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The use of arynes in organic synthesis

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1. Introduction

This review is an update of aryne chemistry and covers the literature from 1990–2002 since early work has already been reviewed extensively.[1] The preceding review covered literature from 1980–1992.[1c] Unlike its predecessor, this review includes the transition metal-catalysed reactions of arynes. The importance of arynes for the synthesis of natural products particularly alkaloids is well illustrated. The term 'arynes' will be used to refer both to derivatives of 1,2-dehydrobenzene (benzyne) and their heterocyclic analogues (heteroarynes). Arynes and heteroarynes are reactive intermediates derived formally by the removal of two adjacent hydrogen atoms from, respectively, an aromatic ring or a heterocyclic aromatic ring. Prototypical examples are *o*-benzyne and 3,4-didehydropyridine (3,4-pyridyne) as depicted in Figure 1.

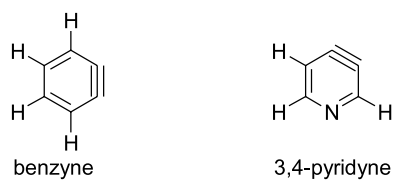

Figure 1. Structures of benzyne and 3,4-pyridyne.

2. Structure and reactivity

In 1953, Roberts' experiments on the conversion of ^{14}C-labeled chlorobenzene with potassium amide to aniline gave strong support to the intermediacy of *o*-benzyne in this and related reactions.[1b] Finally, benzyne was trapped as a

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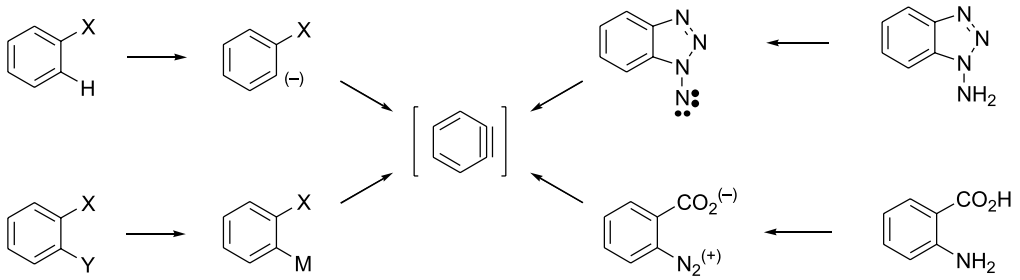


Scheme 1. General methods for the generation of arynes.

stable guest in a hemicarcerand.[2] Additional direct evidence for the existence of *o*-benzyne was provided by the observation of its infrared spectrum,[3] solid-state ^{13}C dipolar NMR spectrum,[4] ^{1}H and ^{13}C NMR in a molecular container[5] and by ultraviolet photoelectron spectroscopy.[6] *o*-Benzyne has been the subject of extensive high-level theoretical studies.[3,7]

The experimental findings and theoretical calculations agree in concluding that benzyne has the general structure as depicted above, in which a degree of triple bond with some diradical character exists between positions 1 and 2. A similar conclusion has been proposed for the heterocyclic analogues.[8]

Even at low temperatures, arynes are extraordinary reactive. Their reactions can be divided into three groups: the pericyclic reactions of arynes; and the nucleophilic additions to arynes; the transition metal-catalysed reactions of arynes.

The pericyclic reactions can be divided into several categories such as the Diels–Alder reactions occurring in an inter- or intramolecular mode; the [2+2] cycloadditions; the 1,3-dipolar cycloadditions; the 1,4-dipolar cycloadditions; and the ene reactions.

Arynes react with practically all kinds of nucleophiles. From a synthetic point of view, the most interesting are the nitrogen-bearing nucleophiles and carbanions.

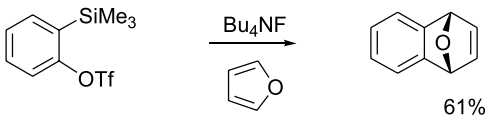
More recently, the transition metal-catalysed reactions of arynes have been studied and particularly those involving palladium. Thus, various polycyclic aromatic hydrocarbons have been prepared through palladium-catalysed co-cyclisation of arynes.

3. Generation of arynes

o-Benzyne is an important reactive intermediate and many studies on its generation and reactions have been undertaken.[1] Because of their extreme reactivity, arynes must be generated in situ. The generation methods most widely used are summarised in Scheme 1.

A halide can be treated with a strong base such as an amide,[1a] to remove the *o*-aromatic proton and generate benzyne via an anion. The use of strong bases which may act as nucleophiles can be avoided by treatment of *o*-dihalosubstituted benzenes with a metal (lithium or magnesium) to give the desired aryne by elimination.[9]

Aryl triflates have been used to generate arynes via other routes than metal–halogen exchange. For example, fluoride ion displacement of the trimethylsilyl group provides a convenient route to benzyne under mild conditions (Scheme 2).[10]

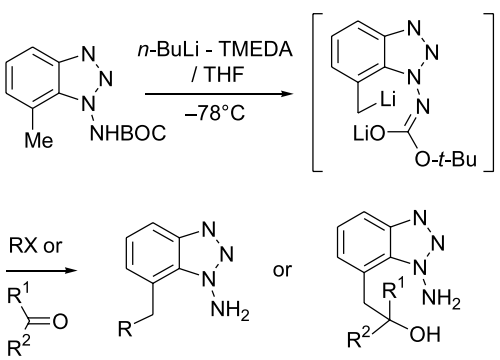


Scheme 2. Generation of arynes from triflates.

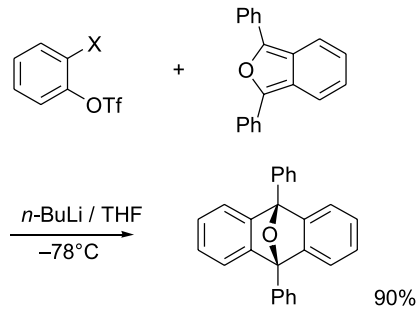
On the other hand, oxidation of aminotriazole usually produces good yields, but has the disadvantage of requiring the presence of an oxidant such as lead tetraacetate in the reaction medium.[11] The use of NBS was also developed by Campbell et al.[11,12]

Deprotonation of 7-methyl-1-aminobenzotriazole derivatives leads to 7-substituted-1-aminobenzotriazoles, precursors of *o*-substituted benzynes (Scheme 3).[13]

Arynes may also be obtained from anthranilic acid, by decomposition of the internal benzenediazonium-2-carboxylate.[14,15] Recent typical examples (reported since 1990) of the different methods and improved methods in addition to several novel methods or variations on these methods which have been described since the previous review[1c] are collected below.



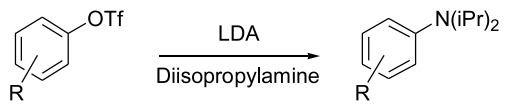
Scheme 3. Generation of arynes from aminobenzotriazoles.



Scheme 4. Generation of arynes from *o*-halotriflates.

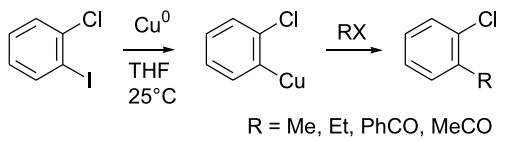
Metal–halogen exchange on *o*-halotriflates occurs at −78°C with *n*-BuLi to produce arynes (Scheme 4).[16]

Aryl triflates generated from the corresponding phenols react with lithium diisopropylamide (LDA) in diisopropylamine to give the corresponding amines in good yields (Scheme 5).[17]



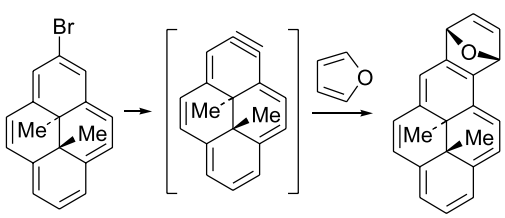
Scheme 5. Addition of arynes to lithium diisopropylamide.

Whereas *o*-halolithium or magnesium arenes readily undergo elimination to arynes, *o*-Cl- and *o*-F-copper reagents do not, and can be used in nucleophilic displacements, as in the following example (Scheme 6).[18]



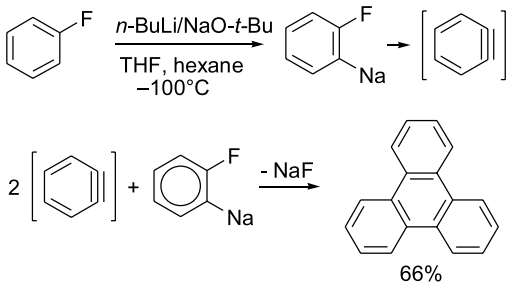
Scheme 6. Reactivity of *o*-Cl-copper reagents.

Annulyne has been generated from the corresponding bromide and sodamide, and has been trapped by various furans, removal of the oxygen bridge leading to the annulated annulenes (Scheme 7).[19]



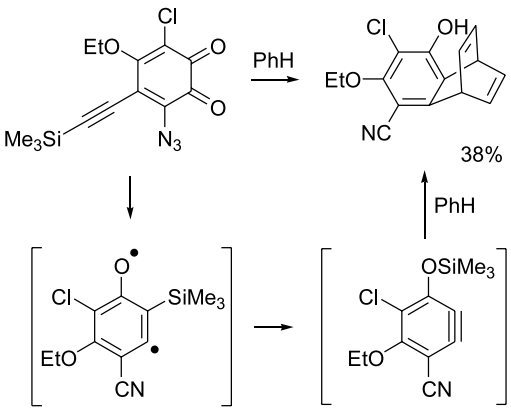
Scheme 7. Generation of annulyne.

An especially efficient triphenylene synthesis involved *o*-sodiofluorobenzene as an intermediate. Its fast decomposition gave rise to a high benzyne concentration and hence a high yield of triphenylene (Scheme 8).[20]



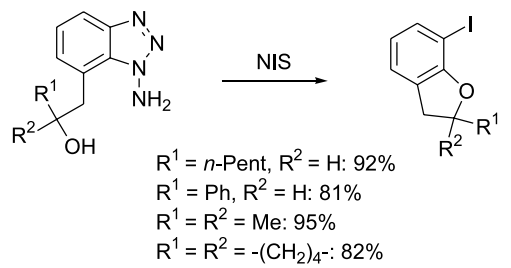
Scheme 8. Synthesis of triphenylene.

A remarkable and so far unique generation of a benzyne intermediate has been proposed in the thermal decomposition of azidoquinone in benzene which provided a cycloadduct by reaction with the solvent (Scheme 9).[21]



Scheme 9. Generation of arynes from azidoquinones.

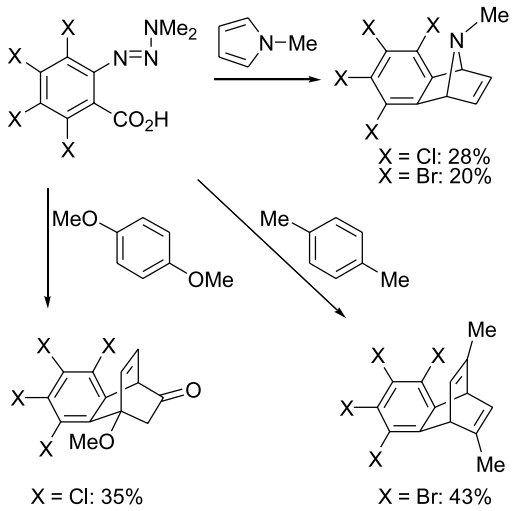
In 1994, Knight reported the generation of benzynes from 1-aminobenzotriazoles containing *o*-hydroxyethyl groups.[22] Intramolecular trapping provided good yields of the iodo-dihydrobenzofurans (Scheme 10).



Scheme 10. Synthesis of iodo-dihydrobenzofurans.

The corresponding bromo-derivatives were previously obtained from NBS but in much lower yields than from NIS.[23]

A study of the decomposition of 1-(2′-carboxyphenyl)-3,3-dimethyltriazene and the tetrabromo- and tetrachloro-analogues showed that the arenediazonium-2-carboxylates were intermediates in the formation of the corresponding arynes (Scheme 11).[24]



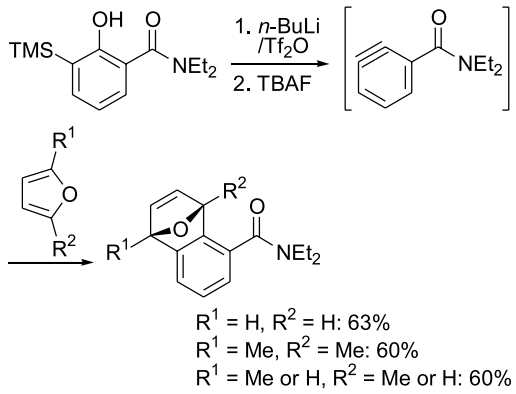
Scheme 11. Generation of arynes from 1-(2′-carboxyphenyl)-3,3-dimethyltriazene.

(Phenyl)[*o*-(trimethylsilyl)phenyl]iodonium triflate readily prepared from *o*-bis(trimethylsilyl)benzene and $PhI(OAc)_2$ was reported to be a new and efficient precursor of benzyne by Kitamura in 1995.[25] Mild and neutral conditions provided adducts with typical trapping agents (Scheme 12).

4. Pericyclic reactions of arynes

4.1. Diels–Alder cycloadditions

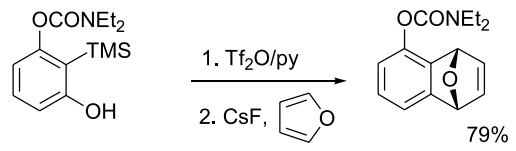
The Diels–Alder reaction is one of the most important reactions of arynes and is used both as a means of detecting arynes and as a synthetic tool. Because of the highly electrophilic character of arynes, the reaction is observed with a very wide range of dienes including simple benzene derivatives or other benzenoid aromatic compounds. This section is organised according to the type of diene partner for the arynes.



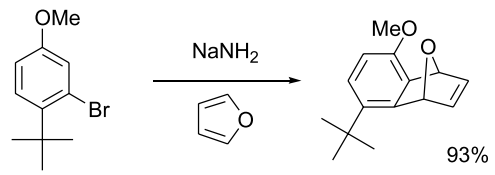
Scheme 13. Diels–Alder reactions with a benzamide benzyne.

4.1.1. With cyclic heterodienes. The reactions of benzyne with various classes of heterocyclic compounds have been reviewed.[26]

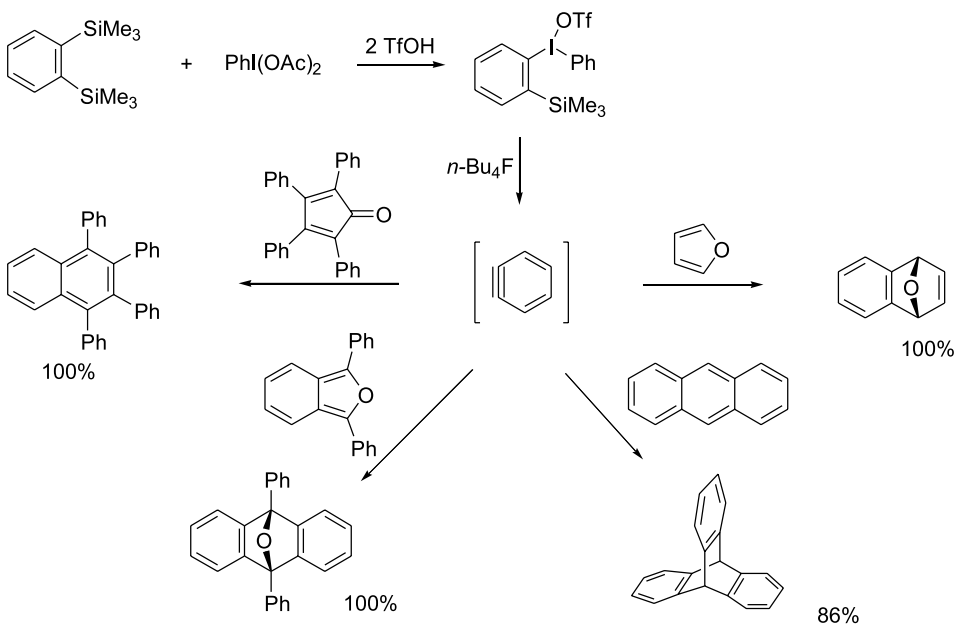
Aromatic five-membered heterocycles react efficiently with benzynes to give the [4+2] cycloadducts. Dienes of this type, particularly furan and its derivatives, have been widely



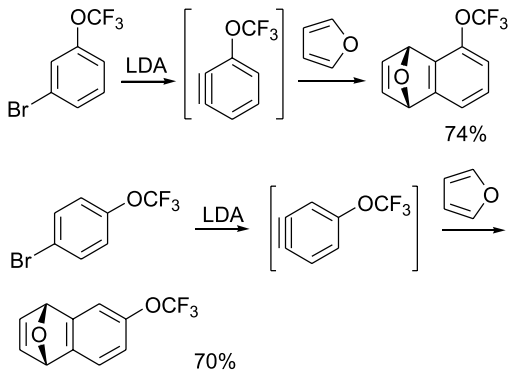
Scheme 14. Diels–Alder reaction with a carbamate benzyne.



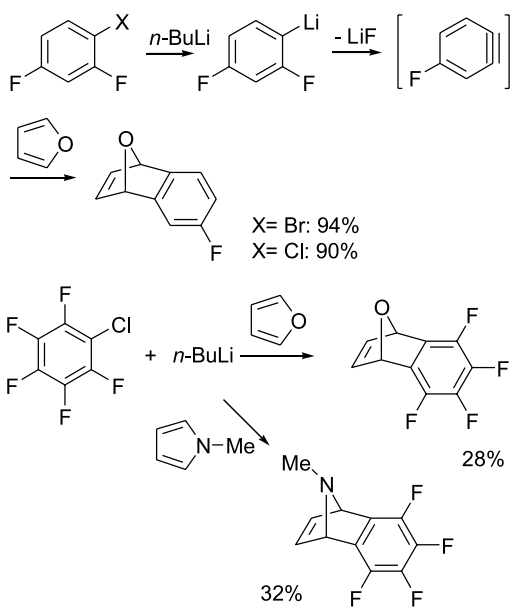
Scheme 15. Diels–Alder reaction with 3-bromo-4-*t*-butyl-1-methoxybenzene.



Scheme 12. Generation of arynes from (phenyl)[*o*-(trimethylsilyl)phenyl]iodonium triflate.



Scheme 16. Diels–Alder reactions with 1-bromo-3- or -4-(trifluoromethoxy)-benzene.



Scheme 17. Synthesis of fluorinated benzonorbornadienes.

used to intercept arynes and their adducts are useful as intermediates in the synthesis of naphthalenes because the endoxide bridge can be readily cleaved by acids. Some recent examples are described here.

The benzamide benzyne intermediate generated from an *o*-TMS-aryl triflate precursor afforded the cycloadducts in good yields (Scheme 13).[27]

Similarly, the carbamate benzyne generated from the analogous precursor led to the corresponding adducts in the presence of furan (Scheme 14).[27]

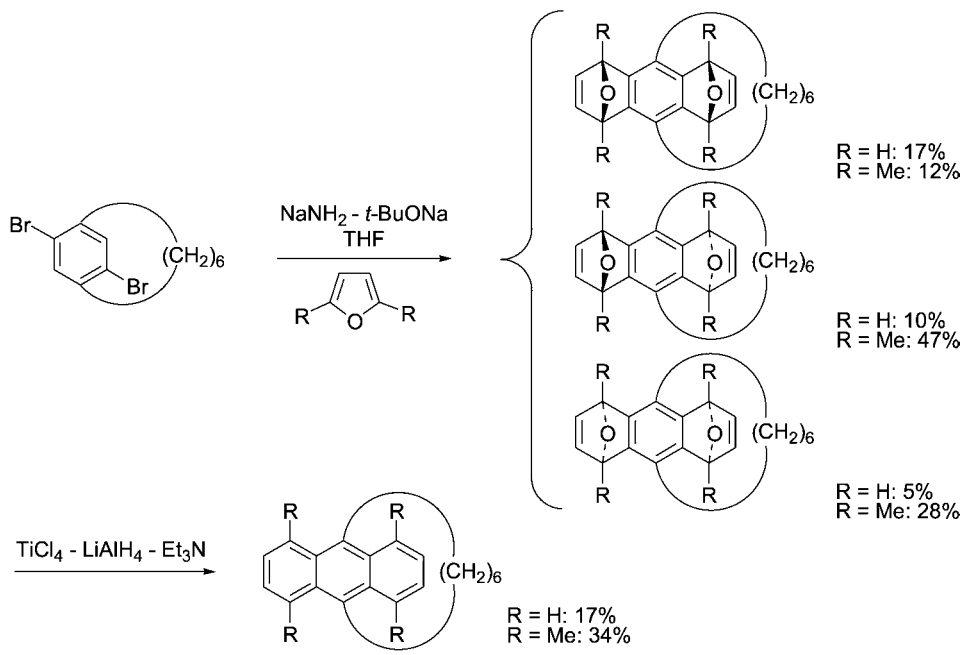
In the course of preparing heterocyclic quinones, Wege[28] observed a very good yield for the cycloaddition of furan with 3-bromo-4-*t*-butyl-1-methoxybenzene, whereas the corresponding cycloaddition of methoxybenzene was previously reported with only 15% yield (Scheme 15).[29]

1-Bromo-3- or -4-(trifluoromethoxy)benzene was added to a solution of LDA in THF and furan leading to the corresponding 1,4-dihydro-1,4-epoxy-5- or 6-(trifluoromethoxy)naphthalenes (Scheme 16).[30]

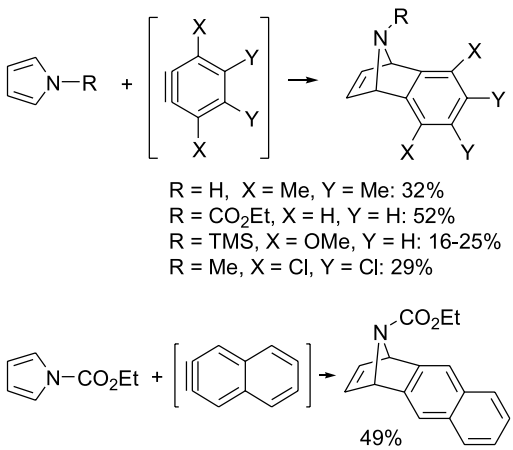
A series of fluorinated benzonorbornadienes were recently prepared in high yields and selectivities by trapping the in situ generated benzynes with furan or *N*-methylpyrrole (Scheme 17).[31]

The smallest 9,10-bridged anthracene has been constructed by bis-benzoannelation from dibromoparacyclophane (Scheme 18).[32]

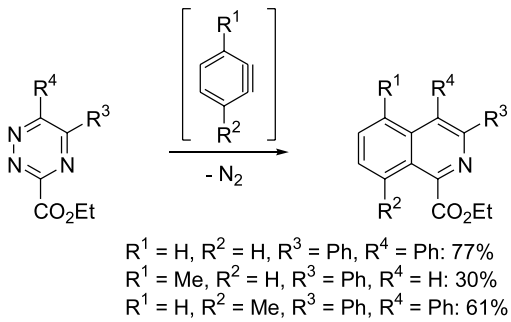
Derivatives of pyrrole have been studied in cycloaddition reactions, leading to various 1,4-dihydro-1,4-iminonaphthalenes or the corresponding anthracenes (Scheme 19).[33]



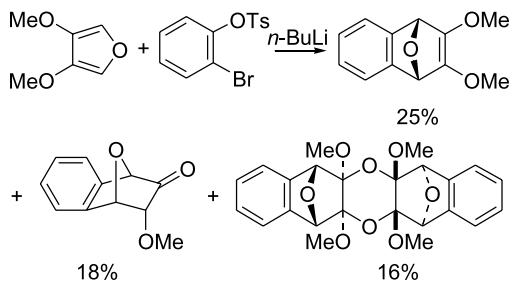
Scheme 18. Synthesis of 9,10-bridged anthracenes.



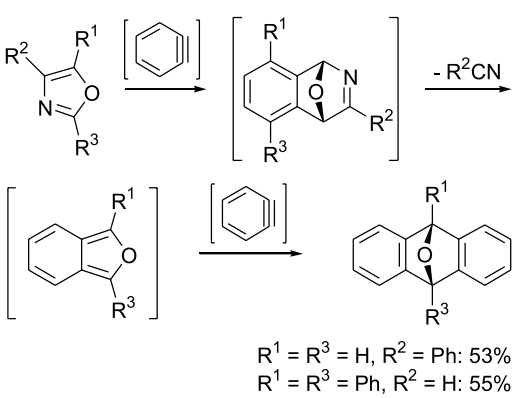
Scheme 19. Synthesis of 1,4-dihydro-1,4-iminonaphthalenes and the corresponding anthracenes.



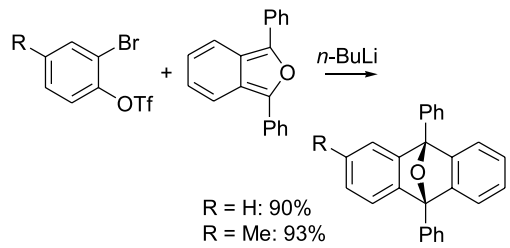
Scheme 20. Synthesis of isoquinolines.



Scheme 21. Synthesis of 2,3-dimethoxy-1,4-dihydro-1,4-epoxynaphthalene.



Scheme 22. Synthesis of bis(benzyne) adducts.



Scheme 23. Synthesis of bis(benzyne) adducts.

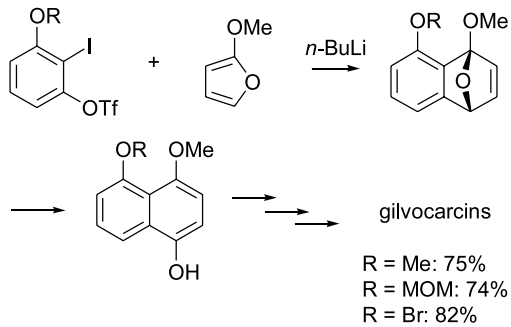
A route to isoquinolines with electron-withdrawing substituents has been developed, starting from the 1,2,4-triazines (Scheme 20).[34]

On the other hand, cycloaddition between benzyne and 3,4-dimethoxyfuran yielded 2,3-dimethoxy-1,4-dihydro-1,4-epoxynaphthalene which was unusually labile. Indeed, chromatography and exposure to air provided a ketone along with an unusual dimer (Scheme 21).[35]

Variously-substituted oxazoles reacted with benzyne to give the bis(benzyne) adducts.[36] This outcome requires each of the following steps: (a) formation of benzyne; (b) Diels–Alder reaction with the oxazole; (c) retro-Diels–Alder expulsion of the nitrile; and (d) Diels–Alder reaction of benzyne with the isobenzofuran (Scheme 22).

A better yield was obtained by Suzuki et al. when the aryne precursor was an *o*-bromophenyl triflate treated with *n*-BuLi in the presence of 1,3-diphenylisobenzofuran (Scheme 23).[16]

Other benzynes such as 2,3-didehydronaphthalene have been involved in Diels–Alder reactions in order to prepare various polycyclic aromatic hydrocarbons (Scheme 24).[37]

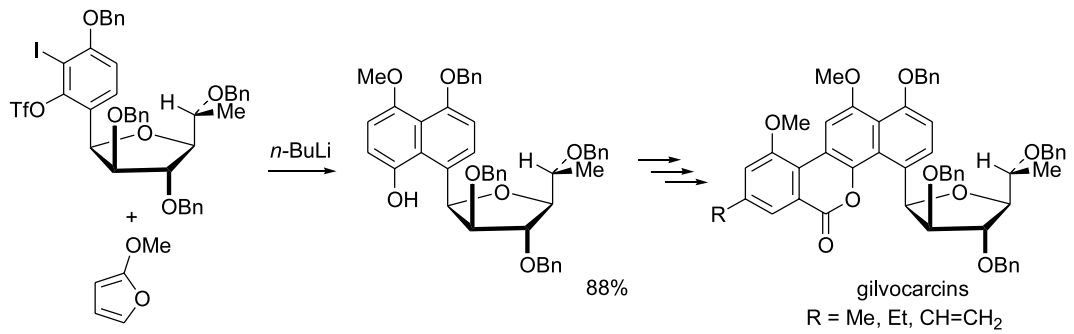


Scheme 24. Synthesis of gilvocarcin intermediates.

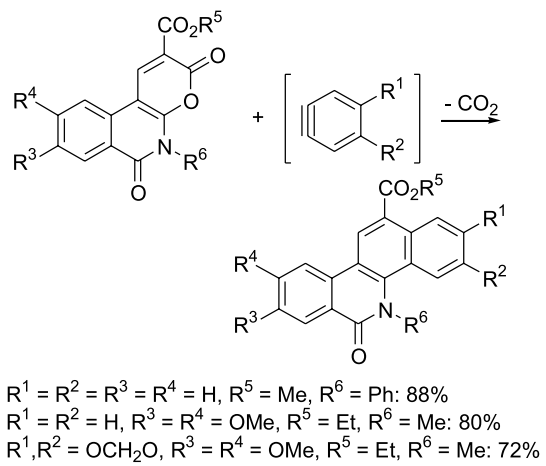
A regioselective [4+2] cycloaddition of a sugar-bearing benzyne species with 2-methoxyfuran was reported by Suzuki et al. and applied to a total synthesis of the gilvocarcins (Scheme 25).[38]

In 1992, Castedo et al. reported a new approach o antitumour benzophenanthridines based on the Diels–Alder reaction between an α-pyrone and an aryne arising from anthranilic acid (Scheme 26).[39]

The cycloaddition of substituted furans to a diterpenoid aryne, generated by in situ diazotisation of the corresponding anthranilic acid followed by cleavage of the annulated



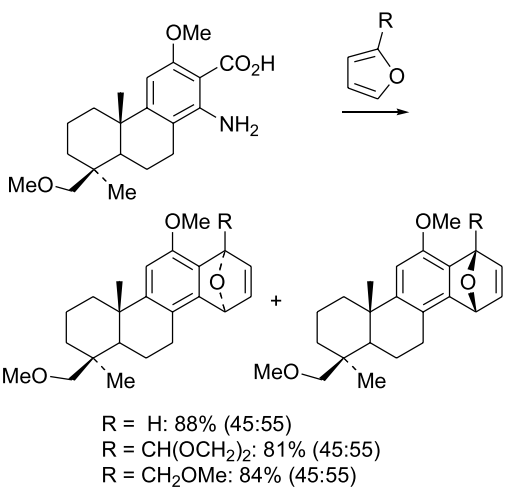
Scheme 25. Synthesis of gilvocarcins.



Scheme 26. Synthesis of benzophenanthridines.

1,4-epoxydecahydrochrysenes, provided a convenient method for the preparation in high yield of the previously unknown 1-substituted octahydrochrysen-4-ols (Scheme 27).[40]

In the field of heteroaryne[41] chemistry, the 3,4-pyridyne species has attracted considerable theoretical and synthetic interest. The most recent successful method for generating 3,4-pyridynes uses 4-trialkylsilyl-3-pyridyl triflates as precursors. They were synthesised by *o*-metallation and silylation of carbamate, the intermediate then being converted to the corresponding triflate. This latter derivative treated with fluoride generated the expected pyridyne which was trapped with several dienes (Scheme 28).[42]



Scheme 27. Synthesis of 1-substituted octahydrochrysen-4-ols.

In order to prepare antitumour ellipticine derivatives, 3,4-pyridyne[43] generated from lead tetraacetate oxidation of the appropriate aminotriazole underwent cycloaddition to isoindoles (Scheme 29).[44]

Very recently, the preceding approach to ellipticine was modified by Castedo et al. by introducing substituents into the 3,4-didehydropyridyne dienophile to control the key cycloaddition step.[45] A chloro-substituent at position 2 improved the yields and the regioselectivities of the cycloaddition and the overall efficiency of the synthesis of ellipticine (Scheme 30).

The corresponding indolopyrroles also underwent cycloaddition with pyridynes and similar regioselectivities were observed (Scheme 31).

4.1.2. With acyclic heterodienes

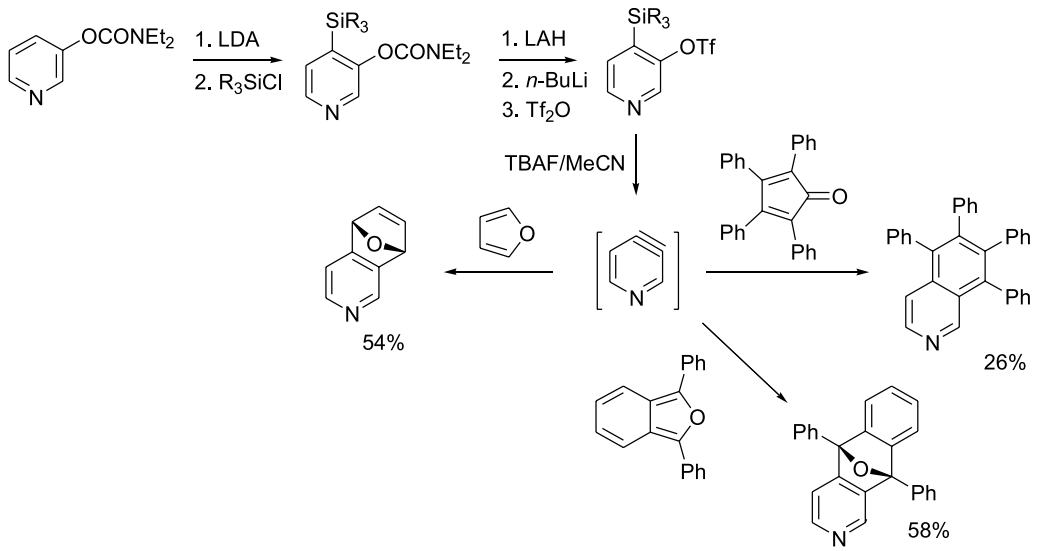
4.1.2.1. Intermolecular cycloadditions. Classes of natural products synthesised via intermolecular aryne reactions of the Diels–Alder type include the aporphinoids, protoberberines, benzophenanthridines, ellipticines, anthracyclines and *o*-naphthoquinones.

The aporphinoid skeleton could be constructed via an intermolecular aryne cycloaddition to the styrene moiety of an alkylidenetetrahydroisoquinoline. In one example, the syntheses of dehydroaporphines and aristolactams were reported by Castedo et al. (Scheme 32).[46]

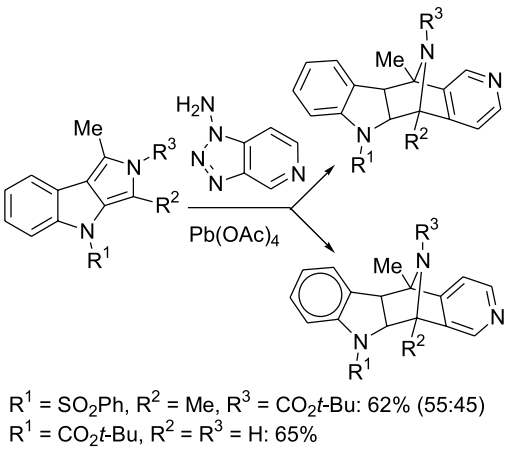
The same strategy was applied to asymmetrically-substituted arynes and led regioselectively to the apomorphine analogues (Scheme 33).[47]

Other tetracyclic alkaloids such as protoberberines were obtained by cycloaddition between pyrrolinediones and arynes generated in situ by thermal decomposition of benzenediazonium-2-carboxylate (Scheme 34).[48]

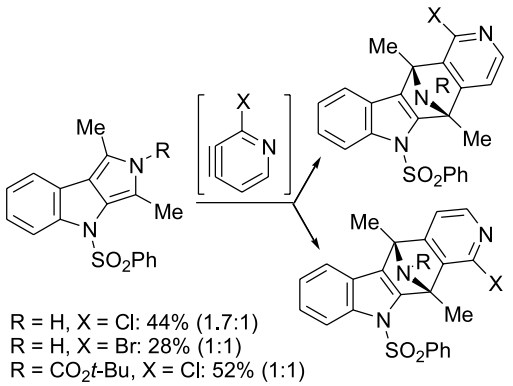
The same author has also prepared various benzo[*c*]phenanthridines according to three different approaches (Scheme 35).[49,39]



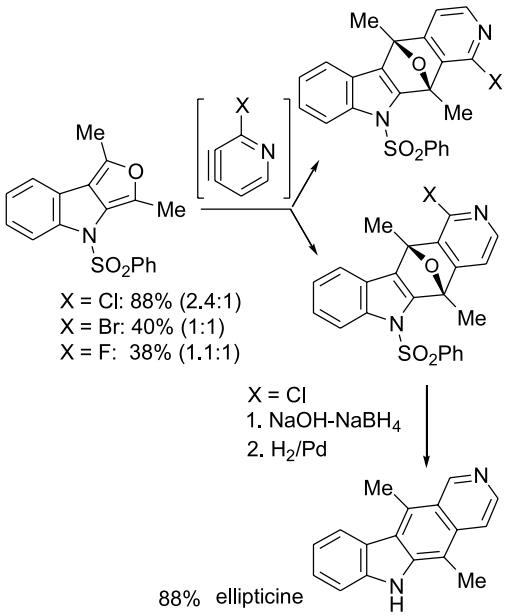
Scheme 28. Diels–Alder reaction with 3,4-pyridyne.



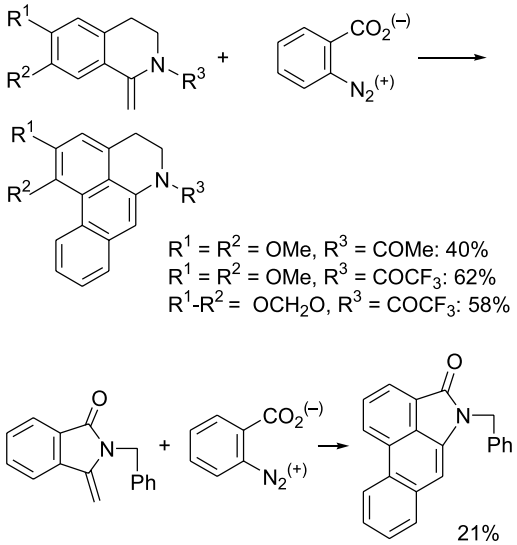
Scheme 29. Synthesis of isoindoles.



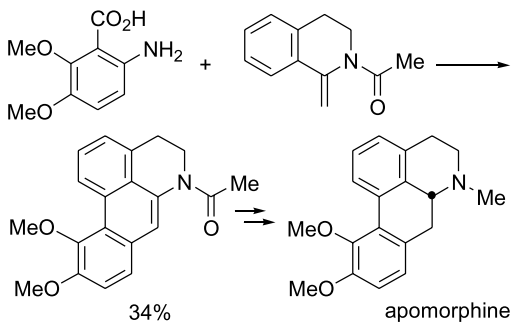
Scheme 31. Diels–Alder reactions of pyridynes and indolopyrroles.



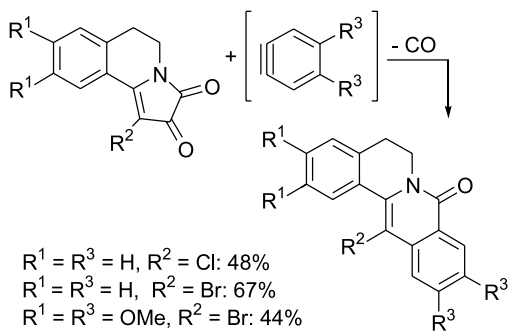
Scheme 30. Synthesis of ellipticine.



Scheme 32. Synthesis of dehydroaporphines and aristolactams.



Scheme 33. Synthesis of apomorphine analogues.



Scheme 34. Synthesis of protoberberines.

More recently, a new approach to the polycyclic framework of dynemicin A was reported,[50] and the key step was a cycloaddition involving benzyne (Scheme 36).

An unexpected [4+2] cycloaddition pathway was reported by Biehl et al. involving the dipolar carbanion α-cyano-α-lithio-*o*-toluonitrile and polarised arynes (Scheme 37).[51]

4.1.2.2. Intramolecular cycloadditions. The intramolecular aryne cycloaddition approach developed by Castedo et al. constitutes a complementary strategy to the intermolecular benzyne cycloaddition methodology with the aim of preparing various types of alkaloids.[52]

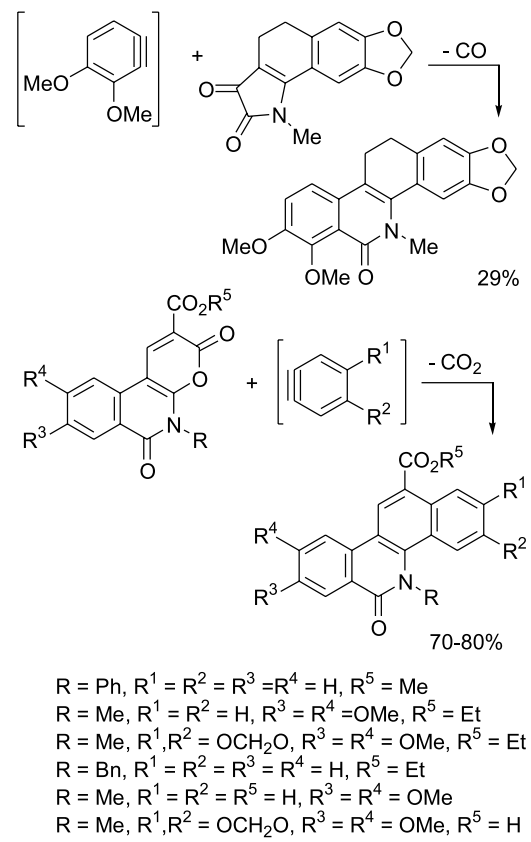
For instance, lycorines could be obtained in good yield by intramolecular benzyne cycloaddition between the aryne and azadiene components arising from the following amides (Scheme 38 and Table 1).[53]

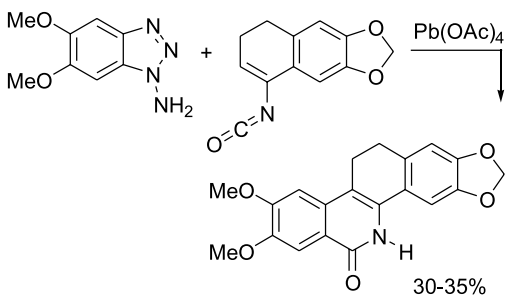
Cleavage of the ring D of lycorines, obtained by an intramolecular cycloaddition of an aryne to an azadiene, led to phenanthridines, which were cyclised to 7-azasteroids (Scheme 39).[54]

The same methodology was applied to an imine as the azadiene instead of an imidate as used previously (Scheme 40).[55]

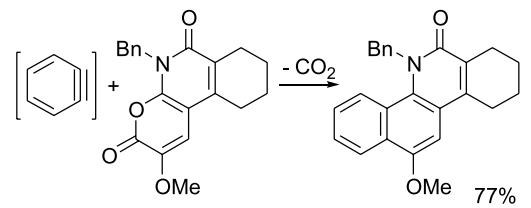
The basic skeleton of ergot alkaloids was also formed by intramolecular aryne cycloaddition of an amide prepared from 2-bromoaniline (Scheme 41).[56]

The intramolecular Diels–Alder reaction between styrenes and arynes allowed a new approach to aporphinoids such





Scheme 35. Synthesis of benzo[*c*]phenanthridines.

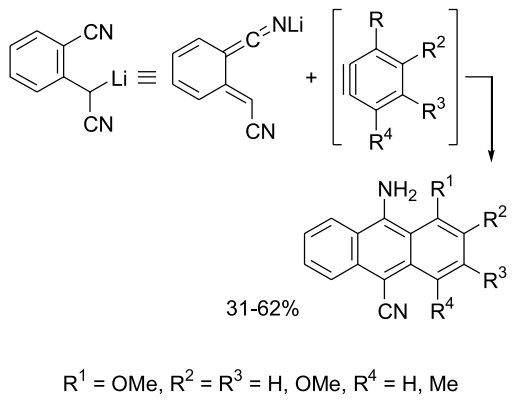


Scheme 36. Synthesis of dynemicin A.

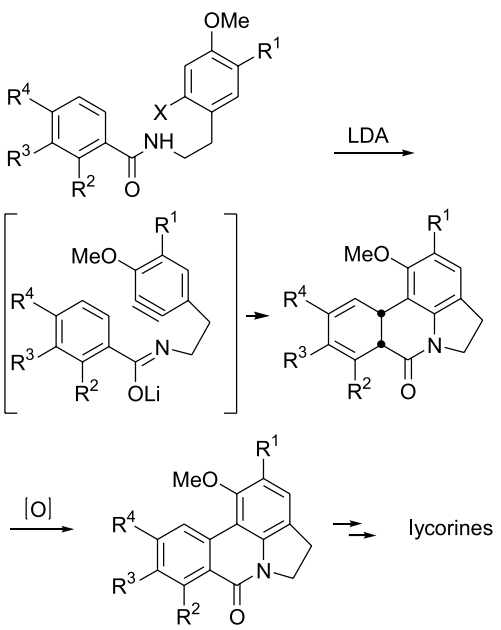
as aristolactams and phenanthrene alkaloids (Schemes 42 and 43).[57]

4.1.3. With other dienes. 1,6-Methano[10]annulene adds benzyne with ring closure to give the cycloadduct (Scheme 44).[58]

In search of new molecules that might function as molecular



Scheme 37. Diels–Alder reaction with α-cyano-α-lithio-*o*-toluonitrile.



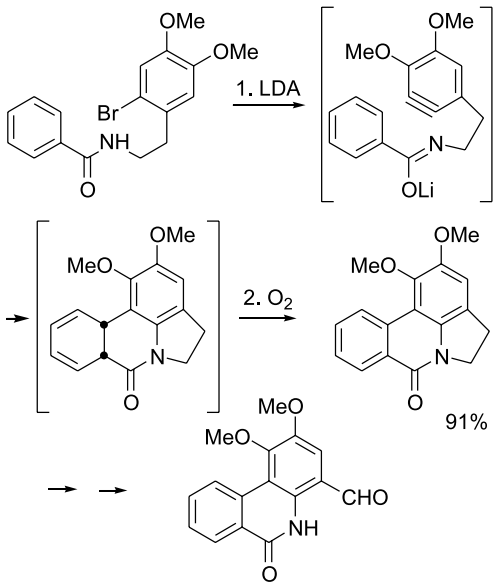
Scheme 38. Synthesis of lycorines.

Table 1.

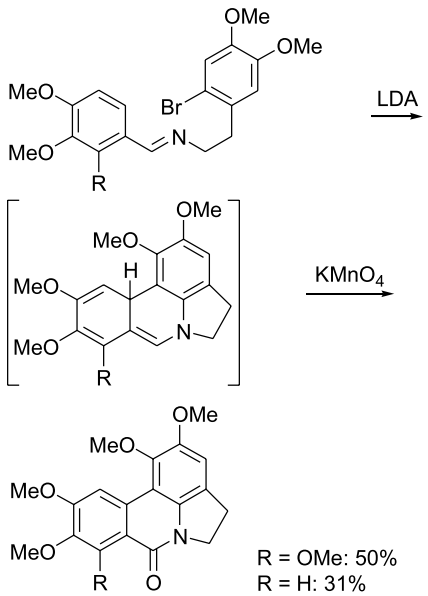
X	R^1	R^2	R^3	R^4	Yield (%)
Br	OMe	H	H	H	91
Br	OMe	OMe	OMe	OMe	69
Br	OMe	H	H	OMe	76
Cl	H	OMe	OMe	OMe	61
Br	OMe	H	OMe	OMe	74

ratchets, Kelly et al. reported the synthesis of triptycene derivatives using benzyne (Scheme 45).[59]

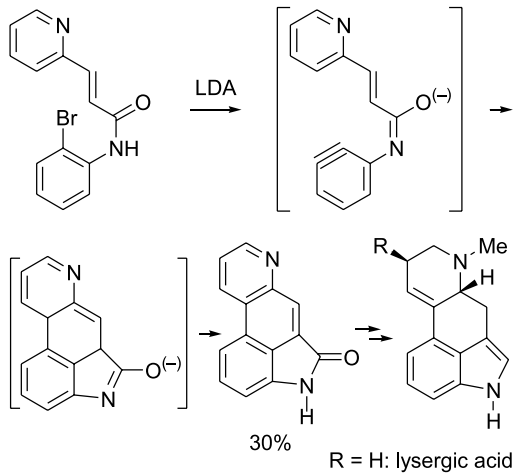
In order to prepare overcrowded aromatic compounds, Yoshida et al. reported the synthesis of 1,2,3,4-tetra-*t*-butylnaphthalene, one of the most crowded aromatic molecules, via a cycloaddition between benzyne and tetra-*t*-butylcyclobutadiene since 2,3,4,5-tetra-*t*-butyl-2,4-cyclopentadien-1-one was known to be unreactive to benzyne (Scheme 46).[60]



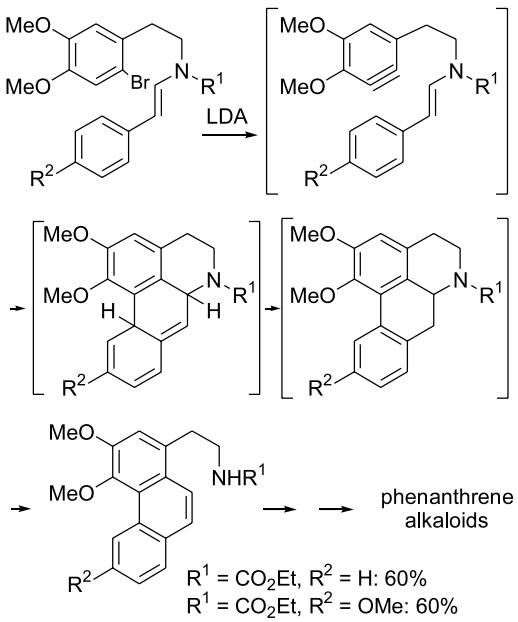
Scheme 39. Synthesis of phenanthridines.



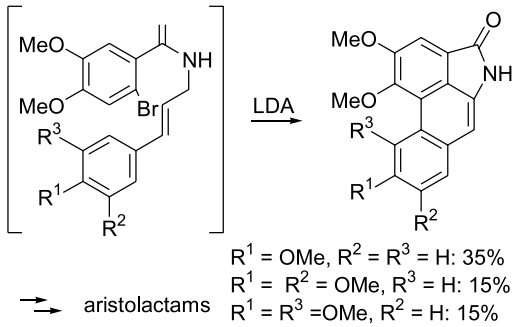
Scheme 40. Diels–Alder reaction with an imine.



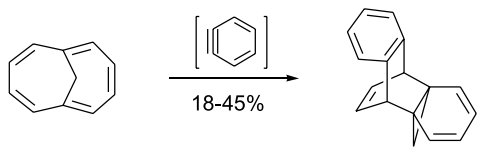
Scheme 41. Synthesis of ergot alkaloids.



Scheme 42. Synthesis of phenanthrene alkaloids.



Scheme 43. Synthesis of aristolactams.



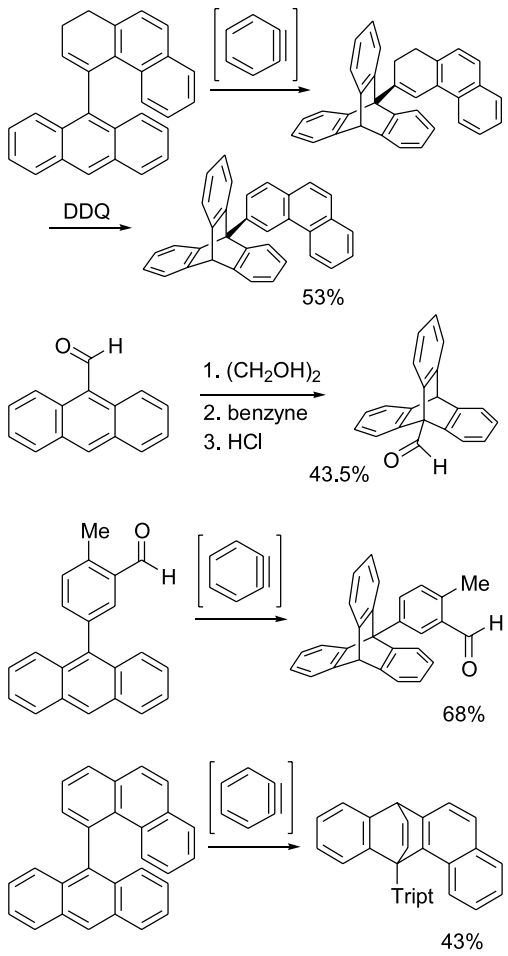
Scheme 44. Diels–Alder reaction with 1,6-methano[10]annulene.

In 1998, Kitamura and co-workers employed 2,3-didehydronaphthalene as a useful intermediate for the construction of polycyclic aromatic hydrocarbons and, in this way, 1,2,3,4-tetraphenylanthracene was prepared by treatment of 2,3-didehydronaphthalene with tetraphenylcyclopentadienone (Scheme 47).[37]

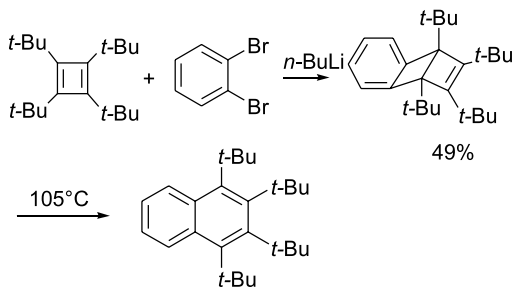
Three stable rotational isomers of 2,2′,3,3′-tetramethoxy-9,9′-bitriptycyl were isolated from the reaction of benzyne with 2,2′,3,3′-tetramethoxy-9,9′-bianthryl (Scheme 48).[61]

4.2. [2+2] Cycloadditions

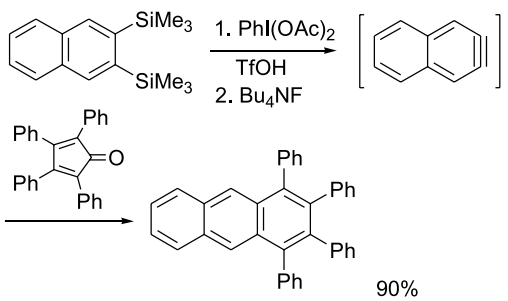
Benzyne reacts with a wide range of olefins to give the [2+2] cycloadducts benzocyclobutenes. Because of the



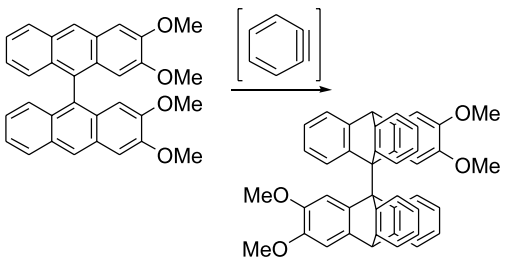
Scheme 45. Synthesis of triptycene derivatives.



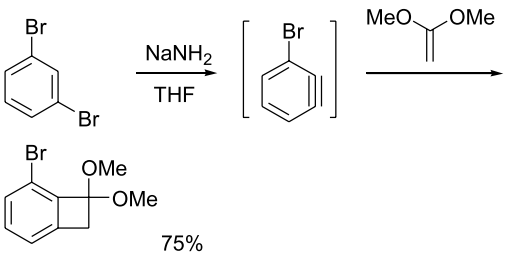
Scheme 46. Synthesis of 1,2,3,4-tetra-*t*-butylnaphthalene.



Scheme 47. Synthesis of 1,2,3,4-tetraphenylanthracene.



Scheme 48. Synthesis of 2,2′,3,3′-tetramethoxy-9,9′-bianthryl.



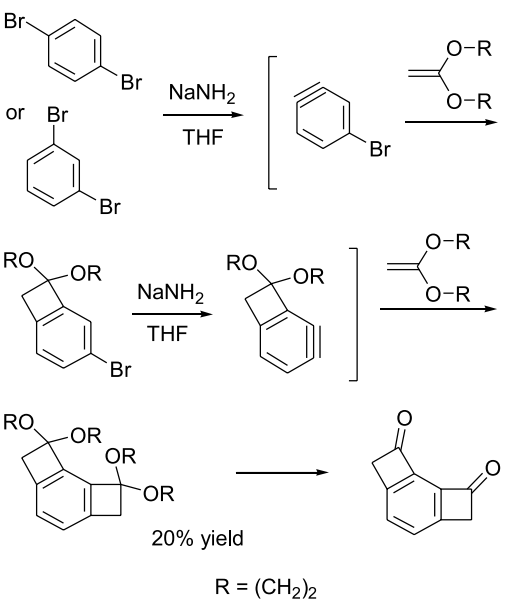
Scheme 49. Synthesis of benzocyclobutene.

electrophilic nature of benzyne, the reactions proceed best with alkenes bearing electron-donating substituents and this reaction offers a simple and direct route to useful synthetic intermediates.

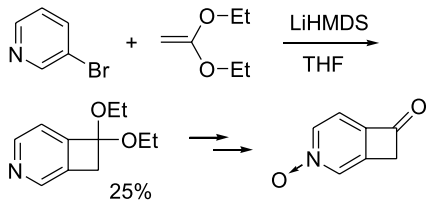
The [2+2] cycloaddition of dimethoxyethylene and bromoaryne provided the corresponding benzocyclobutene in 75% yield (Scheme 49).[62]

Treatment of 1,3- or 1,4-dibromobenzene with $NaNH_2$ in the presence of a ketene acetal leads to a benzo-bis-cyclobutenone derivative precursor of tricyclo[6.2.0.0^{2,5}]-deca-1,5,7-triene-3,10-dione (Scheme 50).[63]

The 3- and 4-halopyridines and a ketene dialkyl acetal were



Scheme 50. Synthesis of tricyclo[6.2.0.0^{2,5}]deca-1,5,7-triene-3,10-dione.



Scheme 51. Synthesis of pyrido[*b*]cyclobutene derivatives.

shown to permit the synthesis of pyrido[*b*]cyclobutene derivatives (Scheme 51).[64]

Benzocyclobutenes on heating lead to *o*-xylylenes which can be used in intramolecular Diels–Alder cycloadditions. This result has been used independently by Oppolzer[65] and Kametani[66] for the generation of the BC ring system of steroids.[67,68]

We have been widely involved in using benzocyclobutenes in the total synthesis of steroids (Scheme 52).[69]

Benzyne reacts with enamines through a combination of ene and [2+2] cycloaddition (Scheme 53).[70]

In 1995, Suzuki et al. reported the first observation of the stereospecificity in the benzyne–olefin [2+2] cycloaddition. The key points reside in the choice of a ketene silyl acetal as the partner olefin and the halogen–lithium exchange reaction of *o*-haloaryl triflates as the method for generating benzyne (Scheme 54).[71]

The ketene silyl acetals proved to be efficient partners for *o*-haloaryl triflates in the regioselective synthesis of benzocyclobutenones (Scheme 55).[72]

The rigorous regioselectivity of the cycloaddition of an α-alkoxybenzyne and a ketene silyl acetal was observed in other examples, where a single cycloadduct was isolated (Scheme 56).[73]

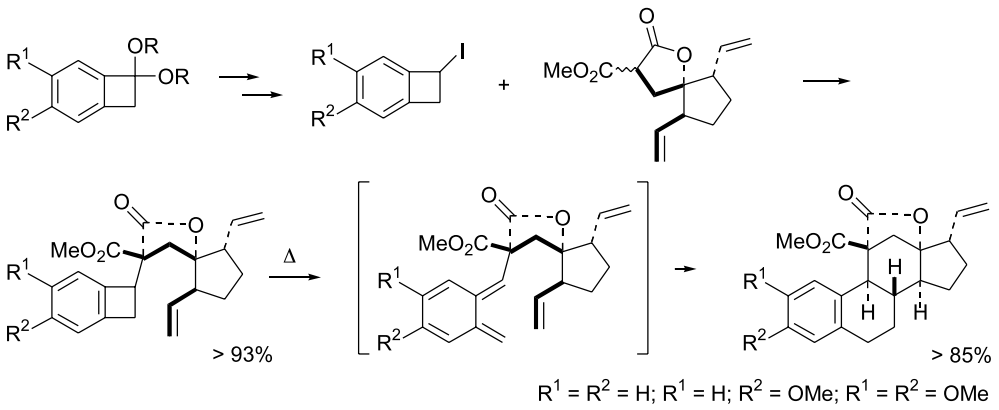
In 1999, it was reported that the reaction between benzyne and diimines led to 1,4-bis(2-substituted acridin-10-yl)benzenes via [2+2] cycloadditions (Scheme 57).[74]

An unusual diterpenoid aryne generated from the corresponding anthranilic acid underwent a [2+2] cycloaddition with 1,1-dimethoxyethene in the presence of isoamyl nitrite, but the *N*-methyliminofuranone formed was unstable and rearranged to the *N*-methylphthalimide upon prolonged handling or storage, according to the following mechanism (Scheme 58).[40]

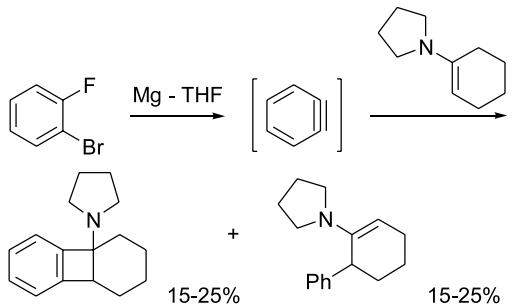
4.3. 1,3-Dipolar cycloadditions

A wide variety of stable 1,3-dipolar compounds undergo cycloadditions with arynes.[1a,b,26]

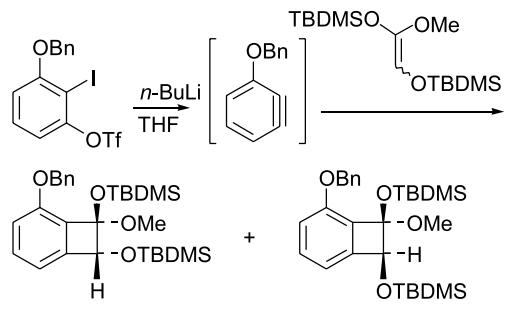
The inner salts of 3-oxo-pyrazolidinium and 3-oxo-1,2-diazetidinium hydroxides react with benzyne generated from benzenediazonium carboxylate to give the bicyclic adducts in 50–75% yields, depending on the substituents (Scheme 59).[75]



Scheme 52. Synthesis of various steroids.



Scheme 53. Reactivity of benzyne with enamines.



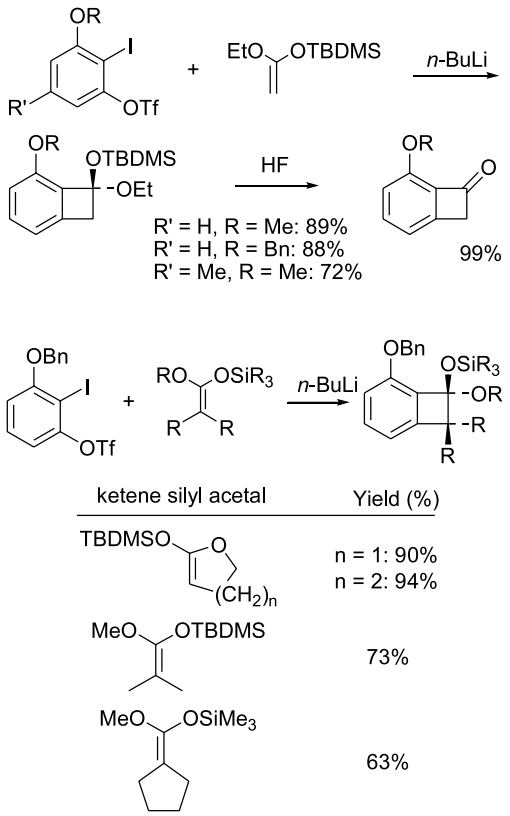
E/Z ratio of ketene	Yield (%)	trans/cis
90/10	81	90/10
47/53	80	46/54
3/97	81	3/97

Scheme 54. Stereospecificity of [2+2] cycloaddition between *o*-haloaryl triflates and ketene silyl acetals.

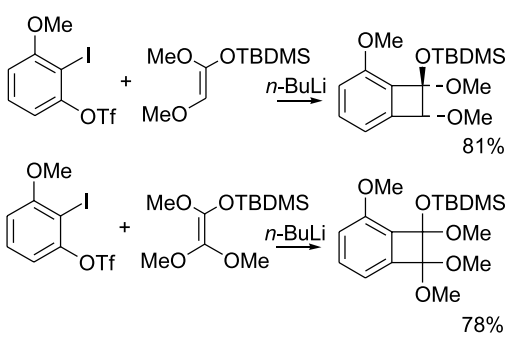
In 1993, Suzuki et al. reported a study on the regiochemistry of cycloaddition of the unsymmetrical arynes with nitrones. They showed the effect of the C(3)-substituent of the aryne on the regioselectivity of the aryne–nitrone cycloaddition (Scheme 60).[76]

The observations could be rationalised as shown in Scheme 61.

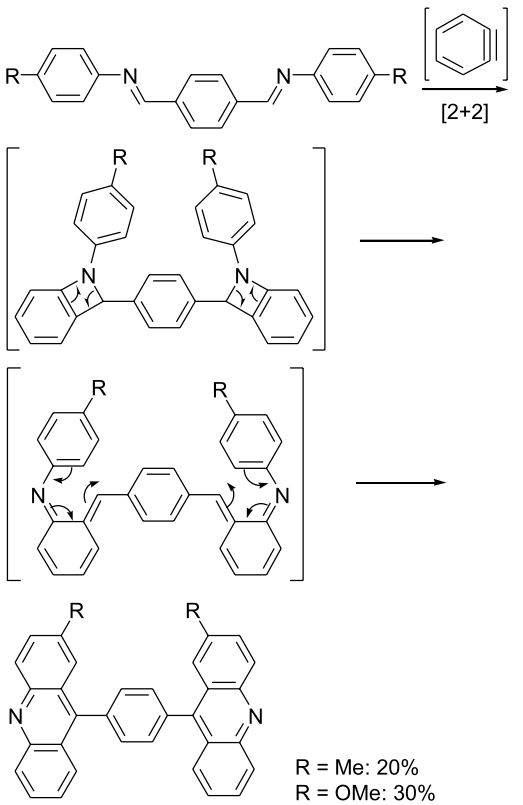
Azaallyllithium species react with benzyne according to a competitive [3+2] and [2+2] cycloaddition reaction followed by rearrangement (Scheme 62).[77]



Scheme 55. Regioselective synthesis of benzocyclobutenones and precursors.

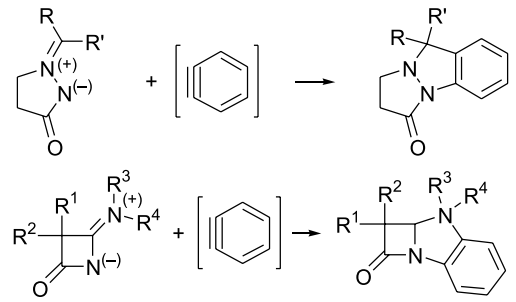


Scheme 56. Regioselectivity of [2+2] cycloaddition between α-alkoxy-benzynes and ketene silyl acetals.

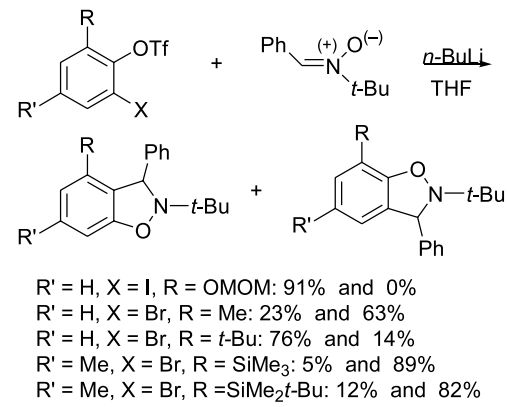


Scheme 57. Synthesis of 1,4-bis(2-substituted acridin-10-yl)benzenes.

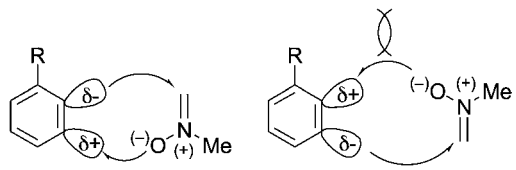
2,3-Didehydronaphthalene, generated from (phenyl)[3-(trimethylsilyl)-2-naphthyl]iodonium triflate, reacted with *p*-tolyl azide or *p*-methoxyphenyl azide according to a 1,3-dipolar cycloaddition in 62 and 72% respective yields, providing 1-arylnaphtho[2,3-*e*]triazoles (Scheme 63).[37]



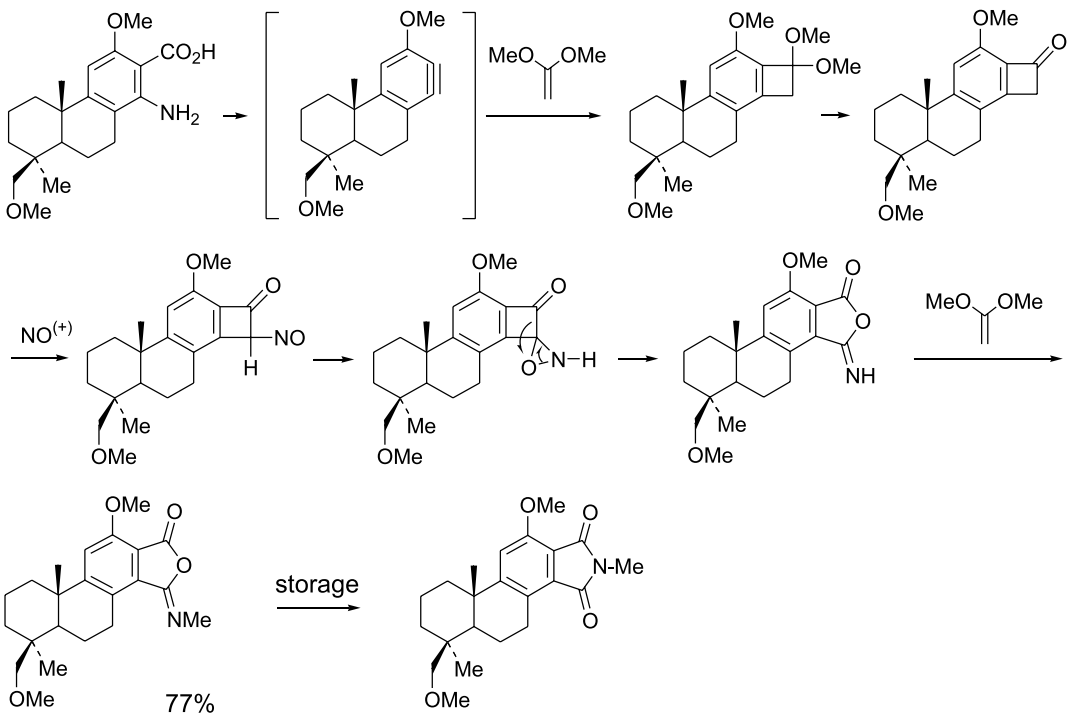
Scheme 59. 1,3-Dipolar cycloaddition of 3-oxo-pyrazolidinium and 3-oxo-1,2-diazetidinium hydroxides.



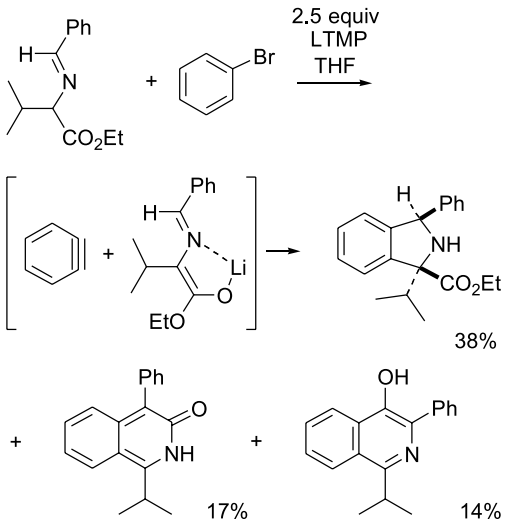
Scheme 60. Regioselectivity of the aryne–nitrone cycloaddition.



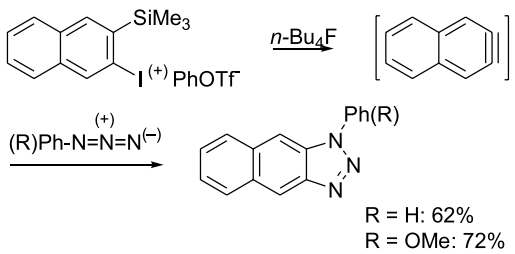
Scheme 61. Proposed explanation for the regioselectivity of the aryne–nitrone cycloaddition.



Scheme 58. Synthesis of an *N*-methylphthalimide.



Scheme 62. Reactivity of azaallyllithium species.



Scheme 63. Synthesis of 1-arylnaphtho[2,3-*e*]triazoles.

Novel fully unsaturated pyrido- and quino-oxepins were obtained from the reaction of pyridazine *N*-oxides with pyridynes and quinolynes (Scheme 64).[78]

In the same way, 4,5-didehydrotropone reacted with pyridazine *N*-oxides, providing novel tropono[4,5-*b*]oxepines (Scheme 65).[79]

Finally, Tsuchiya has reported the reaction of 1,2,4-triazine 1-oxides with benzyne which afforded 1,3-benzoxazepine and 1,3,5,6-benzoxatriazonine derivatives (Scheme 66).[80]

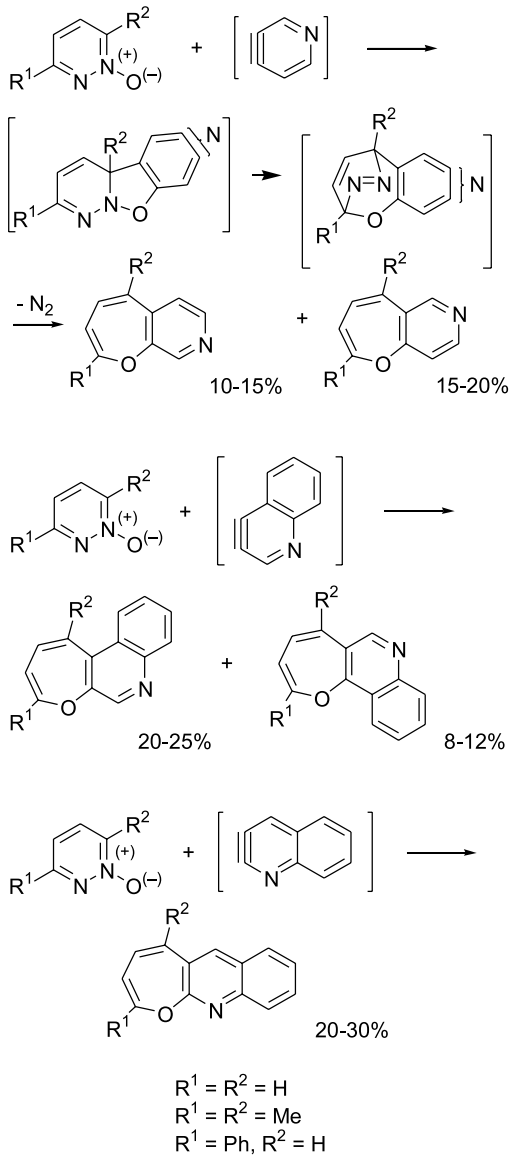
The following triazole was obtained in good yield by the treatment of a diterpenoid anthranilic acid with isoamyl nitrite in the presence of phenyl azide (Scheme 67).[40]

4.4. 1,4-Dipolar cycloadditions

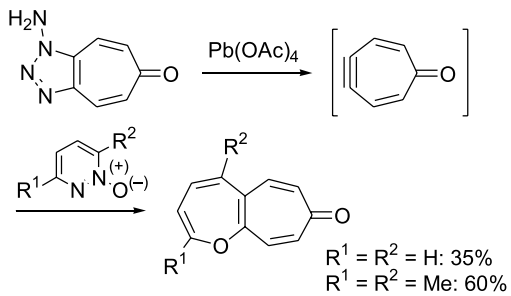
1,4-Dipolararyne cycloadditions were previously used as convergent routes to anthraquinones[81] and anthracyclinone intermediates.[82]

Based on this approach, a novel synthesis of azaacridones and diazaacridones was reported by Biehl et al. (Scheme 68).[83]

An important intermediate in the synthesis of daunomycinone was obtained by 1,4-dipolar aryne cycloaddition of a lithiated 3-cyanophthalide and 2-bromo-5,6-dihydro-1,4-dimethoxynaphthalene in the key step (Scheme 69).[84]



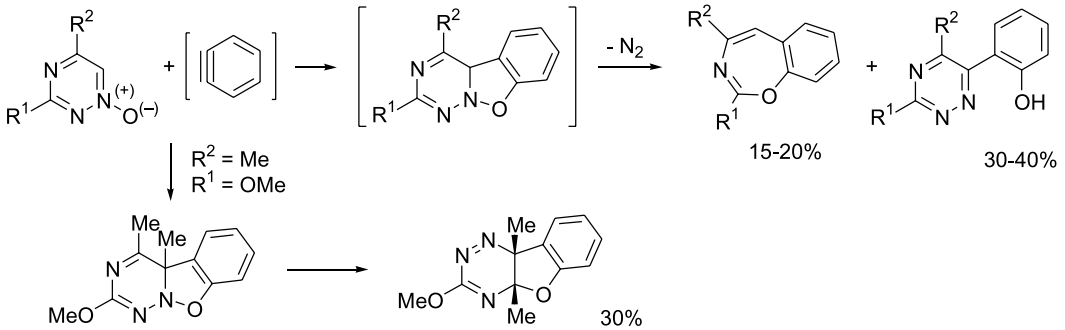
Scheme 64. Synthesis of unsaturated pyrido- and quino-oxepins.



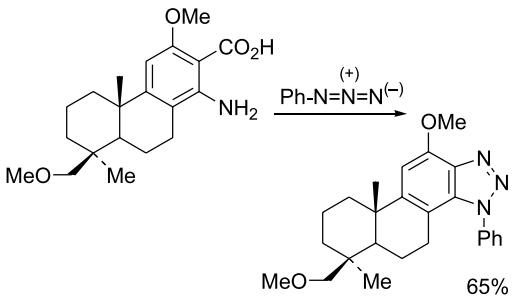
Scheme 65. Synthesis of tropono[4,5-*b*]oxepines.

4.5. Ene reactions

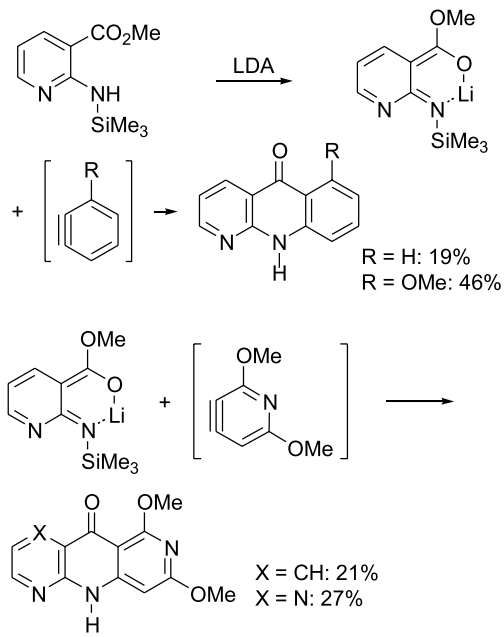
The ene reaction of benzyne with olefins bearing an allylic hydrogen atom has been used essentially to detect benzyne, but it has not been extensively employed for synthesis.



Scheme 66. Synthesis of 1,3-benzoxazepine and 1,3,5,6-benzoxatriazonine derivatives.



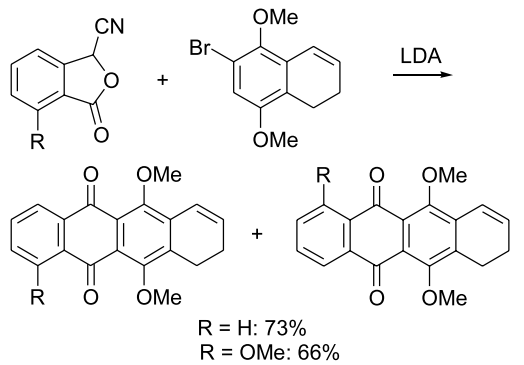
Scheme 67. Synthesis of a triazole derivative.



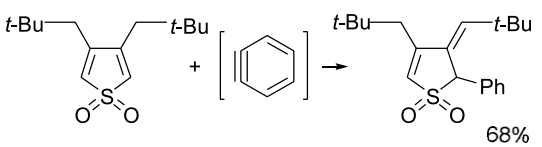
Scheme 68. Synthesis of azaacridones and diazaacridones.

In 1994, Nakayama et al. reported an unexpected ene reaction of 3,4-dineopentylthiophene 1,1-dioxide with benzyne instead of the Diels–Alder process (Scheme 70).[85]

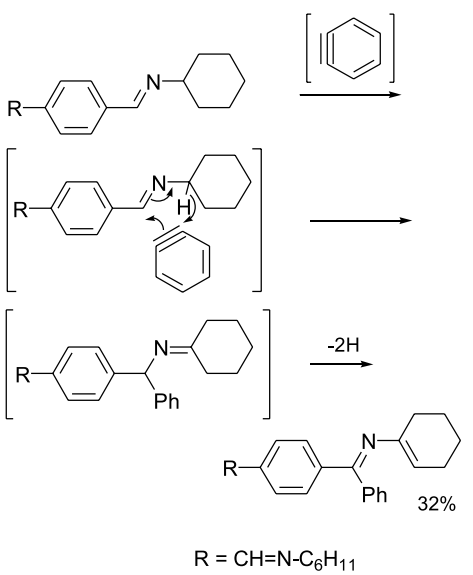
Recently, the reactivity of benzyne with diimines has been studied. Most of the time, [4+2] or [2+2] cycloadditions were observed, but in the case of cyclohexyl(4-cyclohexyliminomethylbenzylidine)amine, an ene reaction led to the major product according to the following mechanism (Scheme 71).[74]



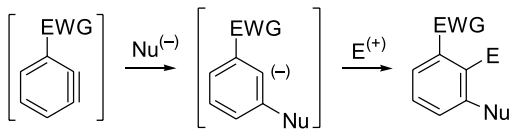
Scheme 69. Synthesis of daunomycinone intermediates.



Scheme 70. Ene reaction of benzyne with 3,4-dineopentylthiophene 1,1-dioxide.



Scheme 71. Ene reaction of benzyne with cyclohexyl(4-cyclohexyliminomethylbenzylidine)amine.



Scheme 72. Addition of nucleophiles to arynes.

5. Nucleophilic additions to arynes

The reactivity of arynes with practically all kinds of nucleophiles has been thoroughly reviewed.[1a–c,86]

From a synthetic point of view, the most interesting species are nitrogen-bearing nucleophiles and carbanions. The addition of nucleophiles to arynes is highly regioselective when the position adjacent to the triple bond bears an electron-withdrawing group (EWG) capable of stabilising the negative charge acquired (Scheme 72).

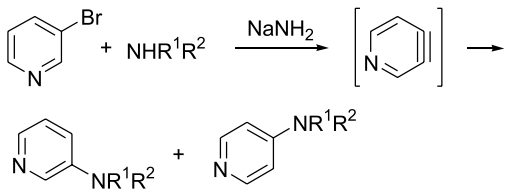
The intramolecular nucleophilic addition has had extensive use in alkaloid synthesis (benzophenanthridines, acridones, ergot-alkaloids and lycorines).

5.1. Addition of nitrogen nucleophiles

The reaction of arynes with primary and secondary amines provides a convenient route to alkylated anilines.[1a,b]

Various precursors of arynes have been involved in this kind of reaction such as TMS–phenols,[27] aryl triflates[17] or iodobenzenes (Scheme 73).[87]

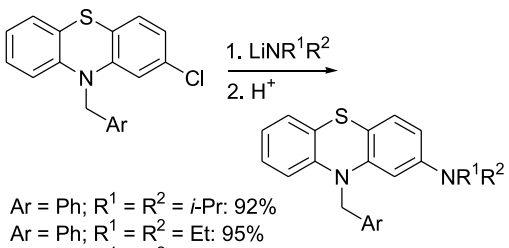
The nucleophilic condensation of 3,4-pyridyne led in good yields to a mixture of two products (Scheme 74).[88]



NHR^1R^2 = morpholine: 41% and 48%
NHR^1R^2 = piperidine: 36% and 44%
NHR^1R^2 = diethylamine: 38% and 34%
NHR^1R^2 = diphenylamine: 35% and 42%
NHR^1R^2 = pyrolidine: 44% and 51%

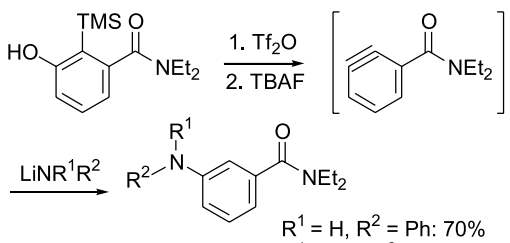
Scheme 74. Reactivity of 3,4-pyridyne with amines.

Various alkali metal amides were added to 2-chloro-10-(4′-fluorobenzyl)phenothiazine and 1-chloro-10-benzylphenothiazine, providing the corresponding 2-amino derivatives with complete regioselectivity (Scheme 75).[89]

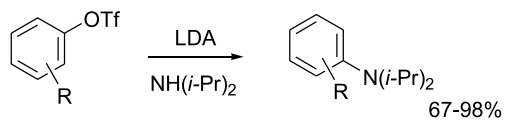


Ar = Ph; $R^1 = R^2$ = *i*-Pr: 92%
Ar = Ph; $R^1 = R^2$ = Et: 95%
Ar = Ph; $R^1 = R^2$ = *i*-Bu: 96%
Ar = Ph; R^1 = *t*-Bu; R^2 = H: 90%
Ar = 4-FC_6H_5 ; $R^1 = R^2$ = *i*-Pr: 94%
Ar = 4-FC_6H_5 ; $R^1 = R^2$ = Et: 93%

Scheme 75. Reactivity of 2-chloro-10-(4′-fluorobenzyl)phenothiazine with amines.

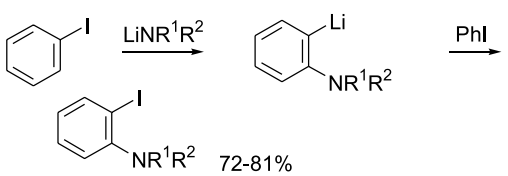


R^1 = H, R^2 = Ph: 70%
R^1 = Me, R^2 = Ph: 83%



67-98%

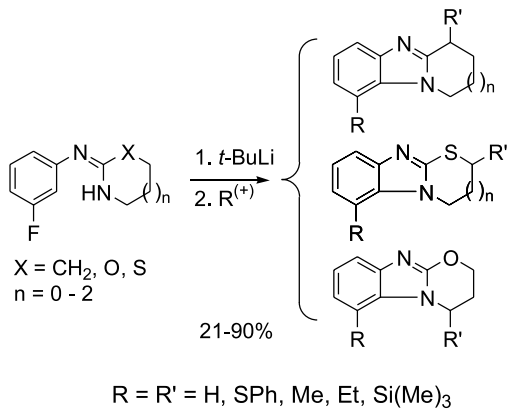
R = H, *p*-Me, *m*-Me, *o*-Me, *o*-MeO, *p*-MeO, *p*-Ph, *o*-Ph, 1-naphthyl, 2-naphthyl



72-81%

$R^1 = R^2 = -C(Me)_2-(CH_2)_3-C(Me)_2-$
$R^1 = R^2$ = *i*-Pr
$R^1, R^2 = -(CH_2)^5-$
$R^1, R^2 = -(CH_2)_4-$

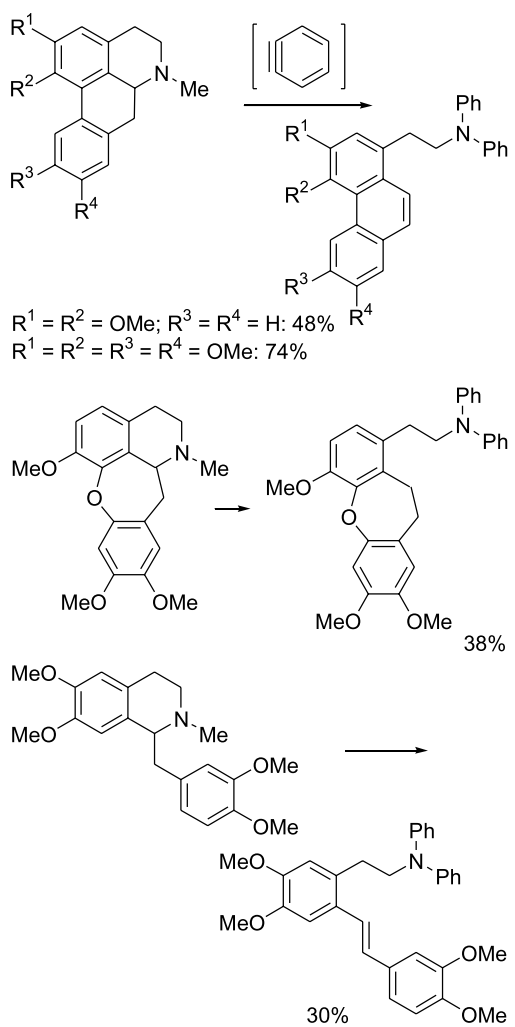
Scheme 73. Reactivity of arynes with amines.



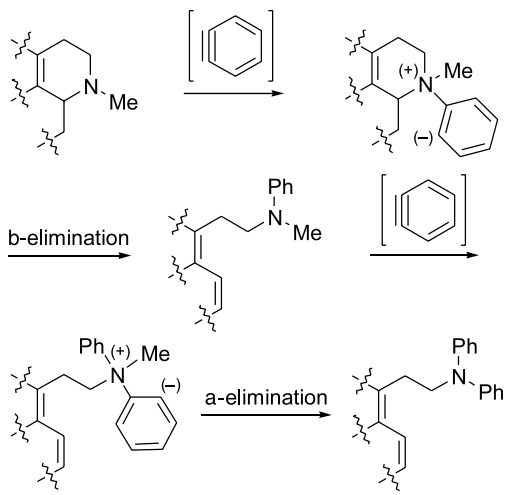
Scheme 76. Synthesis of 1,2-annulated benzimidazoles.

An intramolecular trapping of the benzyne generated from amidines was applied to the preparation of 1,2-annulated benzimidazoles (Scheme 76).[90]

A more complex reactivity of benzyne involving successive β and α-eliminations was observed with tertiary aporphines, benzylisoquinolines and cularines, giving rise to *N*,*N*-diphenylarylethylamines. Secondary aporphines yielded *N*-phenylnoraporphines (Scheme 77).[91]



Scheme 77. Synthesis of *N*,*N*-diphenylarylethylamines and *N*-phenylnoraporphines.

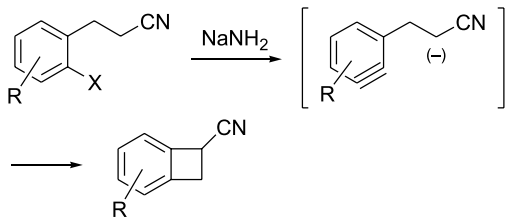


Scheme 78. Proposed mechanism involving successive β- and α-eliminations.

The above results are consistent with the mechanism as shown in Scheme 78.

5.2. Addition of carbon nucleophiles

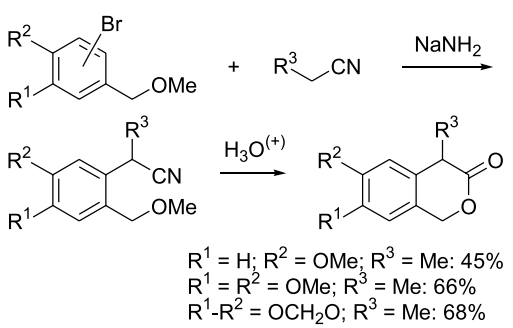
5.2.1. Lithioacetonitrile derivatives as carbon nucleophiles. One of the most general means of preparing benzocyclobutenes is the anion–aryne cyclisation of intermediates generated from nitriles (Scheme 79).[92]



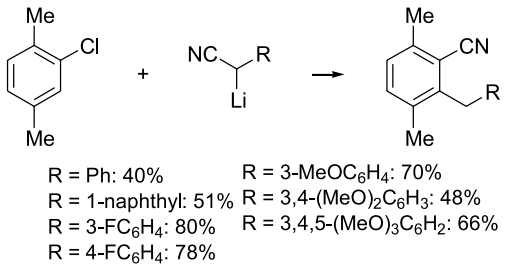
Scheme 79. Addition of lithioacetonitriles to arynes.

This type of benzocyclobutenes have been used for the synthesis of a number of products such as steroids[67] and various alkaloids.

Lithioalkyl- and lithioarylacetonitriles add arynes to give α-cyano(methoxymethyl)arenes which can be further hydrolysed to the corresponding isochroman-3-ones (Scheme 80).[93]



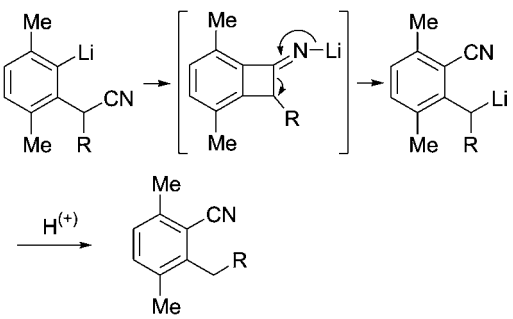
Scheme 80. Synthesis of isochroman-3-ones.



Scheme 81. Unexpected reaction between an aryne bearing two electron-releasing groups and a 2-aryl-2-lithioacetonitrile.

Aryne arylated nitriles, however, can also be obtained from a competitive pathway, depending on the nature of both the haloanisole and the nitrile. This unusual pathway predominates when a 3-methyl- or a 3-methoxyaryne, generated from an appropriate haloanisole possessing at least one electron-releasing group, is used in combination with a 2-aryl-2-lithioacetonitrile (Scheme 81).[94]

The tandem addition-rearrangement pathway is summarised below (Scheme 82).

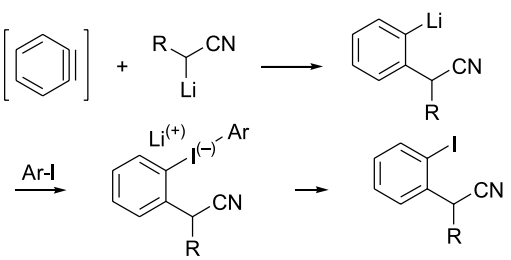


Scheme 82. Tandem addition-rearrangement pathway.

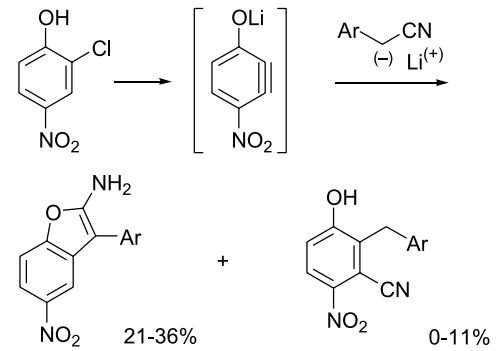
Very recently, Durst et al. reported that 2-iodobenzyl cyanides were the major products if the reaction of benzyne with the α-lithionitrile was carried out in the presence of iodobenzene (Scheme 83).[95]

This result is in agreement with a two-step process for obtaining the intermediate *N*-lithiobenzocyclobutenamine precursors of 2-cyanobenzylnitriles.

In 1998, Biehl reported the first example of a base-initiated aryne reaction involving a nitrobenzyne intermediate which was treated with various arylacetonitriles in the presence



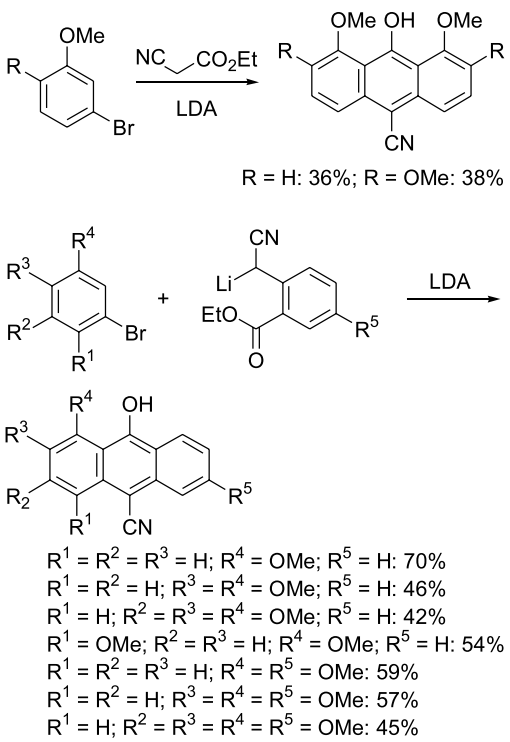
Scheme 83. Reactivity of benzyne with α-lithionitriles in the presence of iodobenzene.



Scheme 84. Synthesis of 2-amino-3-aryl-5-nitrobenzo[*b*]furans.

of LDA to give the 2-amino-3-aryl-5-nitrobenzo[*b*]furans as the major products (Scheme 84).[96]

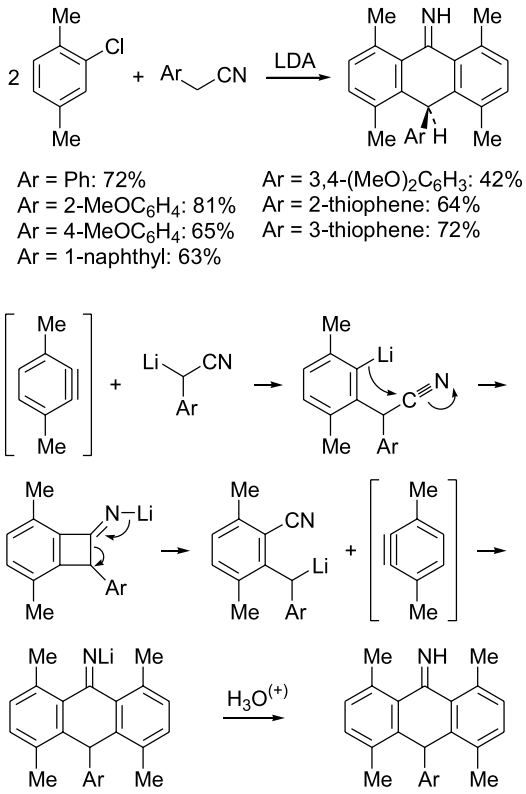
A new method for the brief regioselective synthesis of anthraquinones was reported by the same author via the reaction of the anions of ethyl cyanoacetate or of 2-(carbethoxyaryl)acetonitriles (Scheme 85).[97]



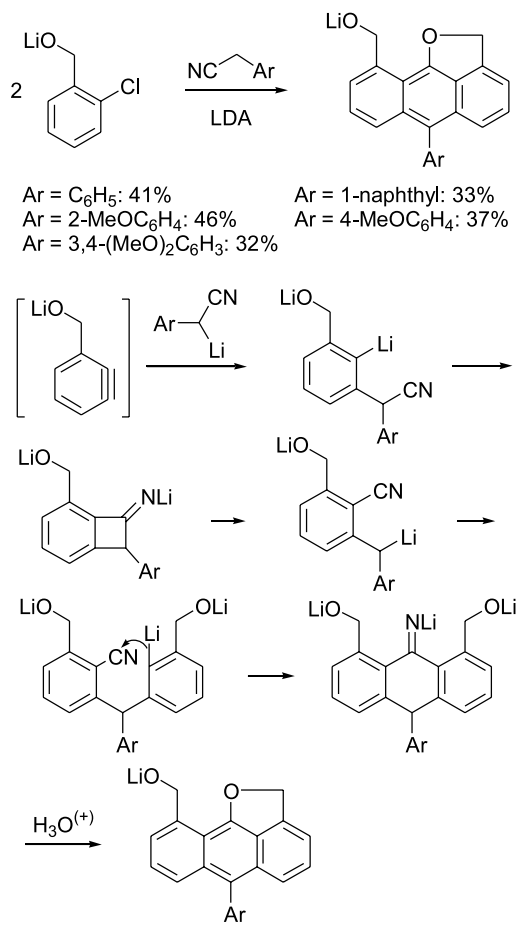
Scheme 85. Synthesis of anthraquinones.

When the reaction was carried out in the presence of two equivalents of benzyne, the products were the anthrone imines arising from the possible pathway shown (Scheme 86).[98]

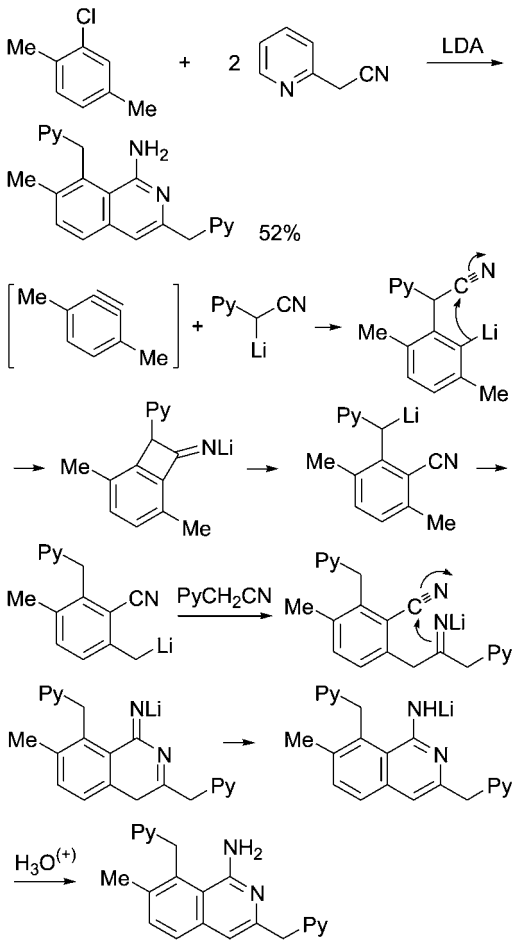
When the benzyne bears a hydroxymethyl group, the reaction provides 1-hydroxymethyl-6-aryl-2*H*-anthra[9,1-*bc*]-furans according to the possible mechanism depicted (Scheme 87).[99]



Scheme 86. Synthesis of anthrone imines.



Scheme 87. Synthesis of 1-hydroxymethyl-6-aryl-2*H*-anthra[9,1-*bc*] furans and the proposed mechanism.

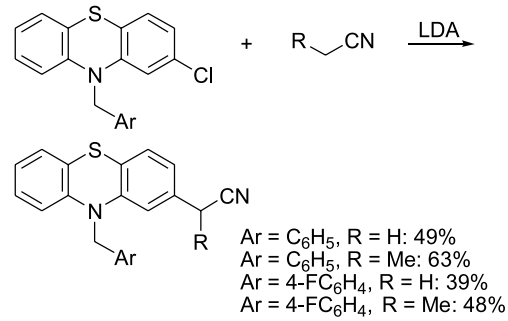


Scheme 88. Synthesis of aminoisoquinolines.

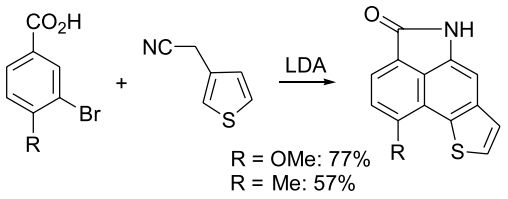
In contrast, when 2 equiv. of a particular nitrile are involved, the aminoisoquinolines are formed in one step (Scheme 88).[100]

The most important results reported from 1990–2002 concerning the reactivity of arynes with lithioacetonitriles derivatives are attributed to Biehl's group. These workers found, for example, that 2-(α-cyanoethyl)phenothiazines could be prepared by the reaction of chlorophenothiazines with nitriles (Scheme 89).[89]

Another finding of this group concerns the synthesis of



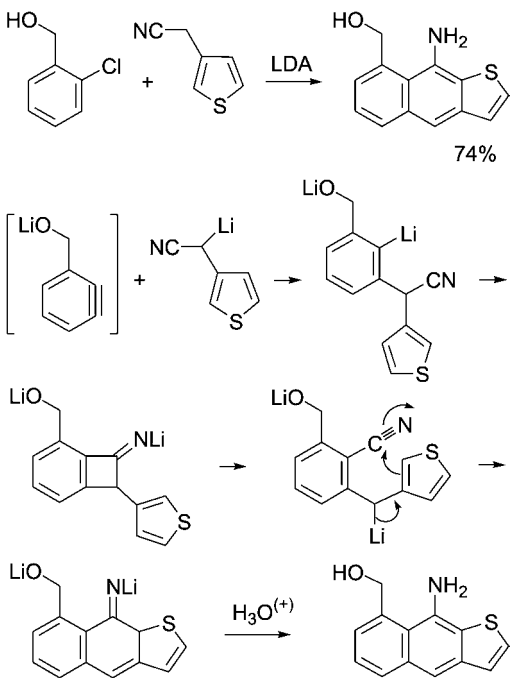
Scheme 89. Synthesis of 2-(α-cyanoethyl)phenothiazines.



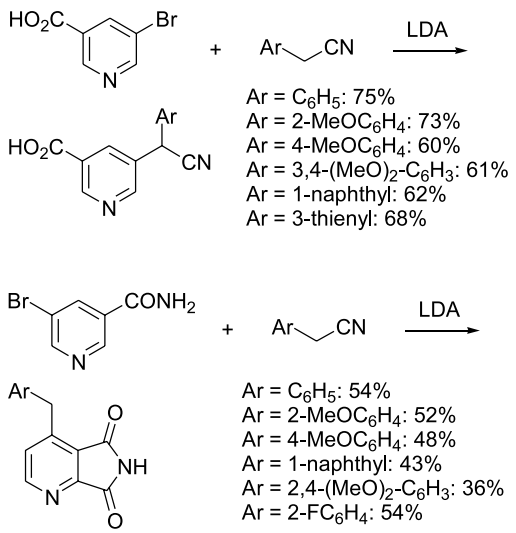
Scheme 90. Synthesis of 1-methoxy- and 1-methyl-thieno[2,3-*f*]benzo[*c*-*d*]indol-4(5*H*)-ones.

1-methoxy- and 1-methyl-thieno[2,3-*f*]benzo[*cd*]indol-4(5*H*)-ones by the reaction of, respectively, 4-methoxy-3-bromo- and 4-methyl-3-bromobenzoic acids with 3-thienylacetonitrile (Scheme 90).[101]

These compounds constitute the basic skeleton of ergot and aristolactam alkaloids.



Scheme 91. Synthesis of 2,9-aminonaphtho[2,3-*b*]thiophen-8-yl-methanol.

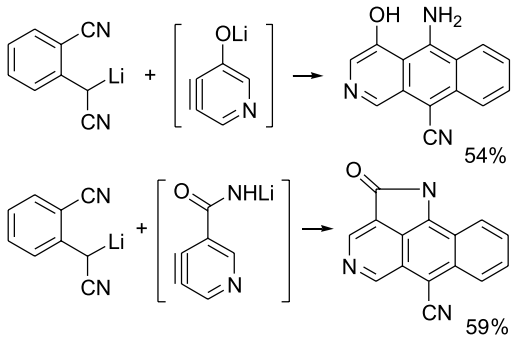


Scheme 92. Synthesis of 3-(α-arylcyanomethyl)nicotinic acids and 7-arylmethyl-1*H*-pyrrolo[3,4-*c*] pyridine-1,3-(2*H*)-diones.

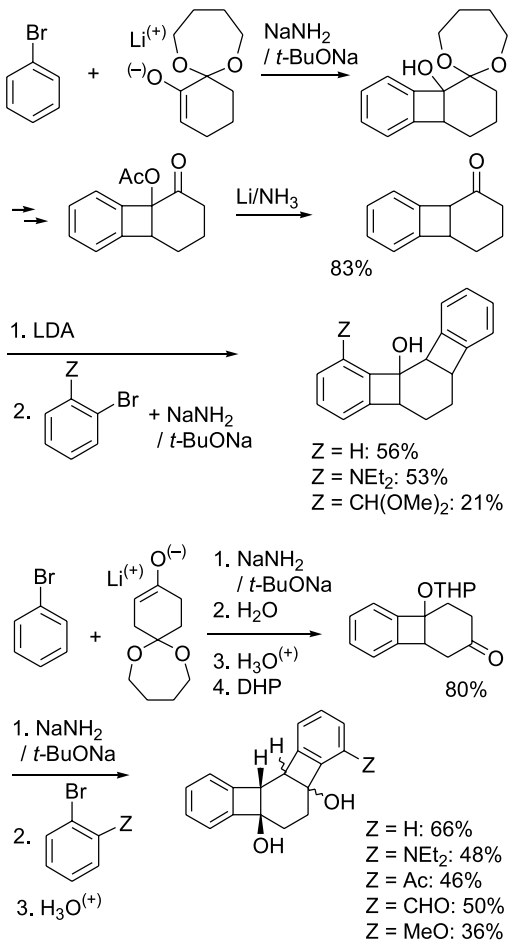
Another mechanism has been proposed to explain the formation of 2,9-aminonaphtho[2,3-*b*]thiophen-8-yl-methanol from the reaction of 3-thienylacetonitrile and 2-chlorobenzyl alcohol (Scheme 91).[102]

Recently, various hetarynes have been involved with arylacetonitriles, providing 3-(α-arylcyanomethyl)nicotinic acids from 5-bromonicotinic acid[103] and 7-arylmethyl-1*H*-pyrrolo[3,4-*c*] pyridine-1,3-(2*H*)-diones from 5-bromonicotinamide (Scheme 92).[104]

A number of nitrogen- and sulphur-containing polycyclic heterocycles were prepared by the reaction of hetarynes possessing charged groups with α-lithio-α-cyano-*o*-toluonitrile and α-lithio-3-thienylacetonitrile (Scheme 93).[102]



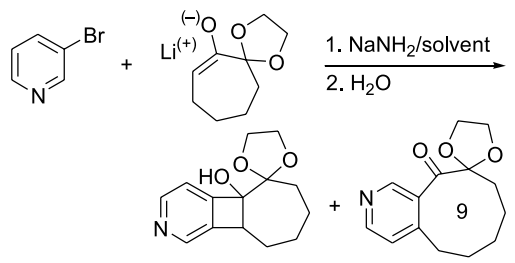
Scheme 93. Synthesis of polycyclic heterocycles.



Scheme 94. Synthesis of hexahydrobenzocyclobutabiphenylenes.

5.2.2. Lithioenolates as carbon nucleophiles. The condensation of enolates of cyclic ketones with arynes was investigated by Caubere et al., providing strained aromatic polycyclic compounds such as hexahydrobenzocyclobutabiphenylene (Scheme 94).[105]

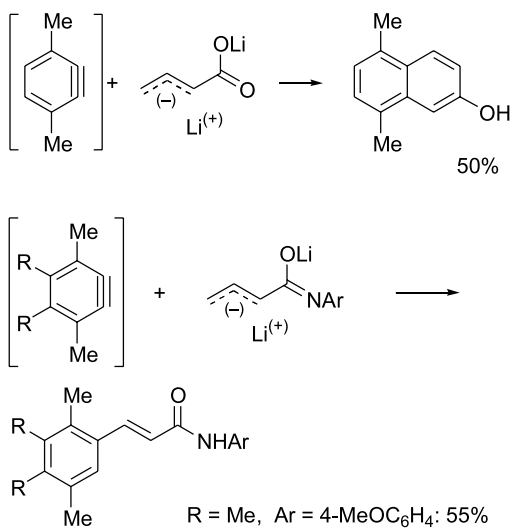
This reaction was extended to 3,4-dehydropyridine generated from 3-bromopyridine. According to the experimental conditions (solvent and temperature), it led to different major products (Scheme 95).[88]



Solvent	°C		Yield (%)
THF	20	40	18
DME	– 60	3	45

Scheme 95. Reaction of 3,4-dehydropyridine with cyclic ketone.

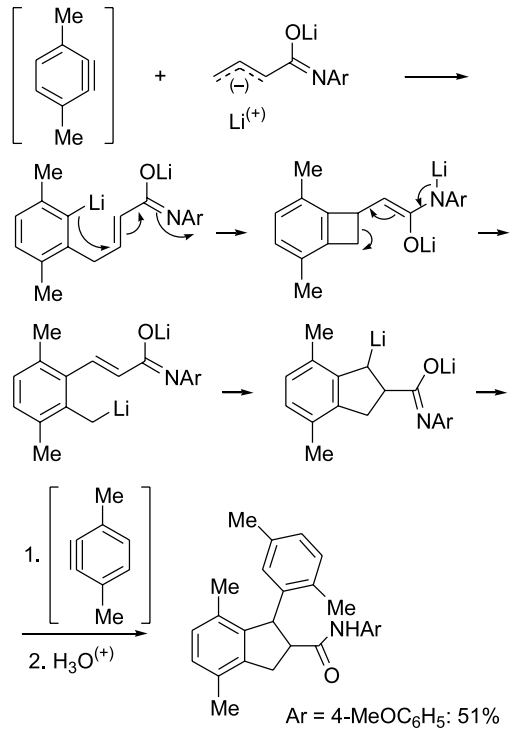
The *N*-(4′-methoxyphenyl)-2-butenamide dianion and 2-butenoic acid dianion reacted with various methyl-substituted benzynes to yield the rearranged cyclic products (Scheme 96).[106]



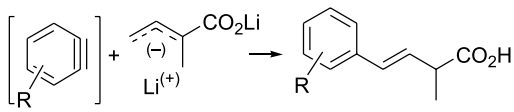
Scheme 96. Reaction of 2-butenoic acid dianion with *N*-(4′-methoxyphenyl)-2-butenamide dianion.

When a second equivalent of benzyne was involved in the course of the preceding reaction, the major product was 4,7-dimethyl-1-(2′,5′-dimethylphenyl)-indan (Scheme 97).

The tiglic acid (2-methyl-2-butenoic acid) dianion reacted with arynes to give (*E*)-4-aryl-2-methyl-3-butenoic acids which should prove to be synthetically useful building



Scheme 97. Synthesis of 4,7-dimethyl-1-(2′,5′-dimethylphenyl)-indan.



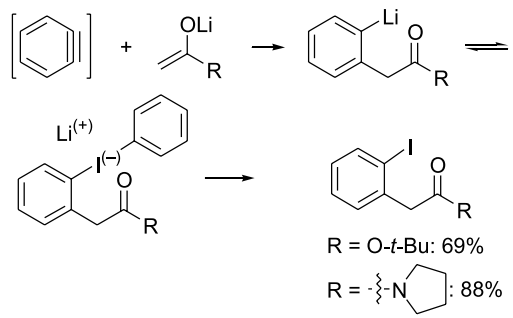
R = H: 75%	R = 3,4-$(MeO)_2$: 56%
R = 3-MeO: 72%	R = 3,4,5-$(MeO)_3$: 50%
R = 2,5-$(MeO)_2$: 59%	R = 5-MeO-2-Me: 70%

Scheme 98. Synthesis of 2-methyl-1-tetralones.

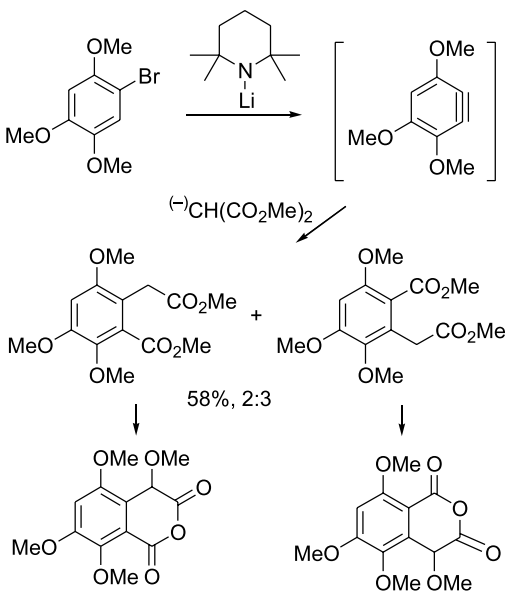
blocks for the construction of 2-methyl-1-tetralones (Scheme 98).[107]

In the presence of iodobenzene, the reaction between benzyne, generated from iodobenzene, and ester or amide lithium enolates gave the 2-iodo derivatives, generated by iodine transfer from iodobenzene to the intermediate 2-lithioaromatics (Scheme 99).[87]

Very recently, Kita et al. reported the total synthesis of a



Scheme 99. Reactivity of benzyne with enolates in the presence of iodobenzene.



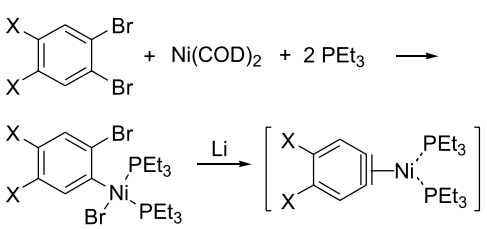
Scheme 100. Synthesis of fredericamycin A.

potent antitumour antibiotic,[108] fredericamycin A (Scheme 100), which involved the addition of malonate anion to benzynes.[109]

6. Transition metal-catalysed reactions of arynes

While alkynes participate in a number of synthetically useful metal-catalysed transformations, the synthetic applications of metal-aryne complexes are still limited owing to the lack of a general and mild method for their generation and the need for stoichiometric amounts of metal in their reactions. Only very recently have some new reactions of arynes, studied primarily by Castedo and by Yamamoto, been reported, amongst which are the efficient palladium(0)-catalysed cyclotrimerisation of arynes and the co-cyclisation of diynes and alkynes, allowing the synthesis of various polycyclic aromatic hydrocarbons.

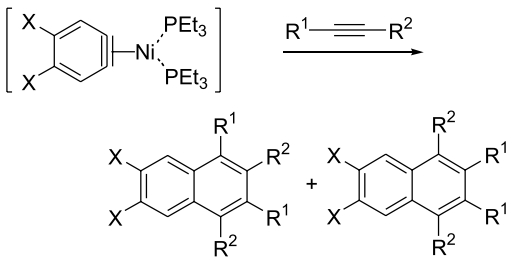
In 1993, Bennett et al. reported a convenient route to nickel(0)–aryne complexes (Scheme 101).[110]



Scheme 101. Synthesis of nickel(0)-arynes.

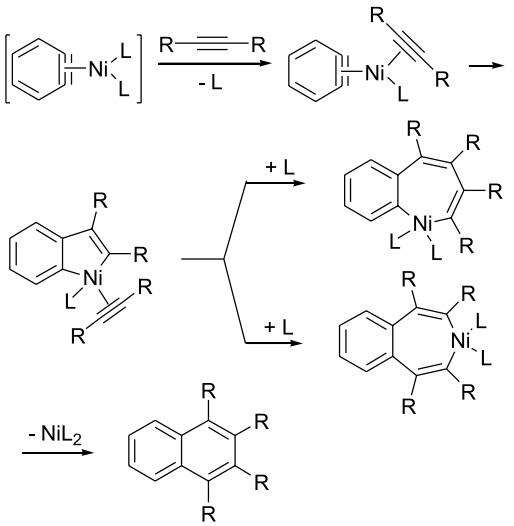
The latter complexes reacted with alkynes giving tetrasubstituted naphthalenes. Surprisingly, good regioselectivities also occurred with unsymmetrical acetylenes (Scheme 102).

The double insertions are supposed to proceed by the



X = H; R^1 = *t*-Bu; R^2 = H: 56% (100:0)
X = F; R^1 = *t*-Bu; R^2 = H: 45% (100:0)
X = H; R^1 = TMS; R^2 = H: 50% (86:14)
X = H; R^1 = TMS; R^2 = H: 55% (85:15)
X = F; R^1 = CO_2Me; R^2 = Me: 57% (0:100)
X = F; R^1 = CO_2Me; R^2 = H: 56% (26:74)
X = H; R^1 = CO_2Me; R^2 = H: 81% (23:77)
X = H; R^1 = CO_2*t*-Bu; R^2 = H: 73% (62:38)

Scheme 102. Reaction of nickel(0)-arynes with acetylenes.

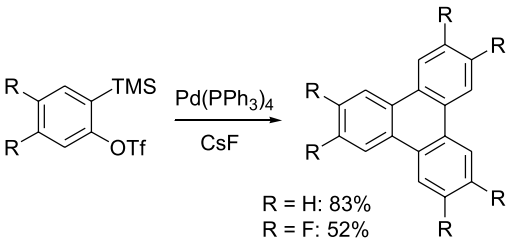


R = H, Me, *t*-Bu, $Si(Me)_3$, CO_2Me, CO_2*t*-Bu

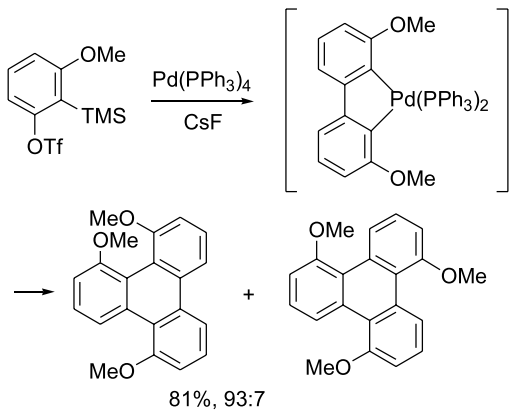
Scheme 103. Proposed mechanism for the reaction of nickel(0)-arynes with acetylenes.

reversible dissociation of one phosphane ligand, according to the mechanism shown in Scheme 103.

In 1998, Castedo[111] reported an efficient catalytic procedure for the trimerisation of arynes yielding triphenylenes which are found at the core of many discotic liquid crystals[112] and have therefore been the target of many synthetic studies (Scheme 104).[113]



Scheme 104. Synthesis of triphenylenes via trimerisation of arynes.

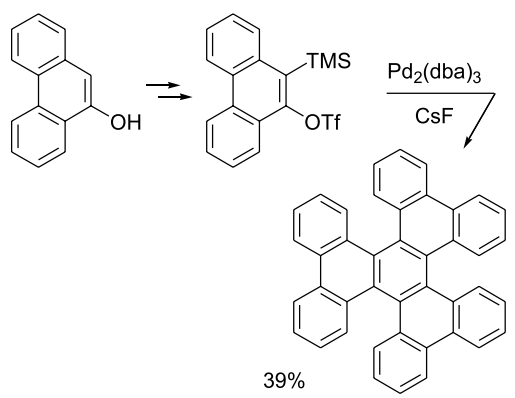


Scheme 105. High regioselectivity explained by a metallacyclic intermediate.

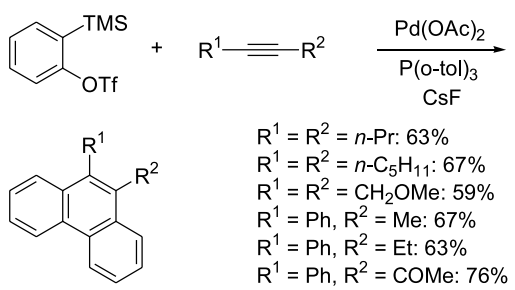
The high regioselectivity observed with 3-methoxybenzyne was explained by the selective formation of a metallacyclic intermediate (Scheme 105) as a result of C–C bond formation between the carbon atoms with less steric hindrance.

In order to evaluate the potential of the palladium-catalysed trimerisation of arynes for the synthesis of strained polycyclic hydrocarbons, the trimerisations of 1,2-didehydronaphthalene and 9,10-didehydrophenanthrene, generated from corresponding *o*-trimethylsilylaryl triflates, respectively, were studied (Scheme 106).[114]

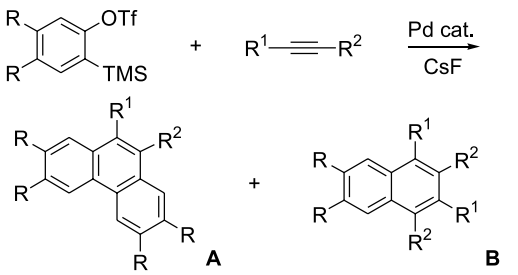
An easy access to complex polycyclic structures was therefore possible starting from the polycyclic arynes arising from the commercially available 9-phenanthrol.



Scheme 106. Trimerisation of 9,10-didehydrophenanthrene.



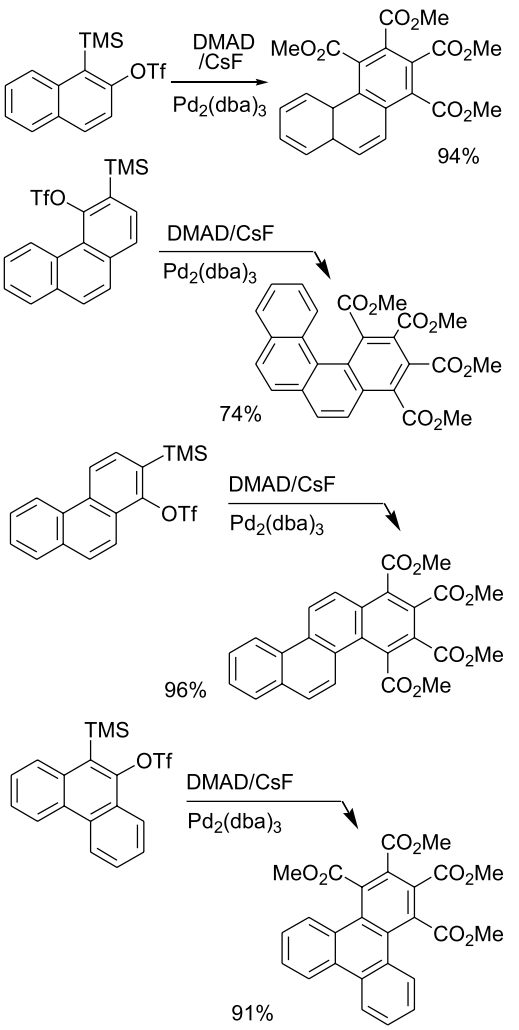
Scheme 107. Co-cyclisation of arynes with alkynes leading to phenanthrene derivatives.



Scheme 108. Co-cyclisation of arynes with alkynes leading to naphthalene or phenanthrene derivatives.

Table 2.

Pd cat.	R	R^1	R^2	Yield (%)	
				A	**B**
$Pd(PPh_3)_4$	H	CO_2Me	CO_2Me	84	7
$Pd_2(dba)_3$	H	CO_2Me	CO_2Me	10	83
$Pd(PPh_3)_4$	F	CO_2Me	CO_2Me	64	8
$Pd_2(dba)_3$	F	CO_2Me	CO_2Me	9	54
$Pd(PPh_3)_4$	H	CF_3	CF_3	65	0
$Pd_2(dba)_3$	H	CO_2Et	Me	63	8
$Pd_2(dba)_3$	H	Ph	Ph	16	1
$Pd_2(dba)_3$	H	Et	Et	28	0



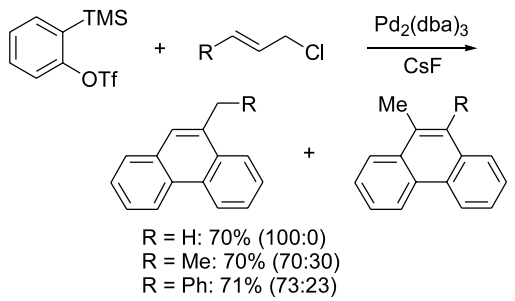
Scheme 109. Co-cyclisation of arynes and DMAD in the presence of $Pd_2(dba)_3$.

The palladium-catalysed co-cyclisation of arynes with alkynes was simultaneously described by Yamamoto's and Castedo's groups. The experimental conditions used by Yamamoto et al. ($Pd(OAc)_2/P(o\text{-}tol)_3$) afforded the phenanthrene derivatives exclusively in good yields, regardless of the electronic nature of the alkynes (Scheme 107).[115]

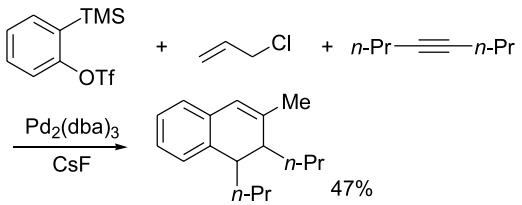
At the same time, Castedo reported that electron-deficient alkynes such as hexafluoro-2-butyne and dimethyl acetylenedicarboxylate (DMAD) gave phenanthrene derivatives in the presence of $Pd(PPh_3)_4$ while, with $Pd_2(dba)_3$, they afforded naphthalene derivatives in good yields.[116] With other alkynes, however no selectivity in the formation of phenanthrenes and naphthalenes was observed. Phenanthrene derivatives were therefore obtained, albeit in low yields, in the case of electron-rich alkynes (Scheme 108 and Table 2).

With the aim of generalising this methodology to more complex arynes, Castedo et al. showed that the palladium-catalysed co-cyclisation of polycyclic arynes with DMAD carried out in the presence of $Pd_2(dba)_3$ led selectively to co-cyclisation of one molecule of aryne and two molecules of DMAD (Scheme 109),[117] while $Pd(PPh_3)_4$ as catalyst induced the co-cyclisation of two molecules of aryne with one molecule of DMAD (Scheme 108).[115,116]

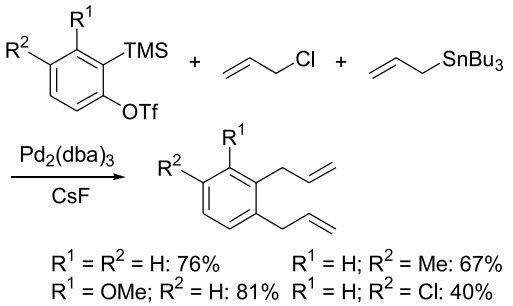
Finally, the intermolecular cycloaddition of arynes with DMAD can be made highly chemoselective and can easily be switched between the formation of phenanthrenes and the formation of naphthalenes by the appropriate selection of



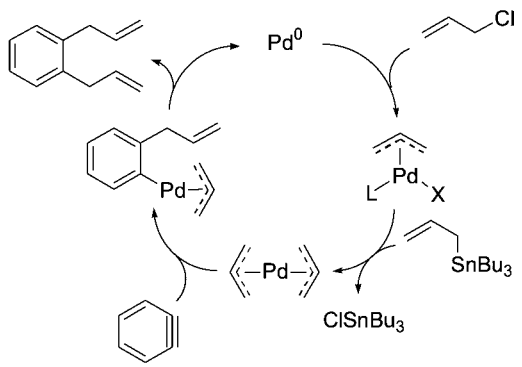
Scheme 110. Palladium-catalysed reaction of allyl chlorides with benzyne.



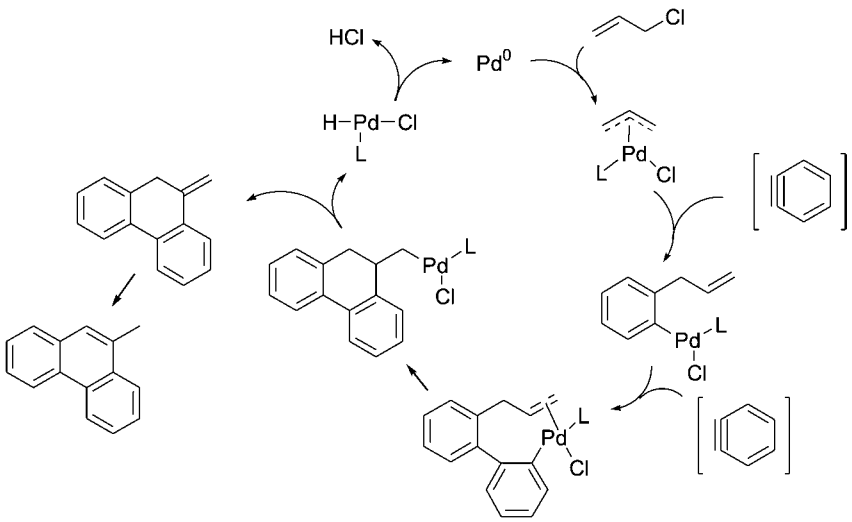
Scheme 112. Palladium-catalyzed reaction of allylchloride, benzyne and alkyne.



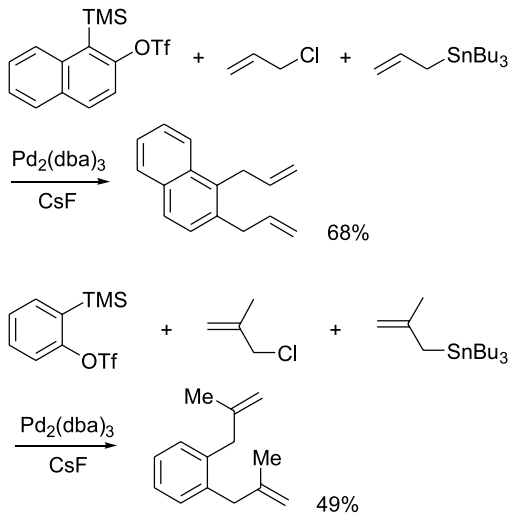
Scheme 113. Palladium-catalysed reaction of allyl chloride, benzyne and allyltributylstannane.



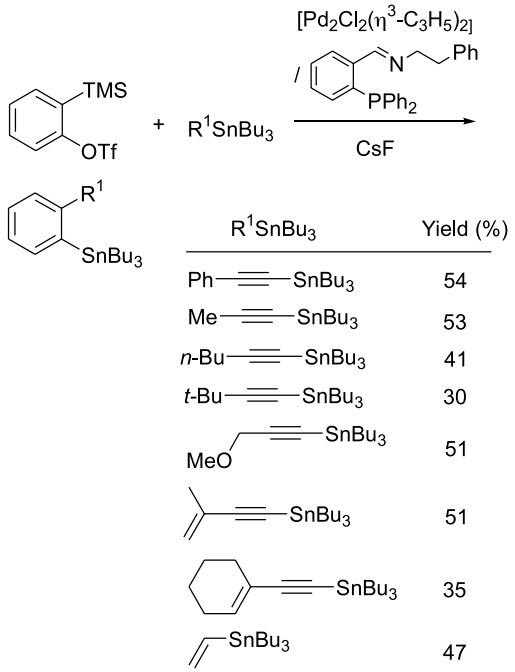
Scheme 114. Proposed mechanism for the reaction between allyltributylstannane, allyl chloride and benzyne.

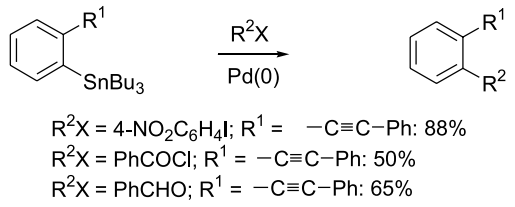


Scheme 111. Proposed mechanism for the palladium-catalysed reaction of allyl chlorides with benzyne.

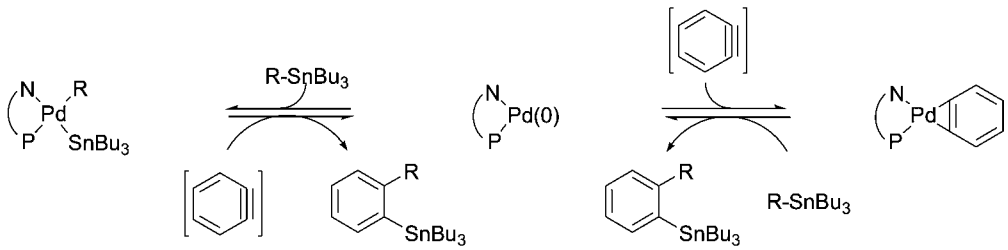


Scheme 115. Palladium-catalysed reaction between allyltributylstannane, allyl chloride and naphthyne.

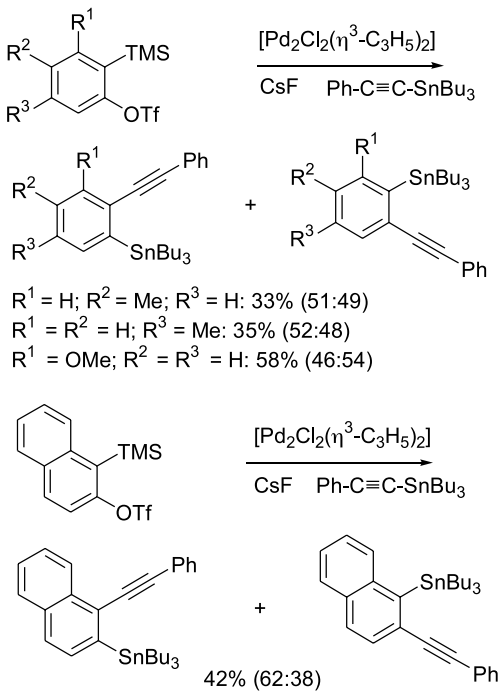




Scheme 116. Synthesis of *o*-substituted arylstannanes.



Scheme 117. Proposed mechanisms for the synthesis of *o*-substituted arylstannanes.



Scheme 118. Reaction of benzynes or 1,2-naphthalynes with phenylethynyltributyltin.

catalyst. In addition, by an appropriate choice of catalyst, the reaction can also be selectively directed either towards the co-cyclisation of one molecule of aryne with two molecules of alkyne or to the reaction of two molecules of aryne with one molecule of alkyne.

Very recently, Yamamoto et al. reported that benzyne was very reactive as a carbopalladation partner of π-allylpalladium chloride. Indeed, the palladium-catalysed reaction of allyl chlorides with benzyne produced phenanthrene derivatives (Scheme 110).[118]

A plausible mechanism for this unprecedented intermolecular benzyne-benzyne-alkene insertion reaction is shown (Scheme 111).

In the same way, a successful insertion of benzyne–alkyne–alkene was carried out (Scheme 112).

1,2-Diallylated derivatives of benzene were prepared by the reaction of arynes with a bis-π-allylpalladium complex generated from allyl chloride and allyltributylstannane (Scheme 113).[119]

Insertion of Pd(0) to allyl chloride gave the π-allylpalladium via the reaction with allyltributylstannane and

susequent addition of the two allyl groups to the benzyne led to the final product (Scheme 114).

Extension of this reaction to other arynes or allyl systems led to other products (Scheme 115).

Arynes could be converted in the presence of a catalytic amount of a palladium-iminophosphine complex to *o*-substituted arylstannanes which were further transformed into a wide variety of 1,2-disubstituted arenes (Scheme 116).[120]

Two plausible catalytic cycles of carbostannylation are depicted (Scheme 117).

This reaction could be successfully applied to other arynes such as substituted benzynes or 1,2-naphthalynes in the presence of phenylethynyltributyltin (Scheme 118).

7. Conclusions

Despite the fact that they are highly reactive species, arynes are key intermediates for the synthesis of a large number of natural products. In particular, their use in the Diels–Alder process with a wide range of dienes constitutes an important synthetic tool.

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Biographical sketch

Hélène Pellissier was born in Gap, France. She carried out her PhD under the supervision of Dr G. Gil in Marseille and then entered the Centre National de la Recherche Scientifique in 1988. After a postdoctoral period in Professor K. P. C. Vollhardt's group, she joined the group of Professor M. Santelli in Marseille in 1992, where she developed research in electrophilic activation and its large application in organic synthesis. Thus, she elaborated several new very short total syntheses of steroids starting from 1,3-butadiene and benzocyclobutenes.

Maurice Santelli was born in Marseille in 1939. He received his PhD in chemistry working with Professor M. Bertrand (homoallenylic participation, non-classical ion). He had a postdoctoral position at the University of Cambridge (UK) in 1973 (Professor R. A. Raphael) (Prelog-Djerassi lactone). After an appointment at the University of Oran (Algeria) (1975–77), he is presently Professor of Chemistry at the University of Aix-Marseille III. His main research areas are electrophilic activation, palladium chemistry, synthesis of non-natural steroids and poly-unsaturated fatty acids.