1,4]thiazepines and 2,3,4,5-tetrahydro-2*H*-benzo[*b*][1,4]thiazocines were prepared by the cyclization of the respective 2-bromophenylsulfanyl derivatives of propylamine and butylamine (*Scheme 65*).[93]



Scheme 65

Also, hetarynic intermolecular cyclization of 2-alkylamino-3-bromopyridines, in the presence of the complex base $NaNH_2$ / *t*-BuONa, allows their conversion into regioisomeric mixtures of previously unknown dihydrodipyridopyrazines, through the corresponding 3,4-pyridynes (*Scheme 66*).[94]



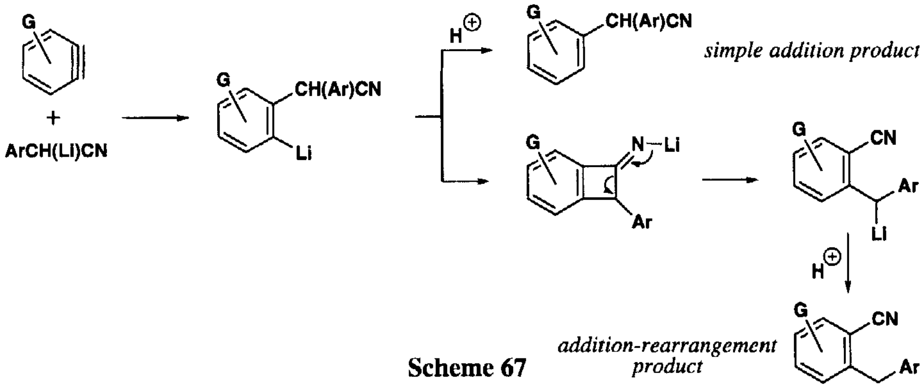
Scheme 66

b) Stabilized Carbanions

i) α-Lithionitriles as Carbon Nucleophiles

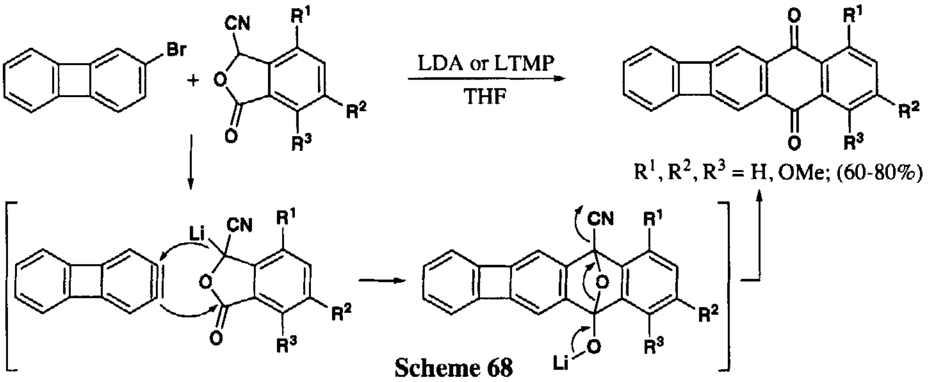
The addition reactions of α-lithioalkyl and α-lithioarylacetonitriles to arynes have been extensively used as a method for the construction of functionalized polycyclic systems.[85b] Biehl and co-workers have shown that arynes, generated by the reaction of haloarenes with LDA, react with preformed α-lithioarylacetonitriles to give either simple addition products or rearranged *o*-(arylmethyl)benzonitriles. These authors proposed that the preferred reaction pathway was highly dependent upon the nature of the substituent on the haloarene, with electron-releasing groups favoring rearranged nitriles and electron-withdrawing substituents favoring simple addition nitriles (*Scheme 67*).[95]

The same research group has prepared a wide variety of functionalized polycyclic quinones from the reaction of haloarenes with 3-lithiophthalides in the presence of sterically hindered bases such as LDA and LTMP.[85b] In this context, this group has shown that 2,3-dehydrobiphenylene, generated from 2-bromobiphenylene in a selective way, serves as a valuable



Scheme 67

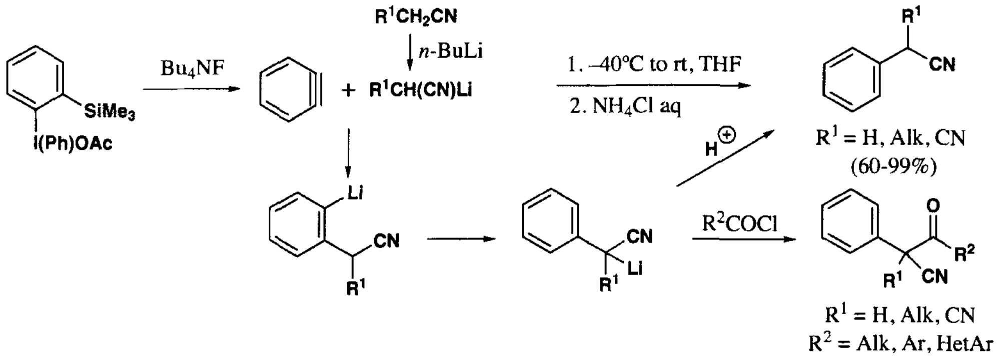
intermediate in the synthesis of functionalized benzo[3,4]cyclobuta[1,2-*b*]anthracene-6,11-diones by their reactions with lithiated 3-cyanophthalides (*Scheme 68*).[96] The same methodology allows the preparation of naphthacene-5,12-diones from 1-methoxy-2-chloronaphthalene.



Scheme 68

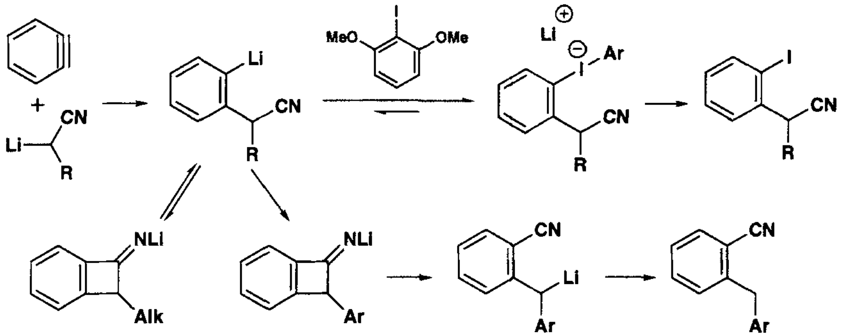
These authors have also found that the yields of the reactions of α-lithiated nitriles with arynes are significantly higher when arynes are generated under neutral conditions in the presence of preformed α-lithiated nitriles instead of the classical basic conditions. In this way, 2-aryl-substituted nitriles were prepared in good to excellent yields in a one-pot reaction. In addition, several 3-keto-2-arylnitriles were obtained when acid chlorides were added at the end of the reaction. Isomerization of the initial addition compound to a more stable α-aryl-α-lithionitrile accounts for their formation (*Scheme 69*).[97]

The presence of an alkyl in the starting nitrile showed to be fundamental for the outcome of the process, as the reaction of 2-lithiophenylacetonitrile gave rise to rearranged 2-benzylacetonitrile. This fact is in agreement with Durst and co-workers who had shown that all benzyne reactions involving nitrile anions proceed through a four-membered ring intermediate. The *N*-lithiobenzocyclobutenamines undergo ring opening to yield either 2-substituted benzonitriles or α-substituted benzylcyanides depending on the substitution pattern on the aryl and



Scheme 69

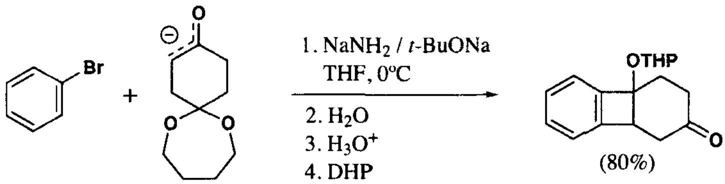
cyclobutene ring. Moreover, they were also able to trap intermediate aryllithiums prior to cyclization with iodobenzene or 2,6-dimethoxyiodobenzene (*Scheme 70*).[98]



Scheme 70

ii) Lithium Enolates and Related Systems as Carbon Nucleophiles

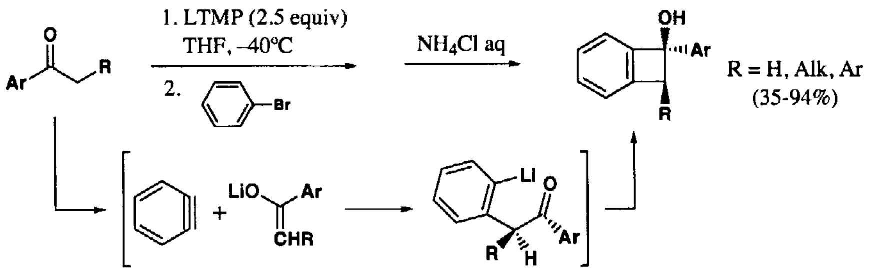
The trapping of arynes with ketone enolates has been investigated extensively by the Caubère group over several years providing strained aromatic polycyclic compounds. Complex bases such as $NaNH_2$ / *t*-BuONa in THF were usually used to generate both the benzyne and the enolate (*Scheme 71*).[99]



Scheme 71

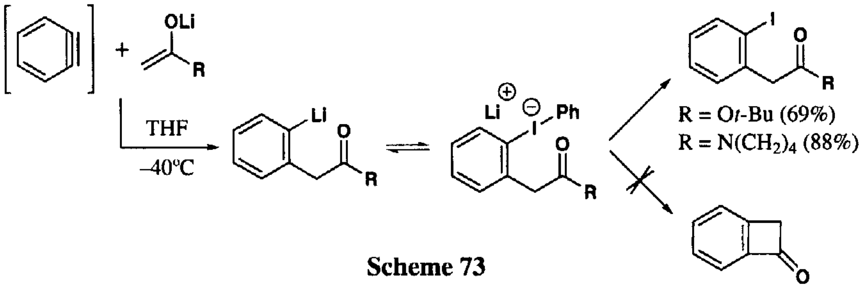
However, under these conditions only a relatively small group of ketone enolates, mainly five- to seven-membered ring ketones, gave rise to benzocyclobutenols. This fact is probably due to the tendency for cycloreversion of the intermediate benzocyclobutene alkoxides.

Durst and co-workers have described that benzocyclobutenols could be isolated in fair to good yields, in particular 1-arylbenzocyclobutenols, from the reaction of ketone enolates with arynes when these intermediates are generated from halobenzenes with LTMP at low temperature (*Scheme 72*).[100]



Scheme 72

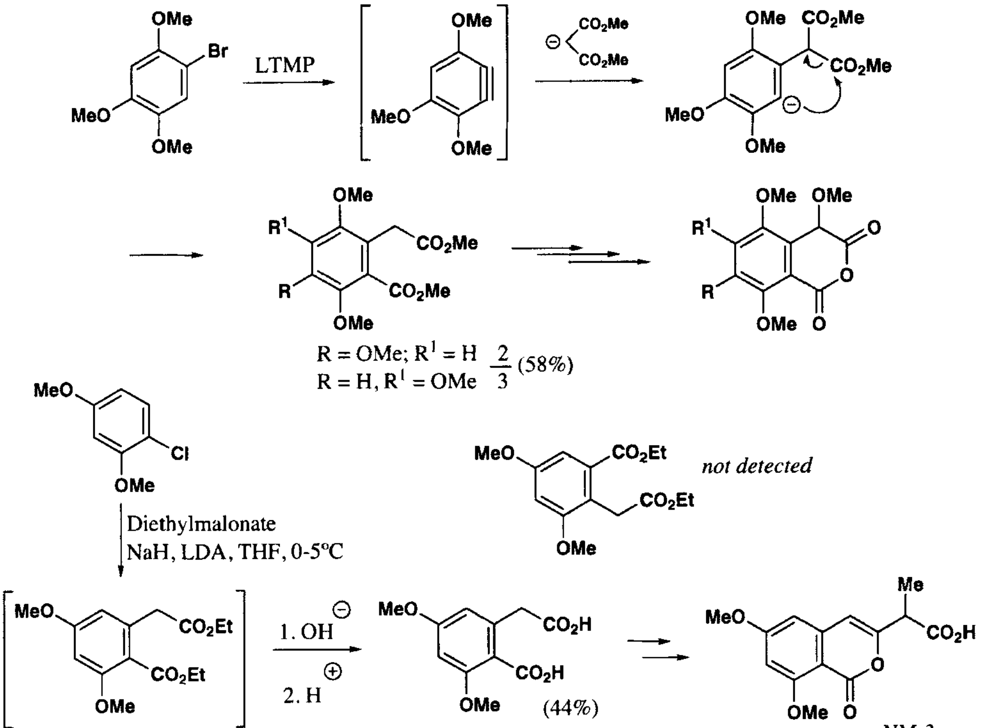
Durst and co-workers had also reported that the generation of benzyne from iodobenzene with LTMP in the presence of amide or ester lithium enolates led mainly to 2-iodo substituted aromatics by iodine transfer from iodobenzene to the intermediate 2-lithioaromatics with no evidence for the formation of the desired benzocyclobutenone (*Scheme 73*).[87]



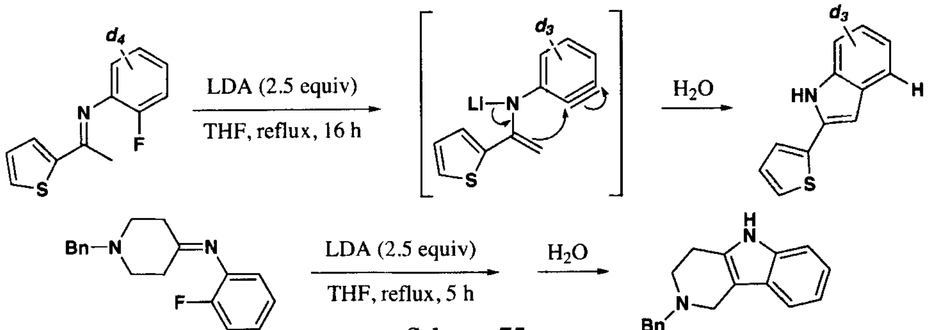
Scheme 73

Based on previous work of Danishefsky,[101] Kita and co-workers have prepared a regioisomeric mixture of homophtalic anhydrides during the enantioselective total synthesis of the antitumor antibiotic *fredericamycin A*. A non-regioselective addition of the lithium dimethylmalonate to 1,2,4-trimethoxybenzyne led to a regioisomeric mixture (2:3) of homophtalates through addition and further rearrangement (*Scheme 74*).[102] In contrast, Bauta and co-workers described a regiospecific addition/rearrangement between 3,5-dimethoxybenzyne with sodium diethylmalonate at unusually high-temperature in the development of a formal synthesis of angiogenesis *inhibitor NM-3* (*Scheme 74*).[103]

2-Substituted and 2,3-disubstituted indoles as well as carbazole derivatives have been synthesized from 2-fluorophenyl imines by arynic cyclization. The intermediacy of a benzyne was demonstrated by the use of 2-fluoroaniline-d_4. This method complements a related route[104] to indole derivatives from 3-chlorophenyl imines and enamines (*Scheme 75*).[105]



Scheme 74

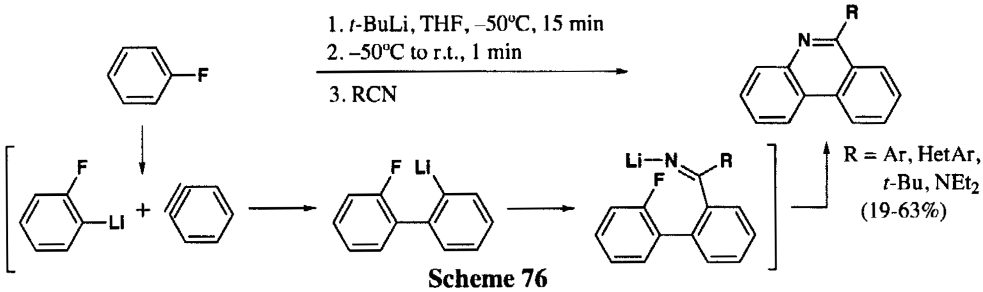


Scheme 75

c) Organometallics

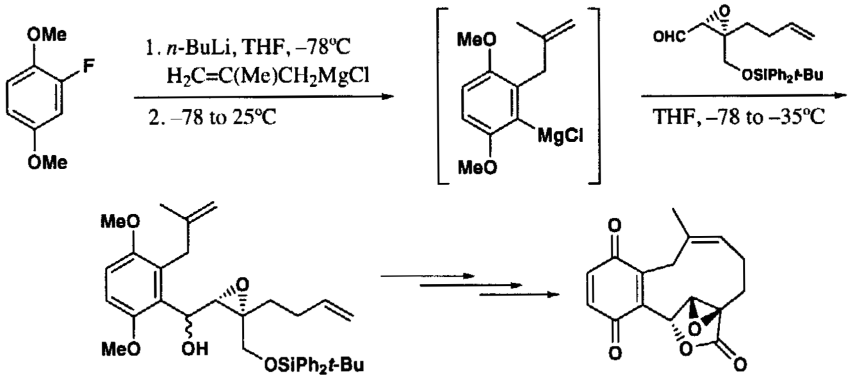
i) Intermolecular Additions

Although intermolecular addition of an organolithium to a benzyne is a well characterized process,[1a] there are no many reports about true synthetic applications of this type of reactions. In this context, Pawlas and co-workers have reported a one-pot access to 6-substituted phenanthridines from fluorobenzene and nitriles. A careful control of reaction conditions is required to obtain efficient addition of *o*-fluorophenyllithium to benzyne and to avoid formation of side-products like triphenylene. Nitriles with α-protons could not be used as 2-fluorobiphenyl was the major product. Moderate yields were generally obtained because byproducts could not be completely avoided (*Scheme 76*).[106]



Scheme 76

In the total synthesis of *ent-clavilactone B*, Barrett and co-workers have used a highly convergent three component benzyne coupling strategy as a key step. Generation of benzyne in the presence of methylallyl Grignard afforded a new aryl Grignard specie that reacted with a chiral epoxy-aldehyde although with low diastereoselectivity (*Scheme 77*).[107]



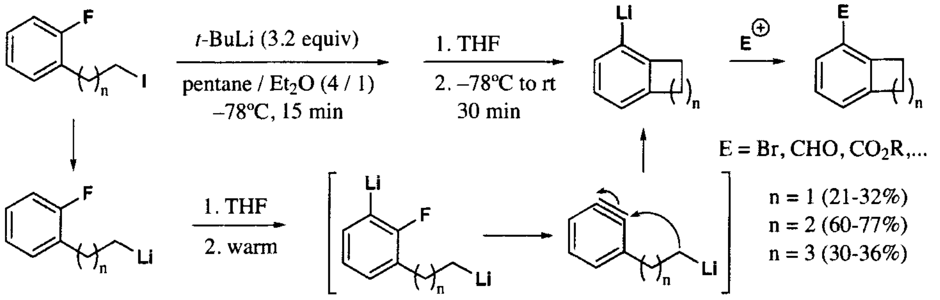
(65%); dr 2:1

Scheme 77

(+)-Clavilactone B

ii) Intramolecular Additions. Anionic Benzyne Cyclization

The formation and cyclization of aryne-tethered organolithiums remains an underexplored area. In addition, this type of cyclization could also be considered as an intramolecular carbolithiation reaction, *i. e.* the addition of an organolithium across a C–C multiple bond leading to a new organolithium compound.[108] Bailey and co-workers have shown that 4-,5-, and 6-*exo* cyclizations of benzyne-tethered alkyllithiums take place with moderate to good yields affording isomerically pure 3-substituted benzocyclobutenes, 4-substituted indans, and 5-substituted tetralins (*Scheme 78*).[109] The 4-*exo* or 6-*exo* cyclization is less efficient in terms of yield than the 5-*exo* cyclization of a benzyne-tethered propyllithium. Careful control of reaction conditions is needed as the initial iodine-lithium exchange is carried out in n-pentane/Et_2O, but deprotonation *ortho* to the fluorine atom must be carried out by an additional equivalent of monomeric t-BuLi.



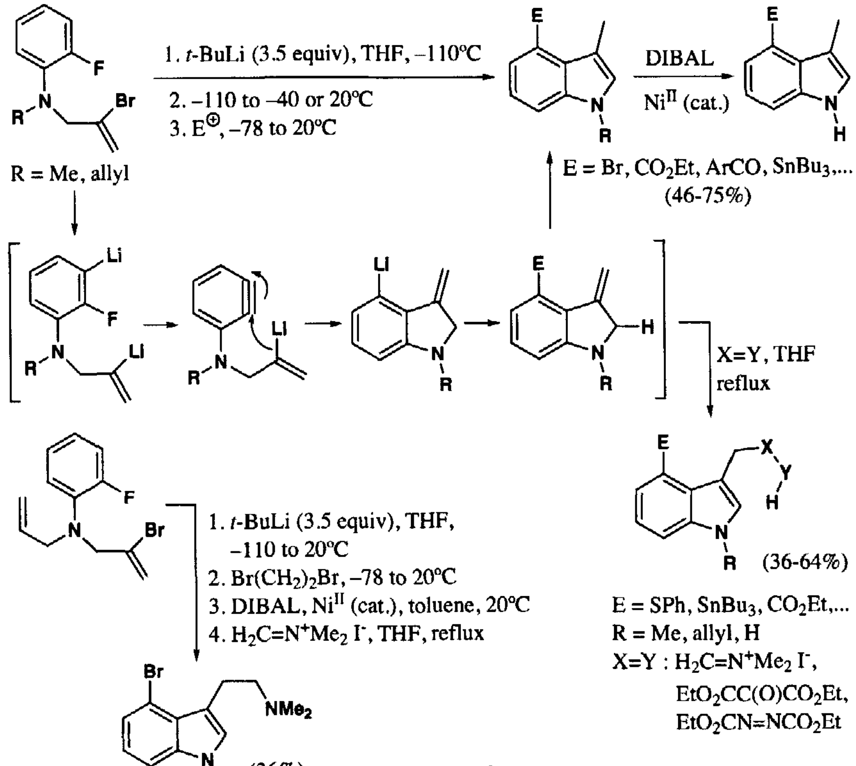
Scheme 78

Thus, strictly dried and deoxygenated THF is added to the α-(2-fluorophenyl)-ω-lithioalkane to initiate the three-step cascade depicted in *Scheme 78*.

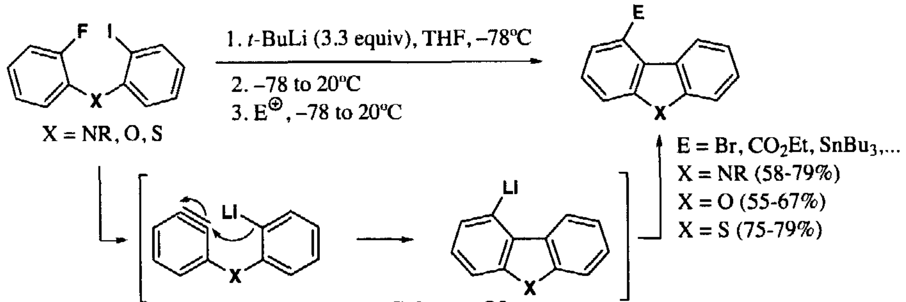
In the last few years, we have been interested in this type of anionic benzyne cyclization, as a particular case of intramolecular carbolithiation reactions, because the possibility to functionalize the cyclized products by further treatment with electrophiles could allow the preparation of regioselectively functionalized heterocycles. This fact represents an important advantage over the corresponding radical cyclizations. Initially we studied the intramolecular 5-*exo* anionic cyclization of benzyne-tethered vinyllithiums and its application to the synthesis of 4-functionalized indoles. Treatment of *N*-alkyl-*N*-(2-bromoallyl)-2-fluoroanilines with *t*-BuLi in THF and subsequent reaction with electrophiles gave rise to the isolated indoles in moderate to good yields (*Scheme 79*).[110] *N*-Unsubstituted indoles were prepared using the allyl group, which could be removed *in situ* by treatment with DIBAL and a catalytic amount of [NiCl$_2$(dppp)]. Moreover, the intermediacy of the C(4)-functionalized 3-methyleneindoline was demonstrated because these intermediates underwent Alder-*ene* reactions with activated enophiles affording interesting 3,4-difunctionalized indoles. For instance, 4-bromo-*N*,*N*-dimethyltryptamine could be prepared in 36% overall yield in a one-pot procedure starting from readily available *N*-allyl-*N*-(2-bromoallyl)-2-fluoroaniline (*Scheme 79*).

In this field, we have also reported the intramolecular 5-*exo* anionic cyclization of benzyne-tethered aryllithiums. By a similar strategy as described above, regioselectively functionalized carbazole, dibenzofuran, and dibenzothiophene derivatives were synthesized in fair to good yields starting from diarylamines, ether, and thioether, respectively, which were prepared by classical aromatic nucleophilic substitution reactions or by Pd-catalyzed processes (*Scheme 80*).[111]

We have also demonstrated the possibility of carrying out 6-*exo* cyclizations starting from 2-bromobenzyl-2-fluorophenyl amines, ethers and thioethers. These processes involve the generation of a benzyne-tethered aryllithium intermediate and subsequent ring closure. This anionic cyclization provides an efficient method for the synthesis of phenanthridine, dibenzopyran, and dibenzothiopyran derivatives regioselectively functionalized at the C-1 position (*Scheme 81*).[110b]

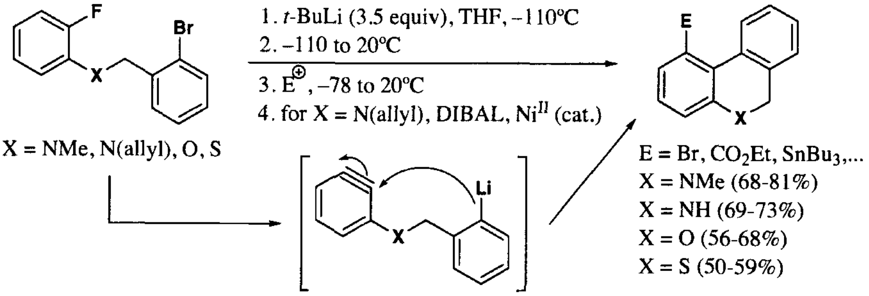


Scheme 79

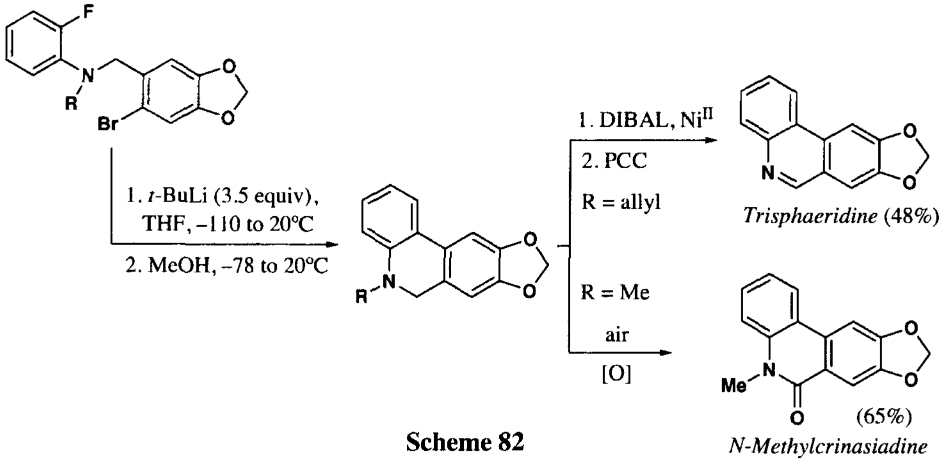


Scheme 80

Based on this methodology, we have recently reported an efficient method for the synthesis of dibenzopyranones, phenanthridinones, and phenanthridines by the *in situ* oxidation of the dibenzo-fused six-membered heterocycles above described. We have also applied it to the total syntheses of *Amaryllidaceae* alkaloids *Trisphaeridine* and *N-Methylcrinasiadine* in a one-pot procedure from readily available starting *N*-alkyl-*N*-(2-bromobenzyl)-2-fluoroanilines (*Scheme 82*).[112]



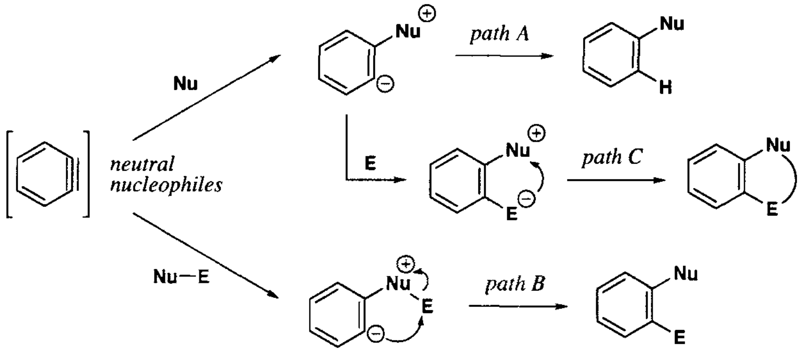
Scheme 81



Scheme 82

2. Neutral Nucleophiles

This section will be devoted to those reactions that involve the addition of initially uncharged nucleophiles to arynes and it will be arranged based on the nature of the nucleophile (heteroatom- or carbon-centered) and on the type of functionalization of the resulting arene (simple or double) based on the three possible pathways outlined in *Scheme 83*. With neutral



Scheme 83

nucleophiles of diminished nucleophilicity, the intermediate zwitterions are also apt to abstract a proton from the cationic site or from the solvent (*Scheme 83*, path A); however, interestingly when an electrophile E is tethered to the nucleophile Nu, the initially formed zwitterions could undergo a subsequent intramolecular reaction with the electrophile leading to the formal insertion of the aryne into the Nu–E σ-bond[113] (*Scheme 83*, path B). Moreover, similar double functionalization, being accompanied by cyclization, could also be achievable by three-component couplings through the capture of the zwitterions with a third electrophilic component (*Scheme 83*, path C). However, because the fluoride anion usually employed to generate arynes in these reactions, is a weak base, *in situ*-generated enolate-type compounds are sometimes proposed as intermediates. Nevertheless, no highly basic reagents are involved in these processes allowing the use of nucleophiles with electrophilic sites in their moieties.

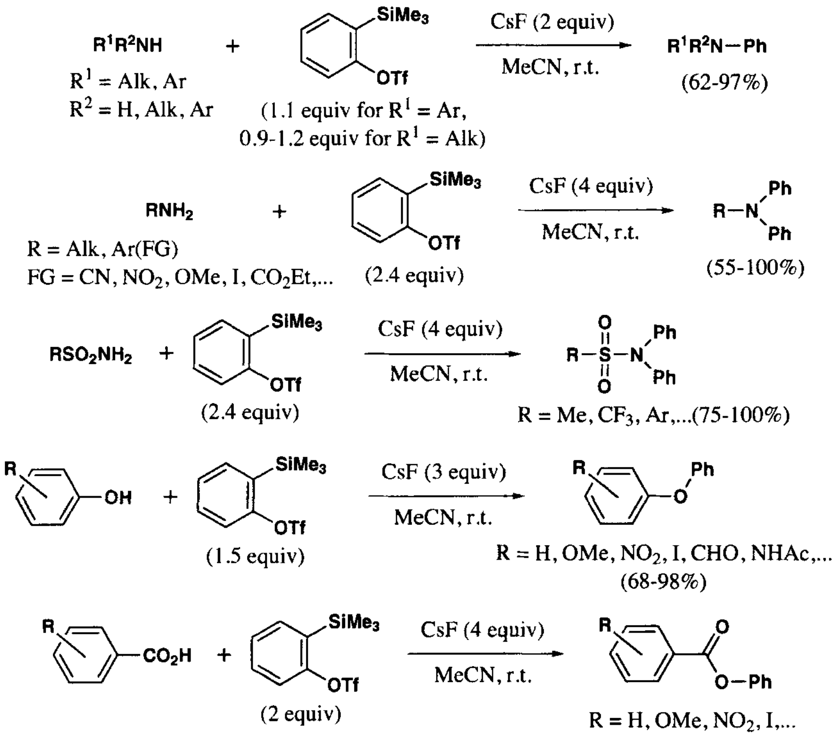
a) Heteroatomic Nucleophiles

i) Formation of Monosubstituted Arenes *via* Pathway A

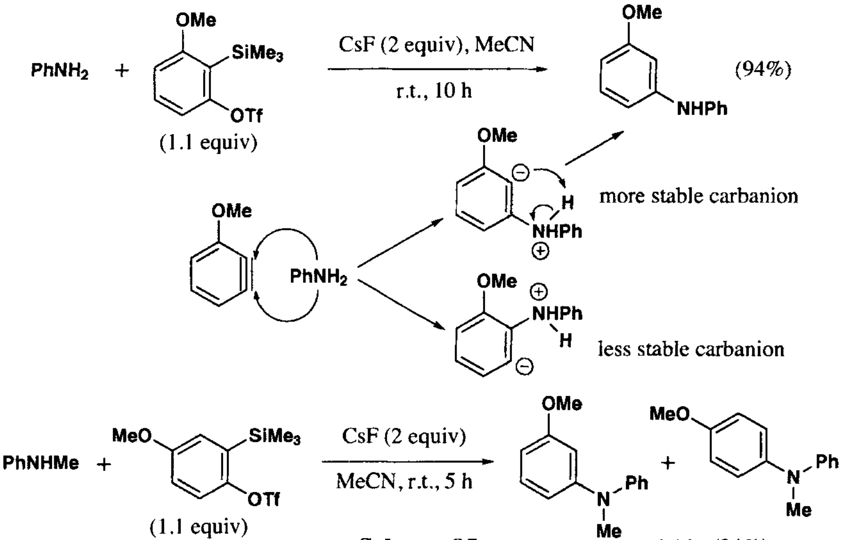
The nucleophilic additions of alcohol and amine derivatives to arynes can also be considered the insertion of arynes into a heteroatom-hydrogen bond. Larock and co-workers have developed an efficient, transition-metal-free procedure for the *N*-arylation of amines, sulfonamides, and carbamates and *O*-arylation of phenols and carboxylic acids by allowing these substrates to react with arynes generated from *o*-silylaryl triflates (*Scheme 84*).[114] A variety of functional groups, including halides, which are not compatible with Pd-catalyzed arylation procedures, readily tolerate the reaction conditions. High yields are usually obtained and monoarylated and diarylated amines can easily be obtained from primary amines by simple control of the ratio of the reactants.

The regiochemistry of the substitution reaction with unsymmetrical arynes resulted to be quite interesting (see *Scheme 57*). Whereas 3-methoxybenzyne afforded a single regioisomer of either the monoarylation or diarylation reactions from nucleophilic attack at the position *meta* to the methoxy group, when 4-methoxybenzyne is employed with *N*-methylaniline two regioisomers were obtained in nearly equal amounts (*Scheme 85*).[114c]

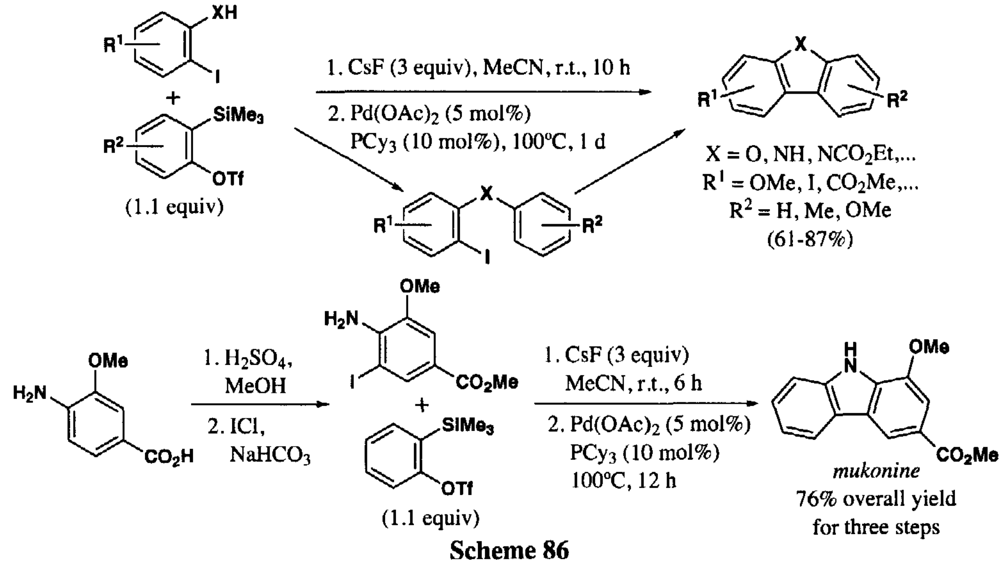
Based on these findings, the same authors have developed an efficient route to synthesize a variety of carbazoles and dibenzofurans. It involves the reaction of *o*-iodoanilines or *o*-iodophenols with arynes to afford the *N*- or *O*-arylated products, which are subsequently cyclized under Pd-catalysis to carbazoles and dibenzofurans in good to excellent yields (*Scheme 86*).[115] Application of this methodology led to a short and efficient synthesis of the carbazole alkaloid *mukonine*.



Scheme 84

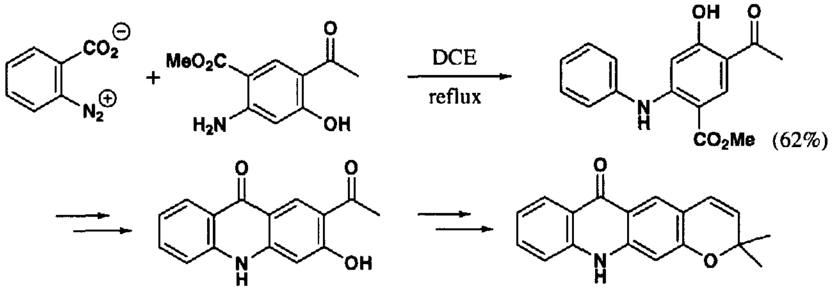


Scheme 85



Scheme 86

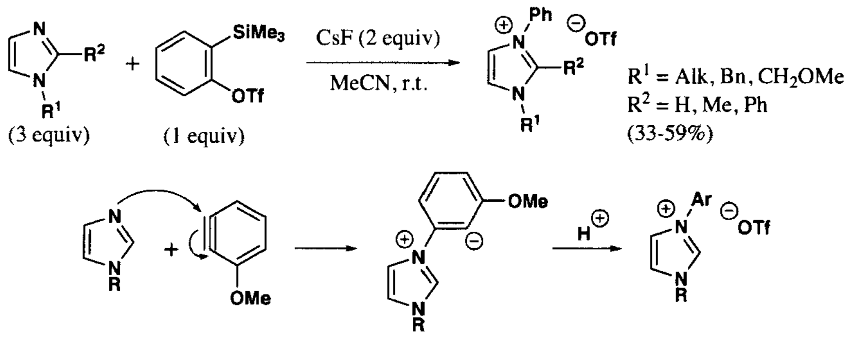
The nucleophilic addition of a tetrasubstituted aniline to benzyne, generated by careful thermal decomposition of benzenediazonium carboxylate, is the key step in the synthesis of *demethoxyisoacronycine* (*Scheme 87*).[116]



Scheme 87 *demethoxyisoacronycine*

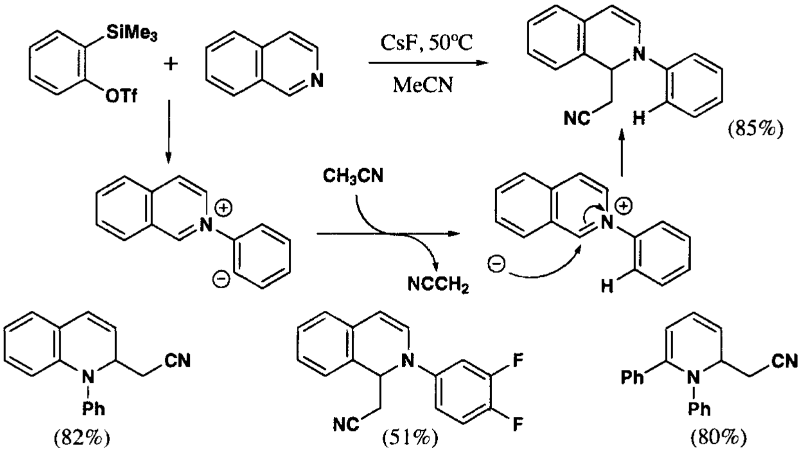
Other nitrogen-centered nucleophiles are also able to add to arynes although no *N*–H bonds are present. Kunai and co-workers have reported that a variety of *N*-alkyl-*N'*-arylimidazolium salts can be synthesized straightforwardly by reaction of *N*-alkylimidazoles with arynes. Again, perfect regioselectivity was observed in the reaction of 3-methoxybenzyne. A nucleophilic nitrogen atom of the imidazole adds to the aryne leading to a zwitterion, which on subsequent abstraction of a proton from the surroundings produces the final product (*Scheme 88*).[117]

Moreover, various *N*-heteroaromatic compounds, including pyridines, quinolines and isoquinoline, react with arynes in nitrile-containing solvents to give *N*-arylated 1,2-dihydro-2-pyridinyl-, -2-quinolinyl-, and -1-isoquinolinylnitriles (*Scheme 89*).[118] Interestingly, this is the



Scheme 88

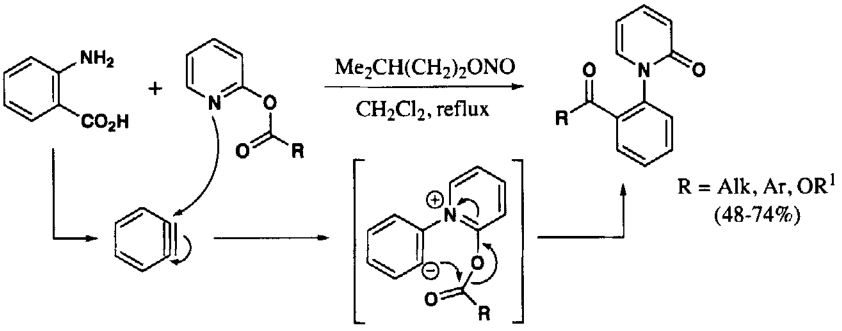
first report of the trapping of the nucleophile-aryne zwitterions by nitrile-containing solvents showing, in addition, that MeCN where arynes are often generated could behave as a proton source for the intermediate zwitterions.



Scheme 89

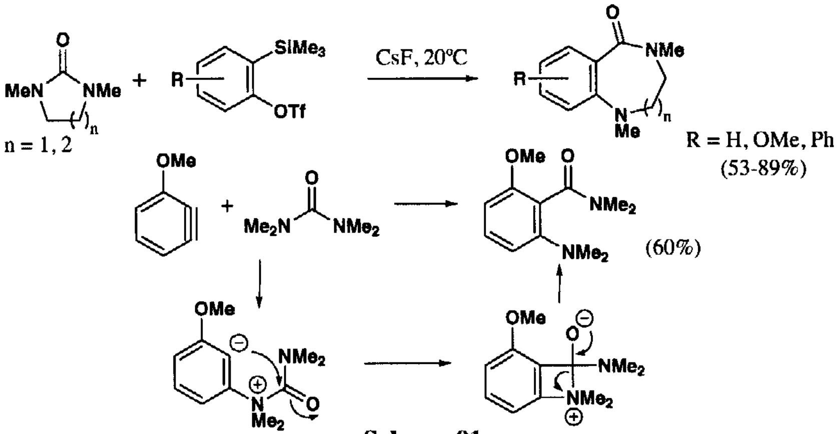
ii) Formation of Disubstituted Arenes *via* Pathway B

The use of a nucleophile with an electrophilic center tethered to it allows the possibility of carrying out formally insertion of arynes into a single bond Nu–E. One pioneering example of this type of chemistry was reported by Cheng and co-workers who described the addition of 2-pyridyl carboxylates to benzynes. A formal 1,4-addition accounts for the formation of the 1-(2-acylphenyl)-2-pyridones obtained. One of the two mechanistic alternatives proposed by these authors involves nucleophilic attack through the nitrogen atom of the pyridyl group and subsequent back attack of the resulting carbanion at the carbonyl carbon of the 2-pyridyl carboxylate, leading to the cleavage of the ester bond (*Scheme 90*).[119]



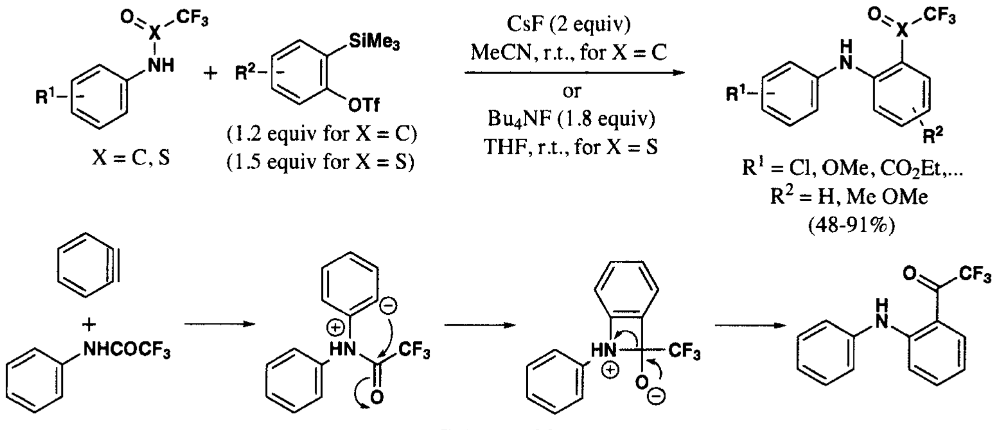
Scheme 90

The reaction of arynes with ureas has been reported to proceed through the formal addition of an N–CO bond of the urea to the aryne providing a wide variety of 1-amino-2-(aminocarbonyl)arenes, including 1,4-benzodiazepine and 1,5-benzodiazocine derivatives which are an important group of therapeutic agents. In connection with the mechanism, again an addition of the urea N-atom gives rise a zwitterion, which furnishes the final product by an intramolecular nucleophilic substitution at the carbonyl carbon atom (*Scheme 91*).[120]



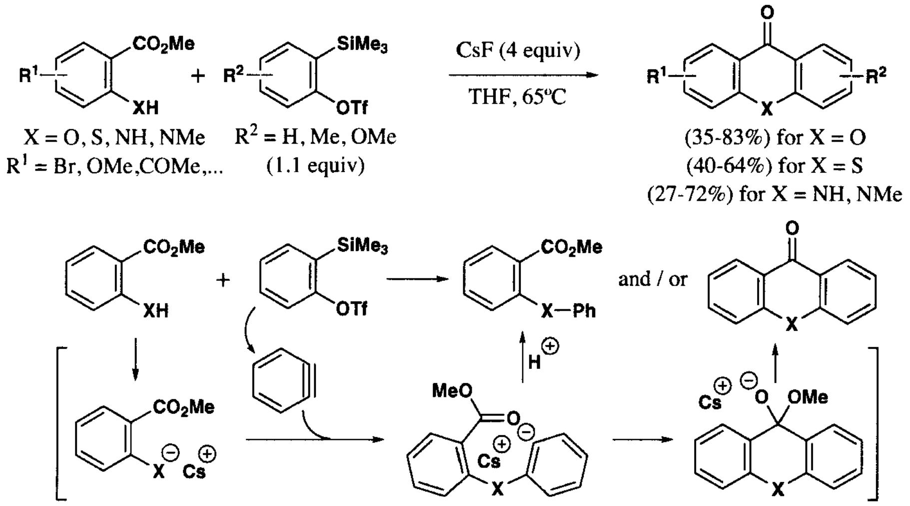
Scheme 91

Larock and co-workers has developed an efficient method for the intermolecular C–N addition of *N*-aryl trifluoroacetamides and S–N addition of the corresponding sulfinamides to arynes. As other related acetamides did not afford insertion products, the presence of the CF_3 and the N–H moieties resulted to be critical to the success of this process, presumably because this group increases the acidity of the amide and also increases the electrophilicity of the carbonyl carbon of the amide and the sulfinyl sulfur atom of the sulfinamide. With respect to the plausible mechanism, the amide could also be deprotonated by the fluoride anion before the nucleophilic attack (*Scheme 92*).[121]



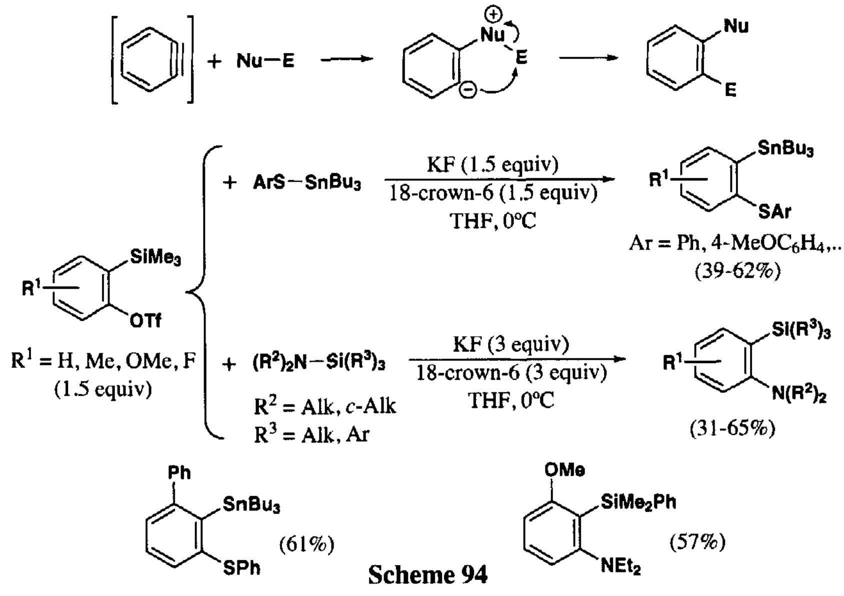
Scheme 92

Larock's group has also reported a synthesis of xanthones, thioxanthones, and acridones by the coupling of arynes and substituted benzoates. In these cases, the fragmentation step, which is inevitable in the above examples, is not involved in this anulation process because the intermediate obtained from the cyclization is a stable six-membered ring system. A careful adjusting of the reaction conditions is required to avoid competitive proton abstraction in the intermediate generated by nucleophilic coupling of the aryne and the aryloxide (*Scheme 93*).[122]



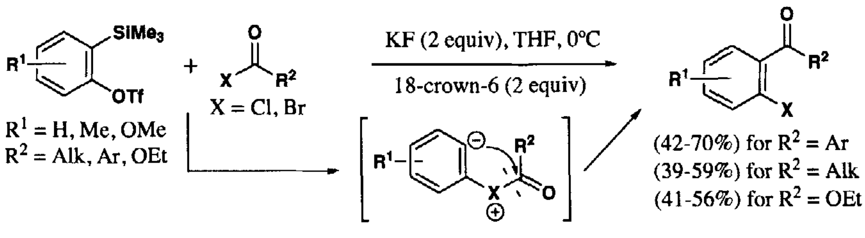
Scheme 93

Throughout their ongoing studies on insertion reactions of arynes into element-element σ-bonds, Kunai and co-workers have reported some useful and interesting examples based on the general pathway B (see *Scheme 83*). A sufur–tin σ-bond of stannyl sulphides adds to arynes without an added catalyst to provide a variety of 2-(arylthio)arylstannanes (*Scheme 94*).[123] In an analogous way, arynes are readily inserted into the nitrogen–silicon σ-bond of aminosilanes to produce diverse 2-silylaniline derivatives (*Scheme 94*).[124] Interestingly, with 3-phenyl- and 3-methoxy-substituted arynes exclusive formation of one regioisomer could be explained by unfavorable steric repulsion between the substituent in the arynes and the incoming nucleophile.



Scheme 94

These authors have also disclosed the convenient acylation of aromatic rings *via* the insertion reaction of arynes into carbonyl–halogen σ-bonds, where the acyl moieties are incorporated into the *ortho*-positions to the halogen, leading to aryl ketones or benzoates, whose regioselective synthesis by conventional Friedel-Crafts acylation would be difficult (*Scheme 95*).[125] As



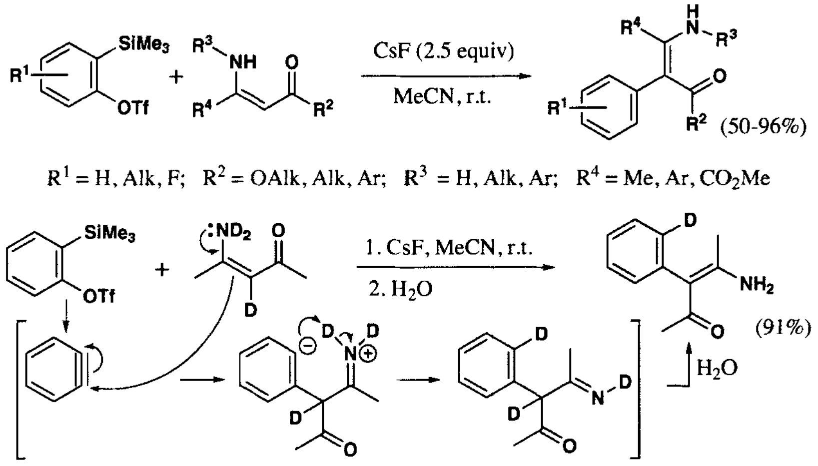
Scheme 95

expected, 4-methylbenzyne afforded a mixture of two regioisomers, whereas the reaction of 3-methoxybenzyne produced solely the regioisomer bearing the chlorine atom at the *meta* position to the methoxy group, which implies that the halogen atom in an acid halide acts as a nucleophilic site in this process.

b) Carbon-centered Nucleophiles

i) Formation of Monosubstituted Arenes *via* Pathway A

Although amino groups are able to add to arynes (see *Schemes 84-87*), the attempt of *N*-arylation of β-enamino esters and ketones with benzyne did not afford the corresponding *N*-arylated products and instead reaction occurred at the α-carbon to generate the C-arylation product in high yields. Deuterium labelling experiments support that the failure of aryne to insert into the α-carbon and carbonyl σ-bond of the enamines is probably due to a rapid intramolecular proton transfer to the initially formed zwitterionic species (*Scheme 96*).[126]



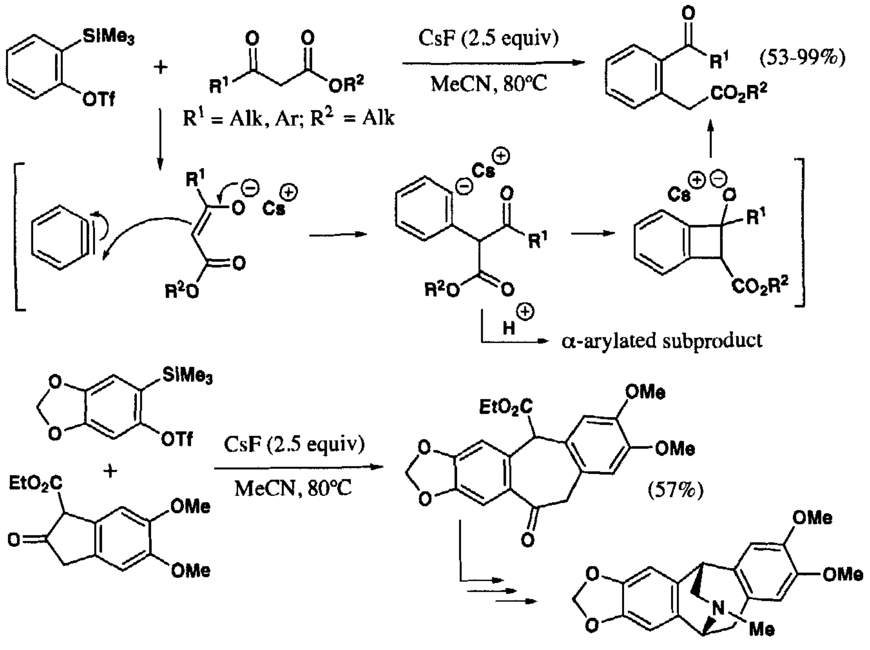
R^1 = H, Alk, F; R^2 = OAlk, Alk, Ar; R^3 = H, Alk, Ar; R^4 = Me, Ar, CO_2Me

Scheme 96

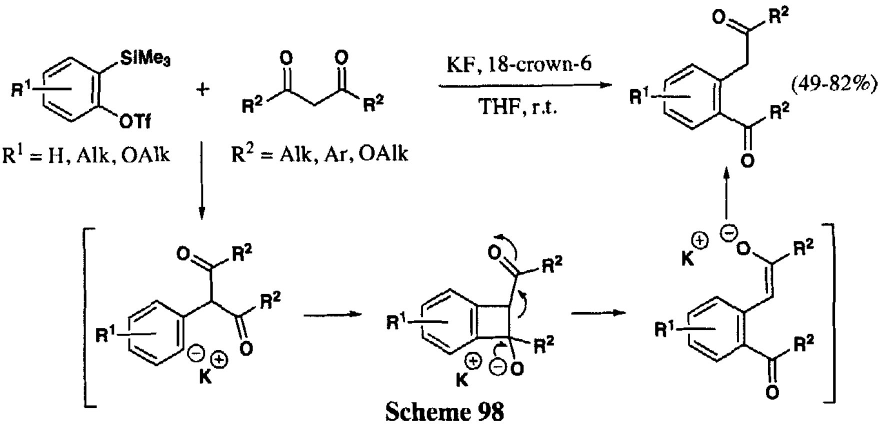
ii) Formation of Disubstituted Arenes *via* Pathway B

β-Dicarbonyl compounds turned out to be appropriate reagents for the insertion reaction of arynes into their active methylene (nucleophile)-carbonyl (electrophile) σ-bonds. The first mild and direct aryne insertion into a C–C σ-bond was described by Stoltz and co-workers who developed the acyl-alkylation of arynes with β-ketoesters through the reaction cascade shown in *Scheme 97*. Notably, cyclic β-ketoesters can be expanded to generate medium-sized carbocycles although lower yields were obtained due to competitive formation of the α-arylation product.[127] These authors have also developed a convergent synthesis of *Amurensinine* that takes advantage of the above methodology to build the benzosuberone core structure of the *isopavines* (*Scheme 97*).[128]

A similar insertion reaction of β-diketones was shortly reported thereafter by the Yoshida and Kunai's research group. Again, a nucleophilic attack of an *in situ*-generated enolate to the aryne to produce an aryl anion with subsequent intramolecular attack to the carbonyl moiety, followed by ring expansion of the resulting benzocyclobutene, was proposed to account for the formation of the final products (*Scheme 98*).[129] However, symmetric β-dicarbonyl compounds are always used, probably to avoid mixtures of isomers.

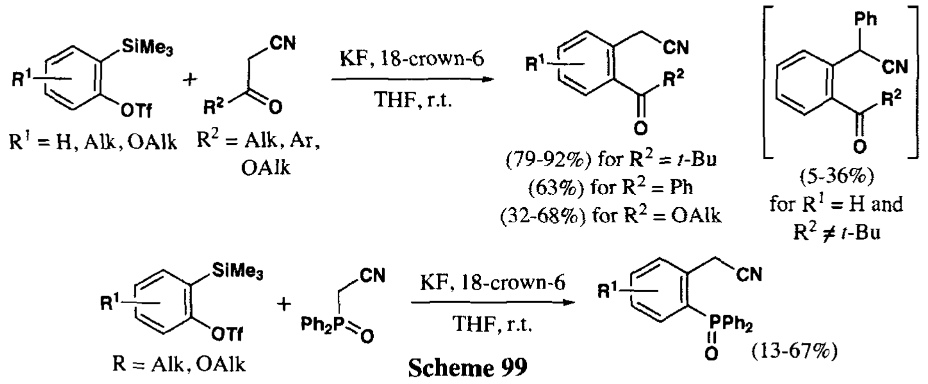


Scheme 97



Scheme 98

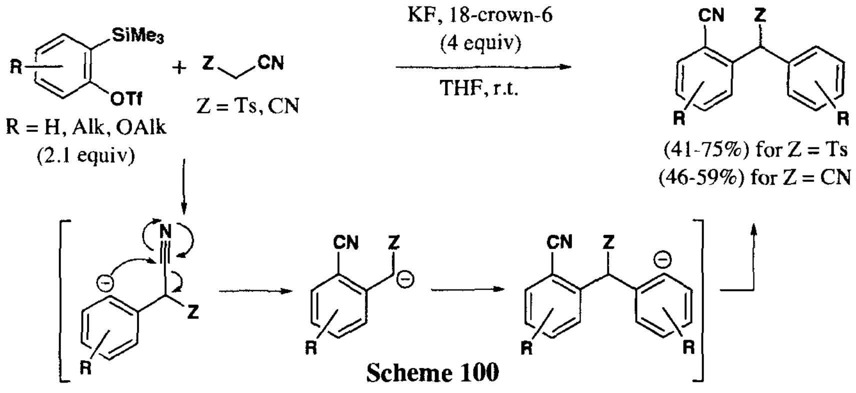
The same authors have extended this aryne insertion methodology to α-cyanocarbonyl compounds allowing the simultaneous introduction of carbonyl and cyanomethyl moieties into 1,2-positions of an aromatic skeleton (*Scheme 99*).[130] However, for compounds other than pivaloylacetonitrile the formation of a 2:1 coupling product which bears an extra phenyl group at the benzylic position, moderate yields were obtained. In this context, cyanomethyldiphenylphosphine oxide was found to behave in an analogous way leading to a carbon-phophorous σ-bond addition reaction to arynes with modest yields (*Scheme 99*).[131] In contrast, reaction of benzyne with ethyl (diphenylphosphinyl)acetate was not synthetically useful as it occurred at both methylene-phosphorous and methylene carbonyl bonds.



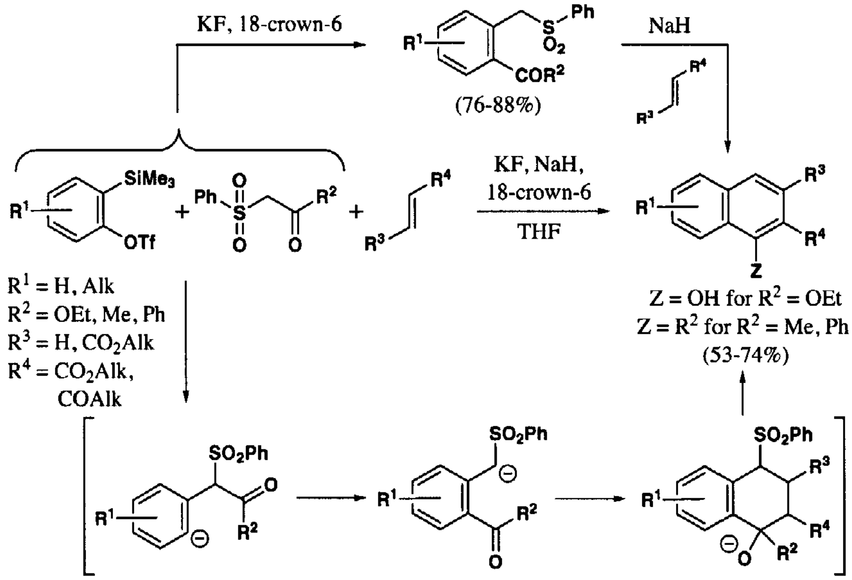
Scheme 99

This research group has also described that two molar amounts of arynes couple with *p*-toluenesulfonylacetonitrile and malononitrile resulting in the direct assembly of diverse diarylmethane skeletons. The overall reaction enables three C–C and one C–H bond forming processes to occur all at once (*Scheme 100*).[132]

By using β-keto sulfones as Nu–E (see *Scheme 83*) in this type of chemistry, Huang and co-workers have successfully trapped the intermediate proposed benzyl anion with electrophiles. They have developed a three-component reaction of arynes, β-keto sulfones, and Michael-type acceptors, providing an efficient method for the preparation of polysubstituted naphthols and polysubstituted naphthalenes (*Scheme 101*).[133] The same final products were obtained by the reaction of *o*-keto benzyl sulfones with Michael-type acceptors in the presence of sodium hydride supporting the postulated pathway.



Scheme 100

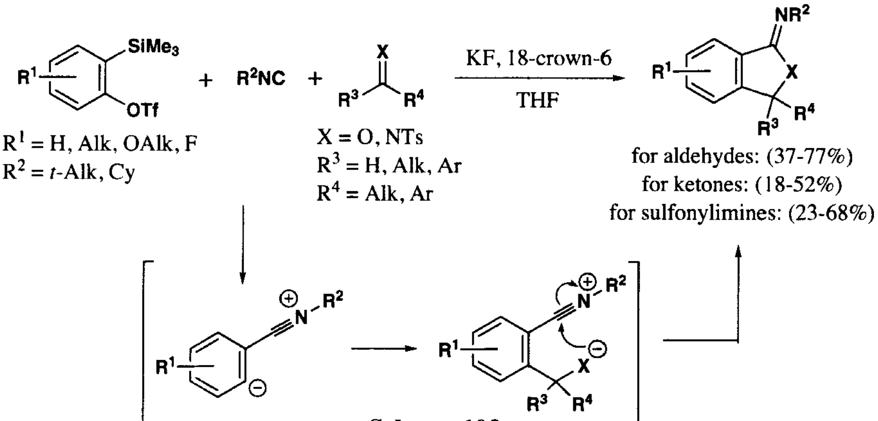


Scheme 101

iii) Formation of Disubstituted Arenes *via* Pathway C

Besides the use of a Nu–E (see *Scheme 83*) for the introduction of two functionalities into both ends of arynes *via* insertion reactions into a nucleophilic-electrophilic σ-bond, similar double functionalization could be also achieved by three-component couplings through the capture of the zwitterion with a third component (electrophile) (*Scheme 83*, path C). Yoshida, Kunai and co-workers have developed the first examples of this methodology using neutral nucleophiles. A variety of aldehydes, ketones, benzoquinones, and sulfonylimines are able to couple with arynes and isocyanides, giving iminodihydroisobenzofuran or iminoisoindoline derivatives of structural diversity in a straightforward manner. The reaction is proposed to commence by a nucleophilic addition of an isocyanide to the arynes, followed by a nucleophilic attack of the resulting zwitterions to an electrophile. The resulting species then undergo an intramolecular cyclization to provide the final products (*Scheme 102*).[134]

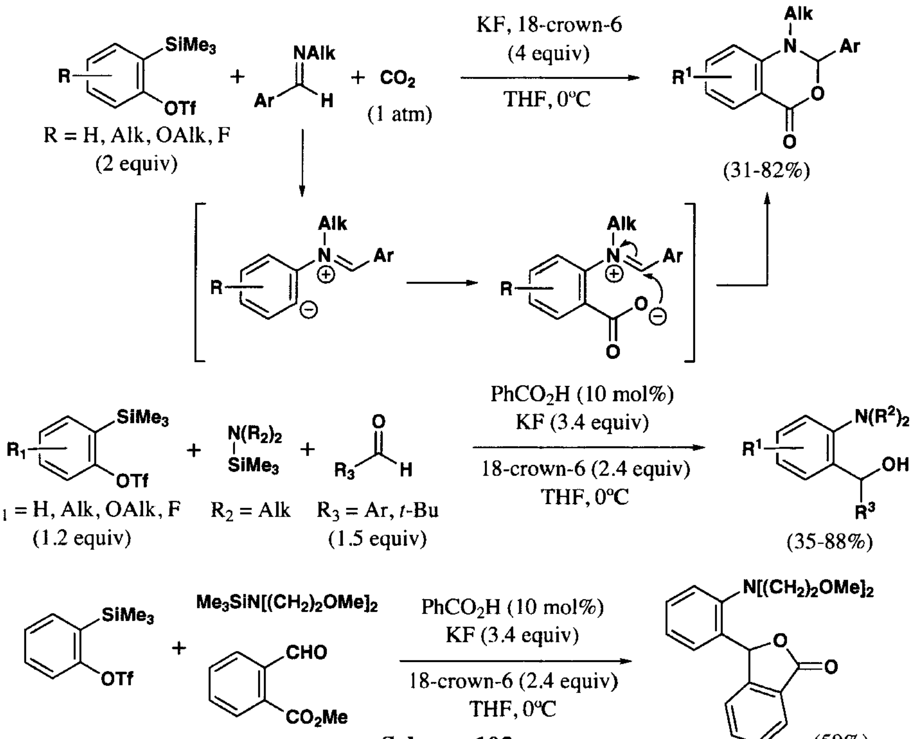
These authors have also shown that the zwitterions arising from nucleophilic addition of imines to arynes are able to capture CO_2, giving rise to benzoxazinone derivatives (*Scheme 103*).[135] Later on, they have developed a new three-component coupling of arynes, aminosilanes, and aldehydes that allows the incorporation of diverse amino and hydroxymethyl groups into 1,2-positions of aromatic rings. Moreover, this coupling, in combination with intramolecular cyclization, enables the synthesis of phthalide skeletons (*Scheme 103*).[136]



Scheme 102

V. TRANSITION METAL-CATALYZED REACTIONS OF ARYNES

Although stoichiometric reactions of zirconium-benzyne and nickel-benzyne complexes have been studied and some useful synthetic applications have been developed,[137] this section will be devoted to such reactions of arynes that are catalyzed by transition metal complexes. In 1998, Guitián and co-workers disclosed the palladium-catalyzed trimerization of arynes, showing

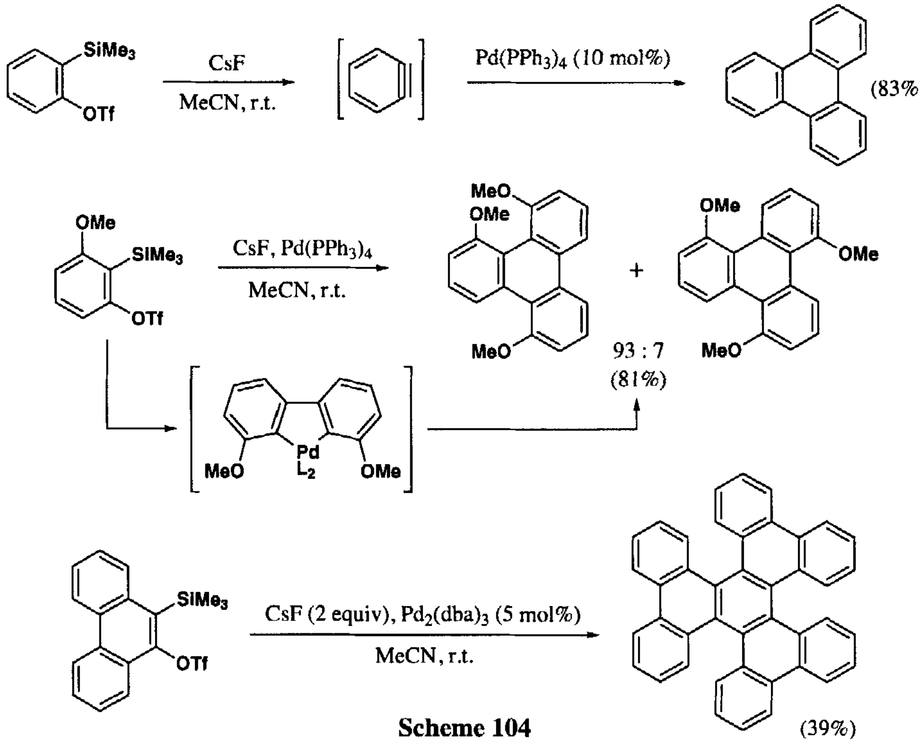


Scheme 103

that the use of an appropriate aryne precursor and a catalyst allows arynes to undergo transition metal-catalyzed transformations selectively.[138] Since this pioneering work, a variety of catalytic reactions of arynes has been developed to offer a novel entry for the synthesis of substituted arenes, which are difficult to access by conventional methods. The success of metal-catalyzed reactions involving arynes does not only depend on the choice of a suitable metal complex as catalyst, but also on the generation of the aryne in a controlled way under mild reaction conditions and, for this purpose, fluoride-induced decomposition of *o*-(trimethylsilyl)aryl triflates is an excellent method.

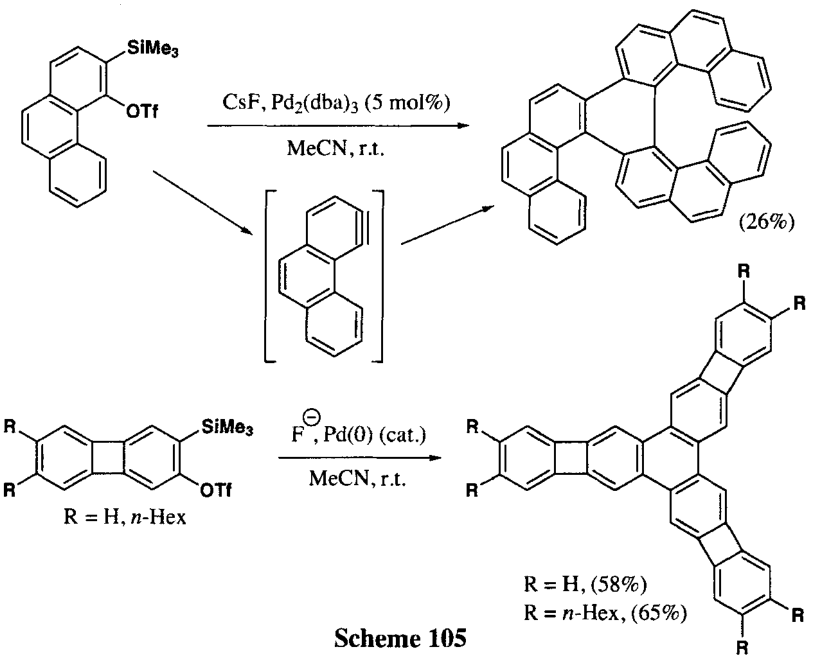
1. Cyclotrimerization of Arynes

Over the last ten years, Guitián, Pérez, Peña and co-workers have developed methods for the preparation of polycyclic arenes based on the palladium-catalyzed cyclotrimerization of arynes.[139] Initially they found that benzyne, generated in the presence of catalytic amounts of a palladium complex, afforded triphenylene in high yield. Moreover, high regioselectivity was found in the cyclotrimerization of 3-methoxybenzyne (*Scheme 104*).[138] The extension of this formal [2+2+2] cycloaddition reaction to 1,2-didehydronaphthalene and 9,10-didehydrophenanthrene has enabled these authors to synthesize sterically congested polycyclic aromatic hydrocarbons (PAHs) (*Scheme 104*).[140]



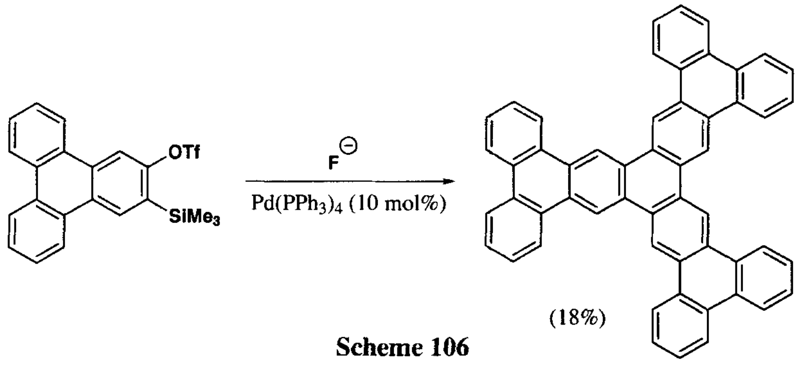
Scheme 104

This research group has also applied this methodology to the synthesis of a configurationally stable double helicene from 3,4-didehydrophenanthrene,[141] and to the preparation of compounds related to the [*N*] phenylenes from 2,3-didehydrobiphenylene (*Scheme 105*).[142]



Scheme 105

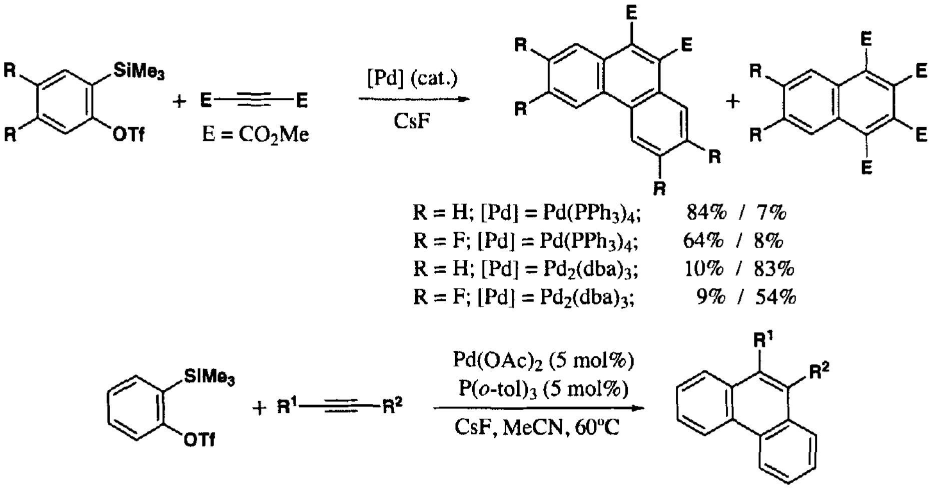
Although with moderate yields, in this field these authors have also synthesized extended triphenylenes by palladium-catalyzed formal [2+2+2] cycloadditions of didehydrotriphenylenes, generated from the corresponding 3-(trimethylsilyl)triphenylenyl 2-triflates (*Scheme 106*).[143]



Scheme 106

2. Co-cyclization of Arynes with Alkynes

The palladium-catalyzed cocyclization of arynes with alkynes was reported by Guitián's[144] and Yamamoto's[145] groups in 1999. The first group showed that arynes can undergo selective palladium-catalyzed cocyclotrimerization with dimethyl acetylenedicarboxylate (DMAD), and that by appropriate choice of the catalyst the reaction can be selectively directed either toward the cocyclization of one molecule of aryne with two molecules of alkyne or to the reaction of two molecules of aryne with one molecule of alkyne (*Scheme 107*).[144] Under the experimental conditions used by Yamamoto and co-workers, the phenanthrene derivatives were exclusively obtained, regardless of the electronic nature of the alkynes (*Scheme 107*).[145]

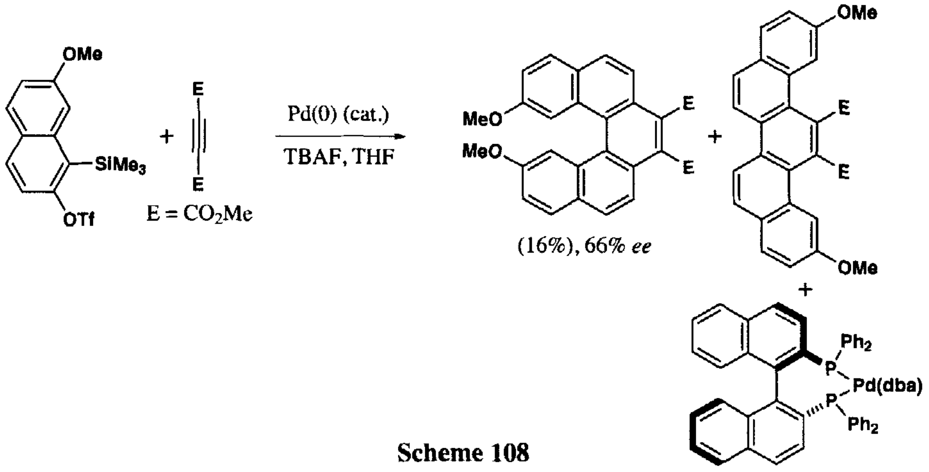


R = H; [Pd] = Pd(PPh$_3$)$_4$; 84% / 7%
R = F; [Pd] = Pd(PPh$_3$)$_4$; 64% / 8%
R = H; [Pd] = Pd$_2$(dba)$_3$; 10% / 83%
R = F; [Pd] = Pd$_2$(dba)$_3$; 9% / 54%

$R^1 = R^2$ = Alk; (59-67%)
R^1 = Ph; R^2 = Alk; (63-67%)
R^1 = Ph; R^2 = COCH$_3$ (76%)

Scheme 107

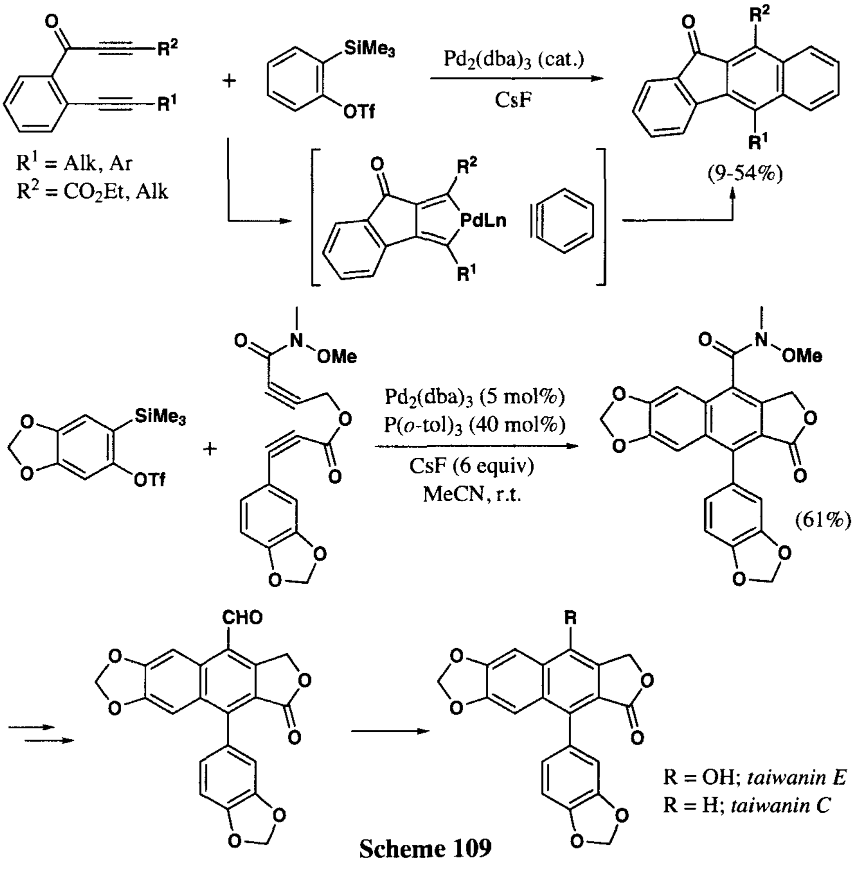
Guitián, Pérez and co-workers have described the first enantioselective version of the Pd-catalyzed cocyclization of arynes with alkynes. Using TBAF as the fluoride source, THF as solvent, and a preformed Pd-(BINAP) complex, a non-racemic 9,12-dimethoxypentahelicene could be isolated in a modest 16% yield with reproducible enantiomeric excess of 66-67% ee, among other cycloaddition products (*Scheme 108*).[146]



(16%), 66% *ee*

Scheme 108

These authors have also extended the above described "purely" intermolecular cocyclization reactions to a partially intramolecular [2+2+2] cocyclotrimerization of benzyne with diynes. Although with moderate yields, a novel approach to the benzo[*b*]fluorenone nucleus has been developed (*Scheme 109*).[147] Using the same concept, Sato and co-workers have reported the total synthesis of the natural arylnaphthalene lignans *taiwanins C* and *E* through a Pd-catalyzed [2+2+2] cocyclization of diynes and arynes as the key step (*Scheme 109*).[148]

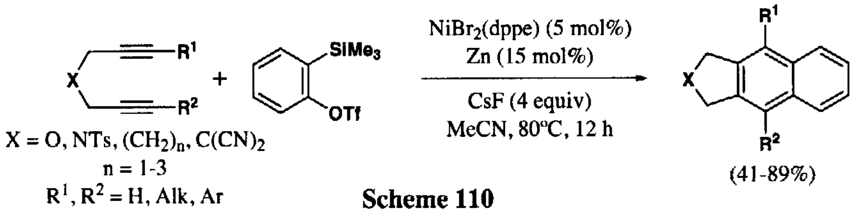


Scheme 109

Also in this context, Cheng and co-workers have reported the first example of a nickel-catalyzed [2+2+2] cocyclotrimerization of arynes with diynes. Excellent tolerance of functional groups and fused-ring sizes was found, providing an efficient method for the synthesis of naphthalene derivatives in moderate to good yields (*Scheme 110*).[149]

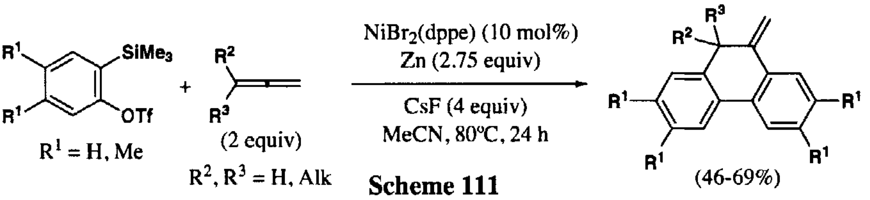
3. Co-cyclization of Arynes with Alkenes and Allenes

The first example of co-cyclization of two arynes with an allene was reported by Cheng and co-workers. The $NiBr_2$(dppe)-Zn system catalyzed this process leading to 10-methylene-9,10-dihydrophenanthrenes in moderate to good yields. Remarkably, the reaction is highly selective as only the internal double bond of the allenes is involved (*Scheme 111*).[150]



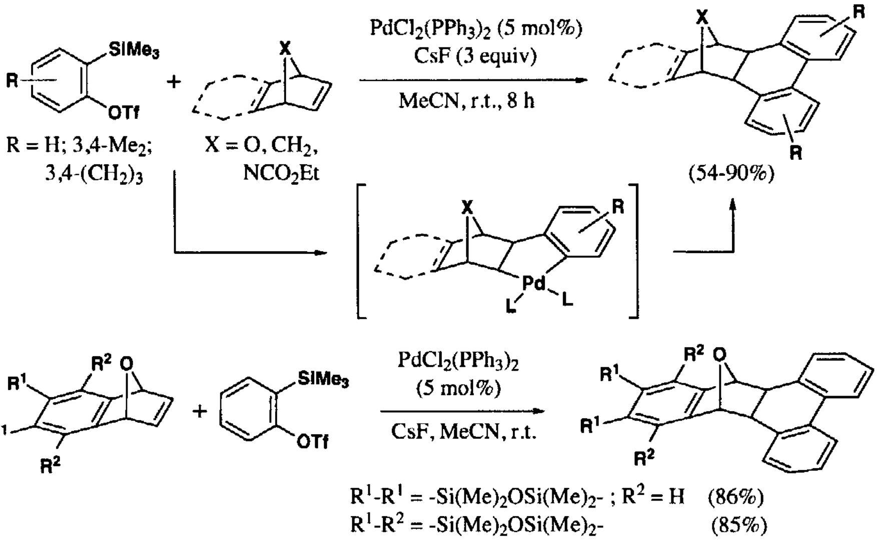
Scheme 110

These authors have also demonstrated the [2+2+2] cocyclization of two arynes with bicyclic alkenes, yielding the norbornane anellated 9,10-dihydrophenanthrene moiety in good yields (*Scheme 112*).[151] The catalysis is likely initiated by the reaction of Pd(0) with bicyclic alkene and benzyne to form the palladacycle shown in *Scheme 12*. A second benzyne insertion



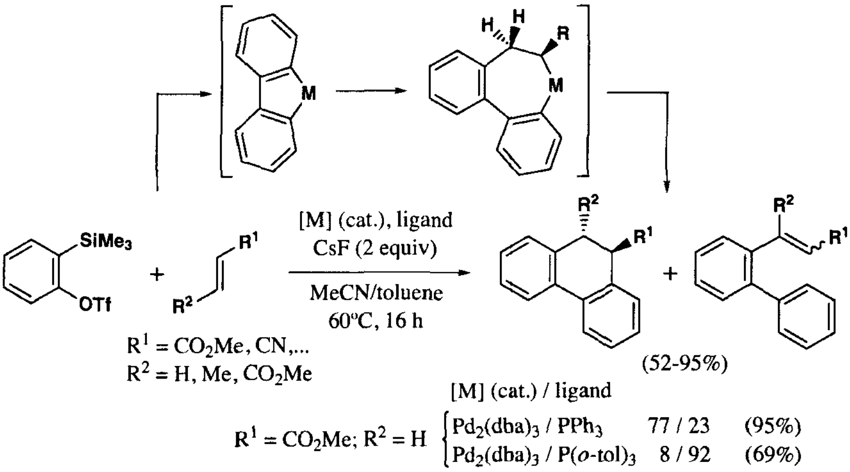
Scheme 111

and subsequent reductive elimination yields the final product and regenerates the Pd(0) catalyst. Similarly, Lee and co-workers have reported that benzobisoxadisilole fused bicyclic alkenes, previously prepared by these authors using benzyne-mediated [4+2] cycloaddition reactions,[48] could also co-cyclize with benzyne with high *exo*-stereoselectivity (*Scheme 112*).[152]



Scheme 112

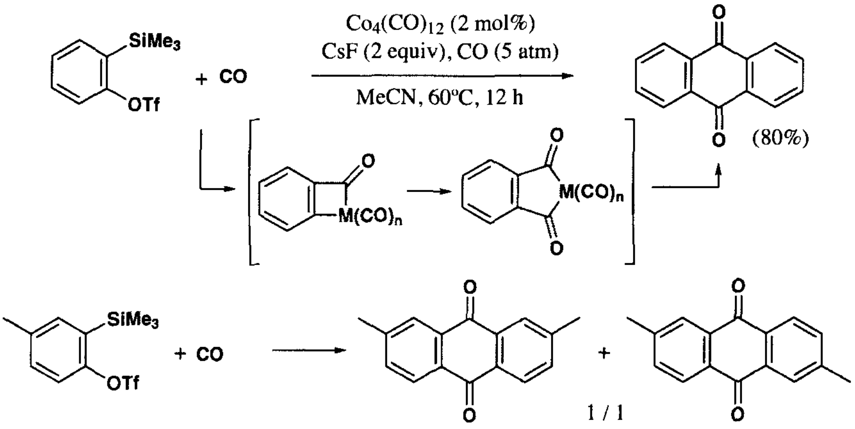
Peña, Pérez and co-workers have also shown that arynes can undergo palladium- and nickel-catalyzed cocylization with acyclic electron-deficient alkenes, selectively affording dihydrophenanthrenes or *o*-olefinated biaryls depending on the catalyst used (*Scheme 113*).[153] For the reaction of disubstituted alkenes, nickel-based catalysts turned out to be more efficient than palladium complexes. The most plausible mechanism involves the formation of a metallacycle derived from the coordination of two benzynes to the metal. Then, insertion of the alkene would lead to a metallacycloheptadiene, which could evolve in two ways affording the final obtained products (*Scheme 113*).



Scheme 113

4. Co-cyclization of Arynes with Carbon Monoxide

The first example of transition-metal catalyzed carbonylation reactions of benzyne was due to Chatani, Murai and co-workers, who found that a cobalt complex was active for this type of process. The formation of the anthraquinone derivatives is consistent with the intermediacy of the metallacycles shown in *Scheme 114* and so, the incorporation of the second benzyne

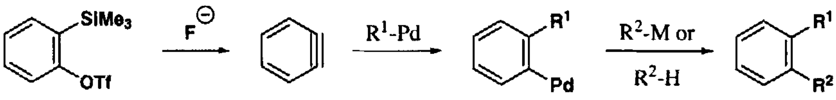


Scheme 114

followed by reductive elimination affords the final product. Mixtures of regioisomers were obtained using 3-methoxybenzyne and 4-methylbenzyne.[154]

5. *Intermolecular Carbopalladation of Arynes*

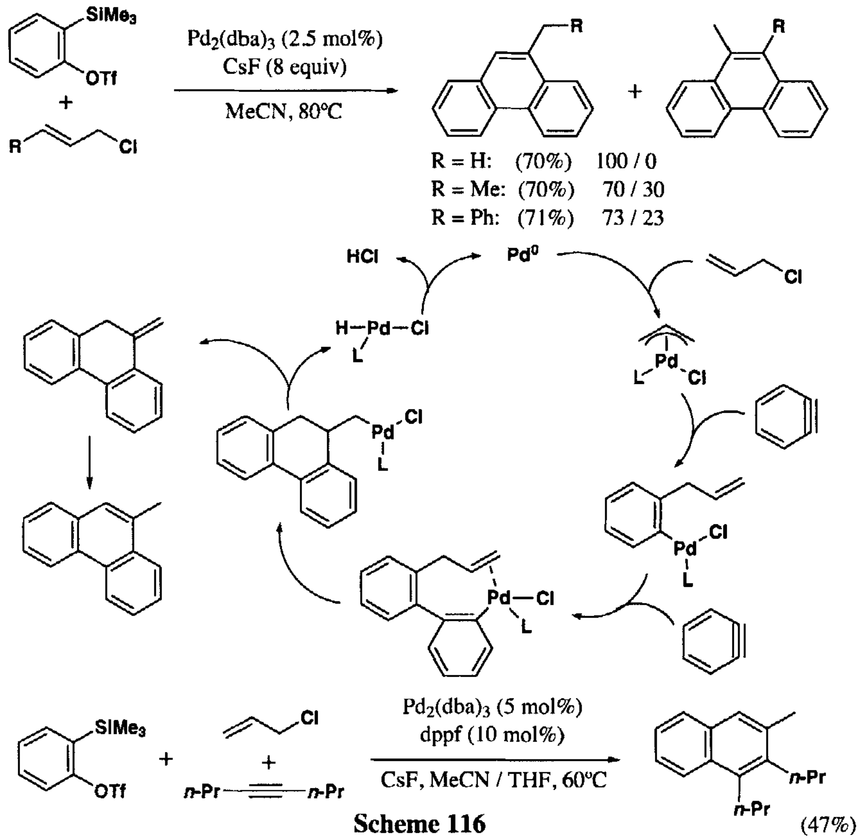
The intermolecular carbopalladation of arynes stands out as a powerful methodology for the construction of diverse 1,2-functionalized arenes through multicomponent coupling processes. *In situ* generated arynes can undergo carbopalladation with an organopalladium species to produce an arylpalladium intermediate. Coupling with a third component gives the 1,2-functionalized benzene (*Scheme 115*).



Scheme 115

a) Carbopalladation of Arynes by π-Allylpalladium and Related Complexes

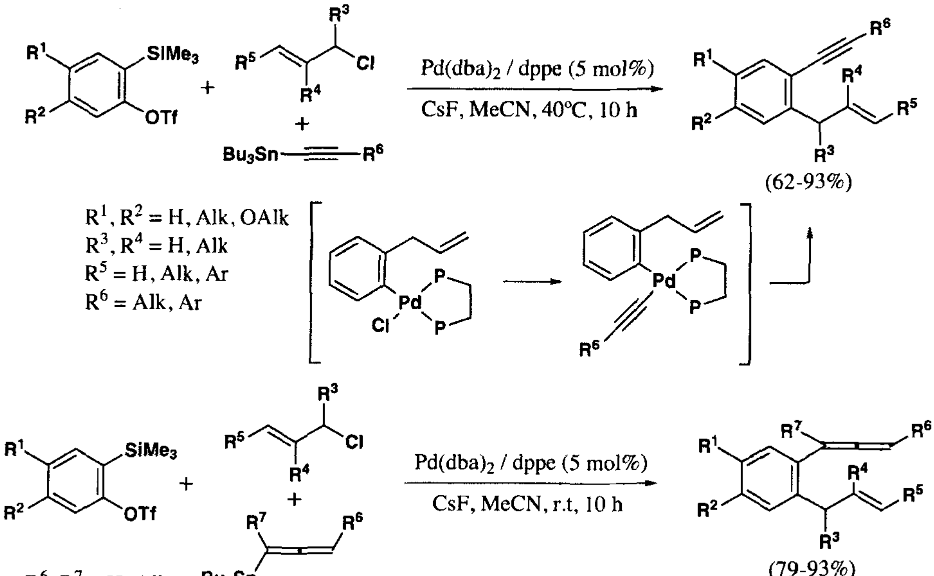
Yamamoto and co-workers have established that π-allylpalladium species are very effective for the intermolecular carbopalladation of arynes and so, the palladium-catalyzed reaction of allyl chorides with benzyne produces phenanthrene derivatives. A plausible mechanism for this unprecedented intermolecular benyne-benzyne-alkene insertion reaction is also shown (*Scheme 116*).



Scheme 116

In the same way, the controlled insertion of benzyne-alkyne-alkene was also successfully carried out under slightly modified conditions to produce naphthalene derivatives (*Scheme 116*).[155]

Using the carbopalladation of benzynes by a π-allyl palladium complex as the key step, Cheng and co-workers have developed some interesting palladium-catalyzed three-component reactions of arynes. The employment of alkynyl- or allenylstannanes, in conjunction with allylic chorides and a benzyne precursor, has allowed the development of useful allylalkynylation[156] and allylallenylation[157] reactions of benzynes, respectively (*Scheme 117*). Good to excellent yields of the corresponding 1-allyl-2-alkynylbenzene or 1-allyl-2-allenylbenzene derivatives are obtained. With respect to the mechanism, a transmetallation of the corresponding stannane with the initially aryl palladium intermediate (see *Scheme 116*), and subsequent reductive elimination affords the final products (*Scheme 117*).

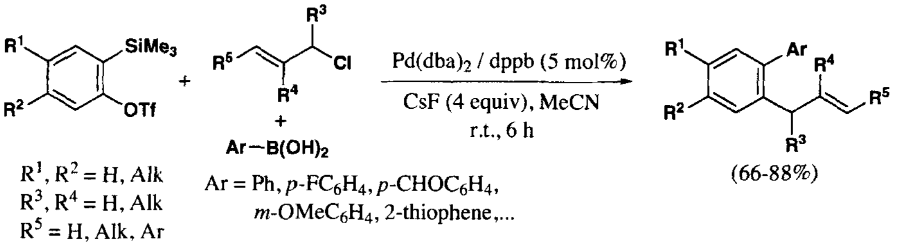


R^1, R^2 = H, Alk, OAlk
R^3, R^4 = H, Alk
R^5 = H, Alk, Ar
R^6 = Alk, Ar

R^6, R^7 = H, Alk

Scheme 117

The same research group reported that aryl organometallic reagents can also participate in this type of three-component reactions with allyl halides and arynes. They found that a benzyne carbopalladated by a π-allylpalladium intermediate can be terminated efficiently with arylboronic acids affording *o*-substituted biaryl derivatives (*Scheme 118*). The addition of a



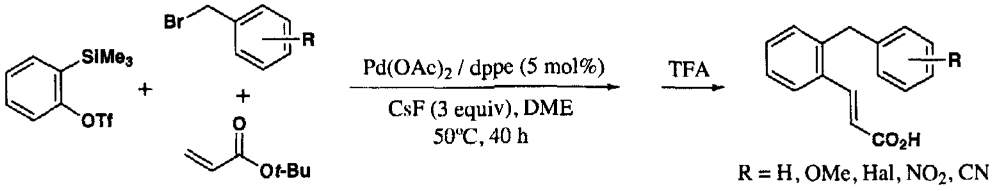
R^1, R^2 = H, Alk
R^3, R^4 = H, Alk
R^5 = H, Alk, Ar

Ar = Ph, p-FC_6H_4, p-$CHOC_6H_4$, m-$OMeC_6H_4$, 2-thiophene,...

Scheme 118

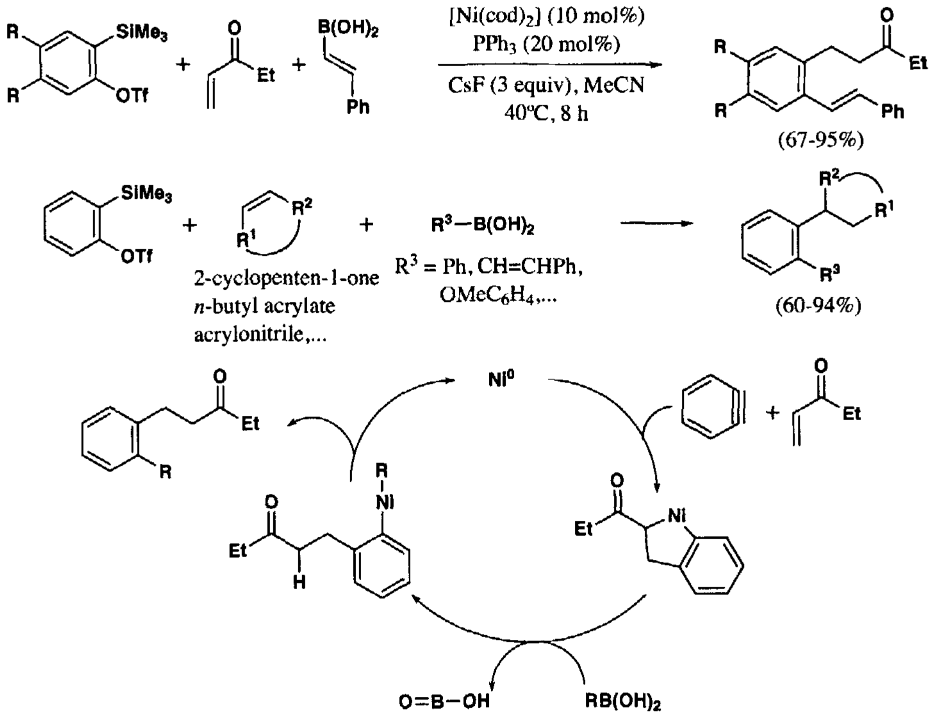
bidentate phosphine ligand is required for the reaction to proceed with high yield. Whereas the allylation of benzyne by cinnamyl chloride is highly regioselective, a mixture of regioisomers was obtained when 1-chloro-but-2-ene or 3-chloro-but-1-ene were used.[158]

Interestingly, Greaney and co-workers have developed a new benzyne three-component coupling using benzyl bromides as the initial carbopalladation electrophile, as alternatives to simple allyl chlorides, and introducing the Heck reaction to capture the arylpalladium intermediate. High yields of benzylphenyl derivatives were obtained using *t*-butyl acrylate and a variety of benzyl bromides (*Scheme 119*).[159]



Scheme 119

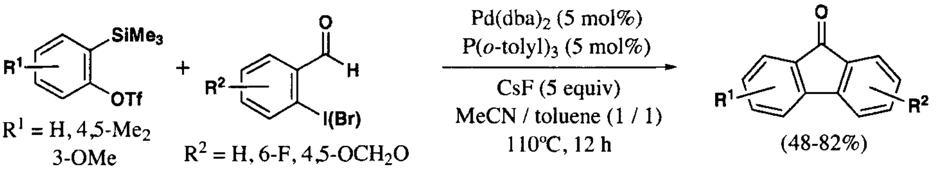
Cheng and co-workers have demonstrated an unprecedented nickel-catalyzed three-component coupling of arynes, enones, and boronic acids. This reaction works well with both acyclic and cyclic enones, but that the process fails with other soft organometallic reagents based on tin and silicon as well as with the pinacol ester of the boronic acid. The boronic acid was crucial for the success of this reaction acting as a proton source and as a carbon nucleophile (*Scheme 120*).[160]



Scheme 120

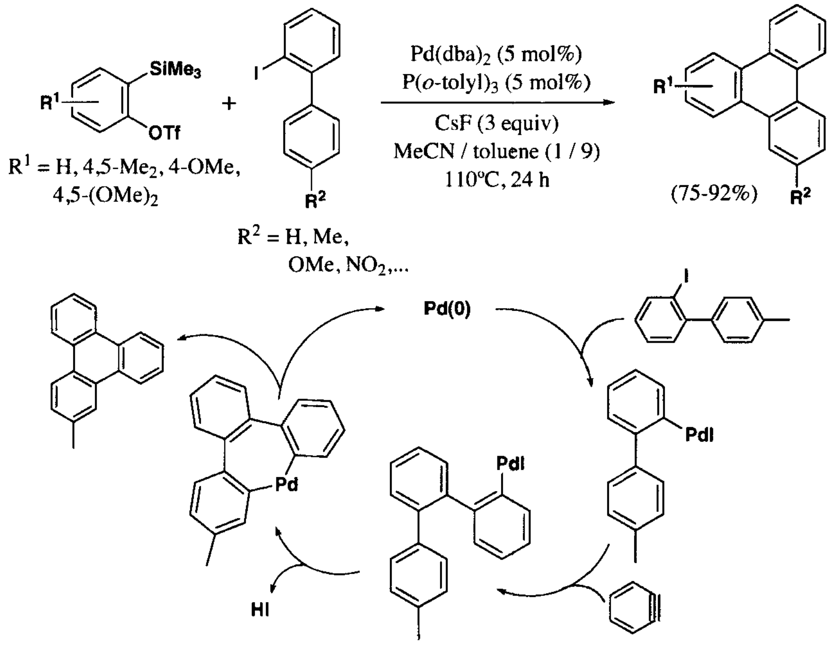
b) Carbopalladation of Arynes by Arylpalladium Complexes

Although the palladium-catalyzed annulation of alkynes by aryl halides has proven to be a very efficient method for the synthesis of a wide variety of heterocycles and carbocycles, similar carbopalladation reaction of arynes were unprecedented until Larock and co-workers reported the preparation of fluorenones by annulation of arynes by 2-halobenzaldehydes (*Scheme 121*).[161]



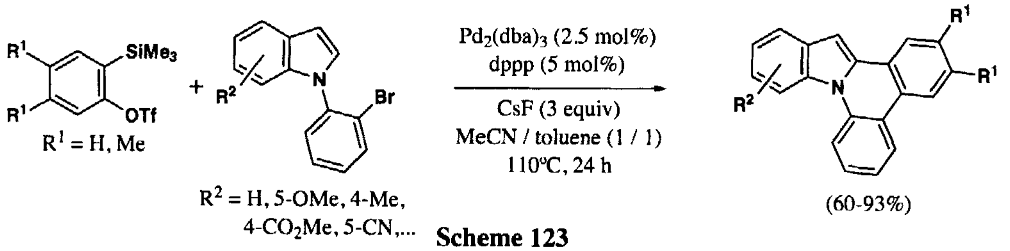
Scheme 121

These authors have also found that 2-halobiaryls and related vinylic halides react with arynes under Pd catalysis to generate the corresponding functionalized triphenylenes in very good yields. Remarkably, the process appears to involve the stepwise coupling of an aryne and an organopalladium species, to generate high yields of cross-coupled products. The most plausible mechanism involves initial oxidative addition of the aryl halide to Pd(0) to generate an arylpalladium intermediate, which then reacts with the aryne to afford a new intermediate that goes on to the product by intramolecular C–H activation and subsequent reductive elimination. An alternative mechanism involving initial oxidative addition of Pd(0) with the aryne as the first step, cannot be ruled out (*Scheme 122*).[162]



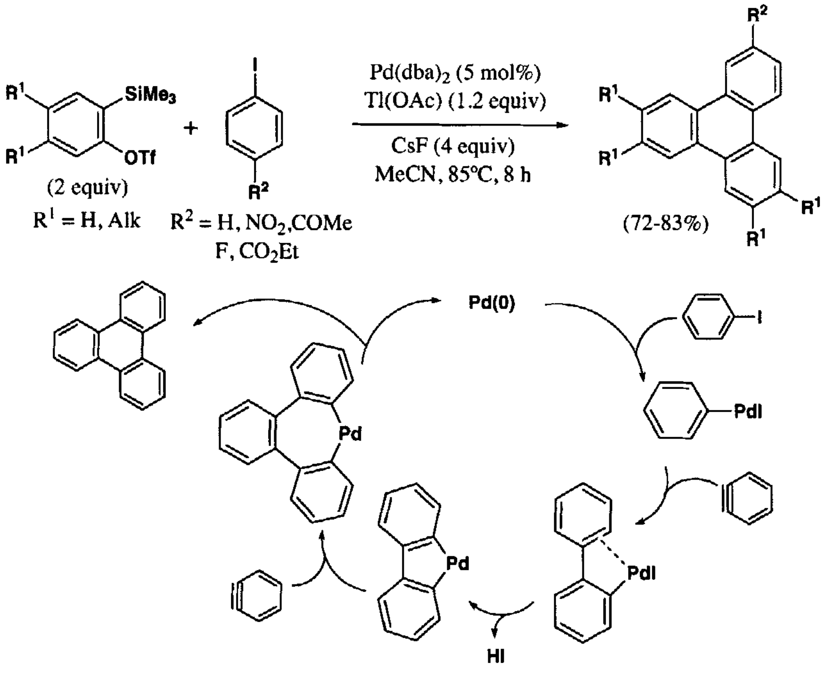
Scheme 122

Closely related to the work of Larock and co-workers is the reported synthesis of indolo[1,2-*f*]phenanthridines from 1-(2-bromophenyl)-1*H*-indoles. With respect to the mechanism, the C–H activation could take place after or before the carbopalladation of the aryne by the initially generated arylpalladium intermediate, from the oxidative addition of Pd(0) to the aryl bromide (*Scheme 123*).[163]



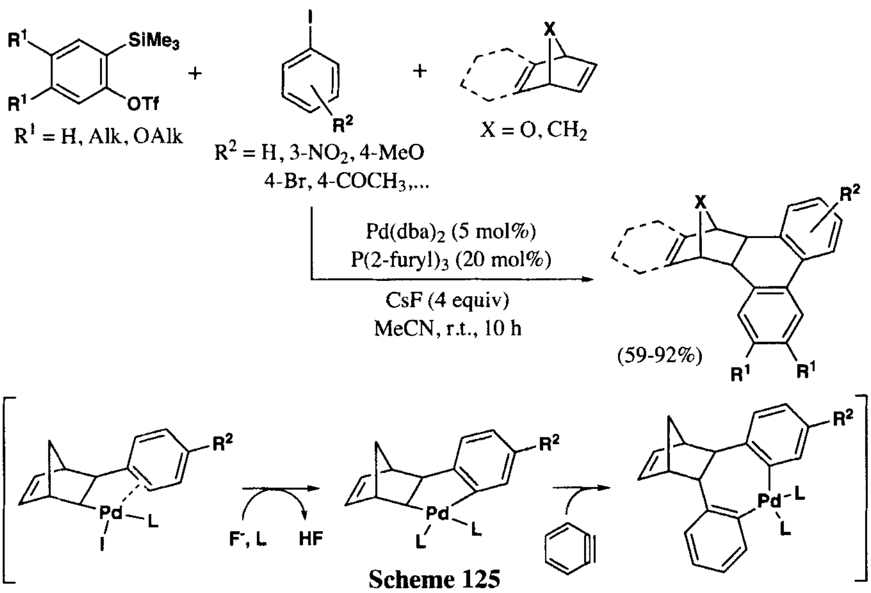
Scheme 123

Cheng and co-workers have shown that arynes can be efficiently employed in the Pd-catalyzed carbopalladation and cyclopalladation sequence directed toward the synthesis of polyaromatic compounds. A careful selection of the reaction conditions is required to undergo cyclopalladation through an intramolecular C–H activation, after the initially carbopalladation of the aryne. The addition of thallium salts is required to obtain reaction conditions useful for various arynes, but their role is not very clear (*Scheme 124*).[164]



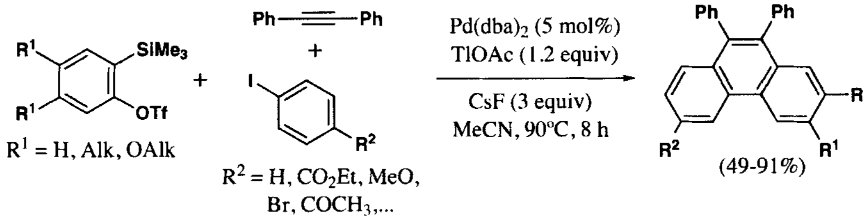
Scheme 124

These authors have explored the possibility of using three different substrates for the benzyne-involved carbocyclization reactions and they have developed a new Pd-catalyzed regioand stereoselective carbocyclization of aryl iodides, bicyclic alkenes, and arynes to give various annulated 9,10-dihydrophenanthrene derivatives. The catalytic reaction involves a facile highly regioselective C–H bond activation promoted by fluoride ion as a key step (*Scheme 125*).[165]



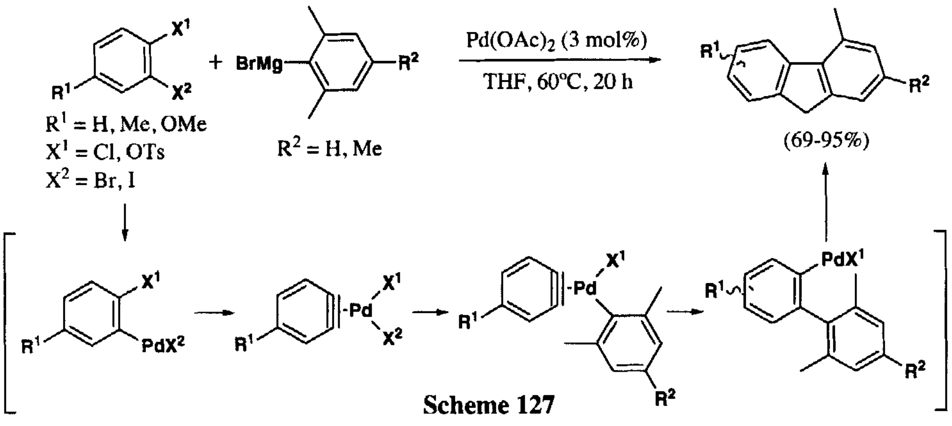
Scheme 125

Moreover, Larock and co-workers have developed a Pd-catalyzed, sequential, three-component cross-coupling of aryl halides with acetylenes and arynes, which affords excellent yields of substituted phenanthrenes. The process appears to involve the stepwise regio- and chemoselective carbopalladation of an internal alkyne and subsequent carbopalladation of the aryne (*Scheme 126*).[166]



Scheme 126

A special case of carbopalladation of arynes by an arylpalladium complex has been reported by Hu and co-workers who have reported a Pd-catalyzed domino reactions of 1-chloro-2-haloarenes and related aryl tosylates with hindered Grignard reagents *via* Pd-associated arynes. They found that this reaction pathway was favoured in the absence of phosphines and NHCs. In these examples, the generated Pd(II)-associated arynes could then undergo transmetallation followed by carbopalladation, which could further undergo intramolecular C–H activation. With substituted starting *o*-dihaloarenes, mixtures of regioisomers were obtained from the carbopalladation of the aryne step (*Scheme 127*).[167]



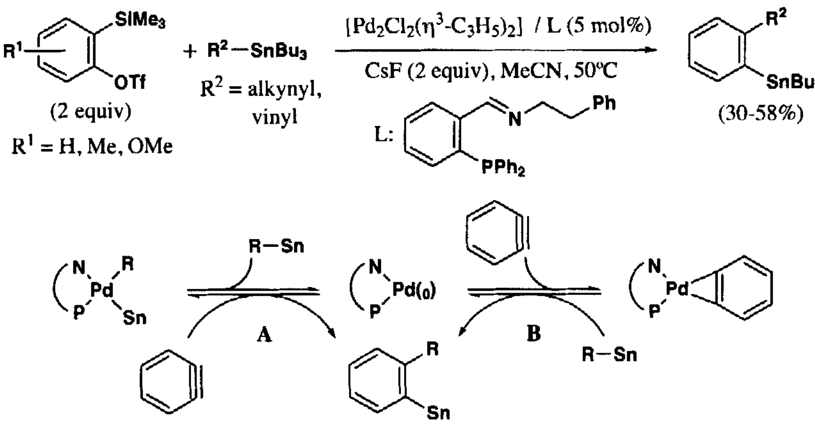
Scheme 127

6. *Catalytic Insertion Reactions of Arynes into σ-Bonds*

Yoshida, Kunai, and co-workers have reported some catalytic addition reactions of an element-element σ-bond to arynes.

a) Carbostannylation of Arynes

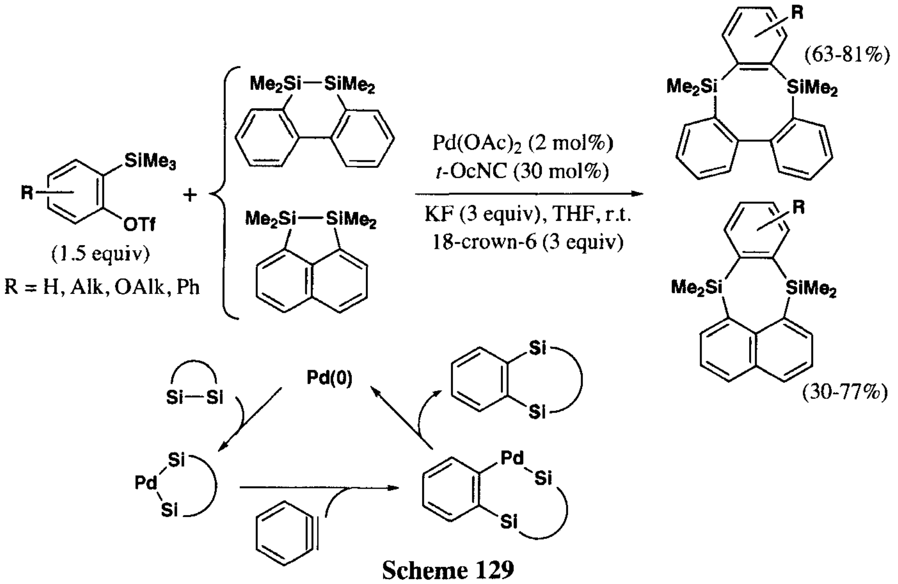
Arynes were found to insert into a C–Sn bond of alkynyl- and vinylstannanes catalyzed by a palladium-iminophosphine complex to afford *o*-substituted arylstannanes. Substituted non-symmetric arynes also underwent carbostannylation affording mixtures of regioisomers. The most plausible catalytic cycle (**A**) would start with an oxidative addition of the organostannane to the Pd(0) complex. Subsequent insertion of the aryne into the C–Pd or Sn–Pd bond followed by reductive elimination affords the product (*Scheme 128*).[168] However, a density functional study on this process showed that the catalytic carbostannylation reaction takes cycle (**B**).[169]



Scheme 128

b) Bissilylation of Arynes

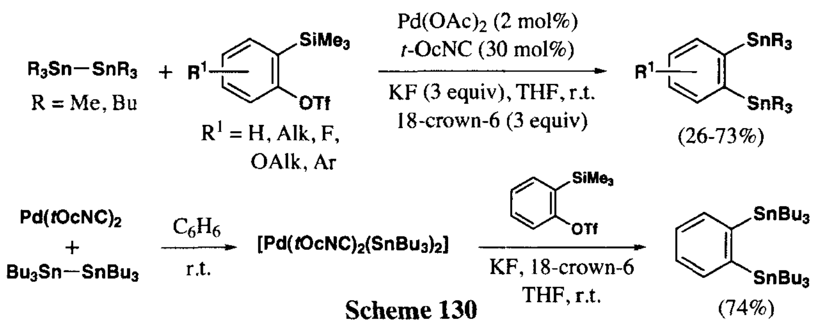
The same research group has demonstrated that the addition reactions of the Si–Si σ-bonds to arynes are catalyzed by a Pd-1,1,3,3-tetramethylbutyl isocyanide complex to give diverse 1,2-disilylated arenes. Although the formation of triphenylene as a byproduct implies that Pd(0) might first interacts with the aryne, the most likely mechanism involves initial oxidative addition of the Si–Si bond to Pd(0). Subsequent insertion of the aryne into the Si–Pd bond and further reductive elimination provides the bissilylation product (*Scheme 129*).[170]



Scheme 129

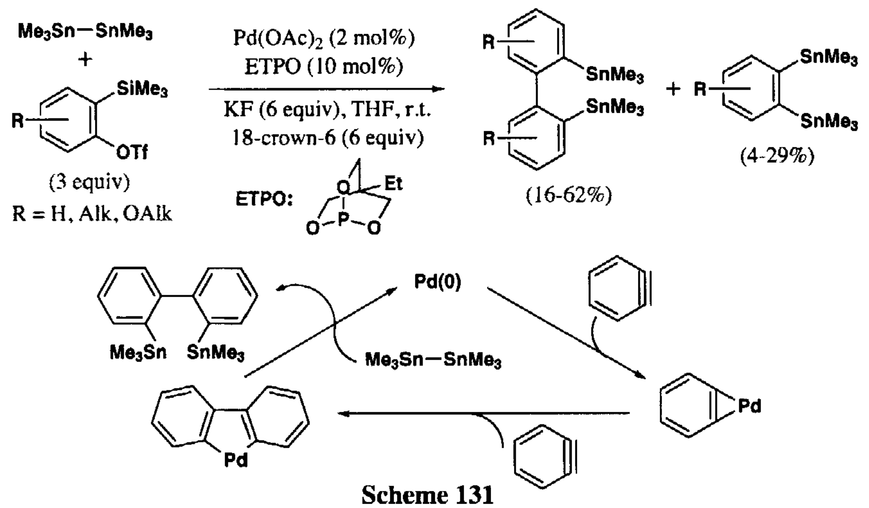
c) Distannylation of Arynes

They have also accomplished the distannylation of arynes, and cyclohexynes, under the catalysis of a Pd–*t*-octyl isocyanide complex. Diverse 1,2-distannylarenes, which could behave as bis(anion) equivalents, have been synthesized. In addition, the catalytic pathway, which includes oxidative addition of a distannane to Pd(0), has been confirmed by the stoichiometric reaction (*Scheme 130*).[171]



Scheme 130

Kunai, Yoshida, and co-workers have also disclosed the first example of an insertion reaction of two molar amounts of arynes into a Sn–Sn σ-bond, which is efficiently catalyzed by a Pd-phophite complex. In this way, diverse 2,2'-distannylbiaryls can be obtained straightforwardly. The major reaction pathway should be initiated by formation of a palladacyclopropene from Pd(0) and an aryne. Subsequent interaction with a second aryne gives a new Pd species, which further reacts with the distannane. Minor amounts of the distannylation products were also obtained (*Scheme 131*).[172]



Scheme 131

CONCLUSIONS

Although arynes have a long history, their synthetic utility has been qualitatively increased in the last few years as a result of mild methods devised for their generation. For the success of the new synthetic methodologies using arynes as intermediates, the generation of arynes in a controlled manner under mild reaction conditions has resulted to be a key feature. The fluoride-induced decomposition of *o*-(trimethylsilyl)aryl triflates is an excellent method, as the rate of aryne generation can be controlled by modifying the solubility of the fluoride source, and the required neutral, room temperature conditions are compatible with transition-metal-catalyzed reactions as well as with the presence of a wide variety of nucleophiles in the reaction media. Nevertheless, sometimes a large excess of these expensive *o*-(trimethylsilyl)aryl triflates is required to achieve good yields and so, it would be synthetically advantageous to generate arynes from readily available, cost-effective starting materials. In my opinion, a rapid expansion of the use of arynes in organic synthesis will probably take place in the near future. Further developments regarding the range of nucleophiles to be coupled with arynes leading to novel multicomponent reactions, as well as new transition-metal catalyzed processes, including enantioselective versions of known reactions, are expected to be reported shortly.

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