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Use of benzynes for the synthesis of heterocycles

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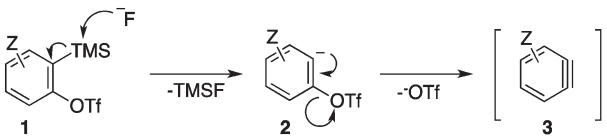
About two decades after Kobayashi's discovery in 1983 of a very mild way of generating highly reactive aryne intermediates, the synthetic community embraced *o*-(trimethylsilyl)aryl triflates as convenient and versatile aryne precursors for the synthesis of carbocycles and heterocycles, as well as natural products and pharmaceutically promising drug candidates. This review provides a comprehensive overview of the construction of heterocycles using Kobayashi's silylaryl triflate aryne precursors. It is organized according to the type of heterocycle generated.

1. Scope of the review

In the last decade, arynes, particularly those that can be generated from the corresponding *o*-(trimethylsilyl)aryl triflates **1**, have emerged as powerful synthons in organic synthesis. Recent reviews have covered the use of aryne-based methodologies in the areas of multicomponent reactions;[1] the insertion of arynes into carbon–carbon, carbon–heteroatom and heteroatom–heteroatom bonds;[2,3] and the synthesis of natural products.[4] The very convenient, mild method for generating arynes from *o*-(trimethylsilyl)aryl triflates developed by Kobayashi in 1983 allows one to conveniently generate a highly reactive benzyne intermediate **3** at reasonable temperatures, using readily accessible solvents and only moderately basic fluoride ion (Scheme 1).[5,6]



Scheme 1 Generation of benzyne using the Kobayashi method.

The Kobayashi method contrasts with other methods of aryne generation involving the use of strong bases and low temperatures, the thermolysis of potentially explosive benzenediazonium carboxylates, and the oxidation of fairly inaccessible 1-aminobenzotriazoles using stoichiometric amounts of toxic $Pb(OAc)_4$.[7] The Kobayashi method takes advantage of the high affinity of fluoride for silicon (the bond dissociation energy of Si–F in TMSF is 158 kcal mol^{-1})[8] and the ease with which the aryl anion **2** formed *in situ* intramolecularly extrudes a good leaving group, *e.g.* triflate, although other leaving groups have been considered lately as well.[9] It is noteworthy that the same basic approach, involving the generation of an

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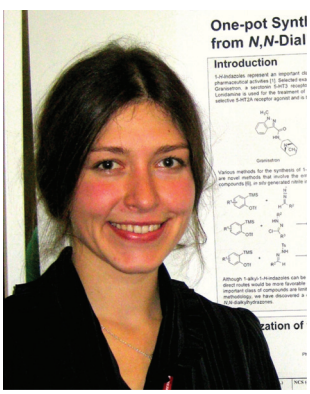

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unstable intermediate due to the high stability of the Si–F bond and departure of a neighboring leaving group, has been used to generate strained cycloalkynes[10] and highly reactive *ortho*-quinone methides.[11]

The great advantage of generating a benzyne by the Kobayashi route is the ability to control the rate of benzyne generation by varying the concentration of the fluoride ion in solution. Thus, one can instantly generate a benzyne in THF using tetrabutylammonium fluoride (TBAF), which is quite soluble in THF. It is possible to slow down the rate of benzyne generation by employing CsF in MeCN (at room and elevated temperatures) or CsF in THF (at elevated temperatures). To further slow down the formation of the benzyne, CsF in toluene (Tol)–MeCN mixtures can be used. The nature and amount of the added fluoride source, the solvent, and the temperature of the reaction can have a profound effect on the overall rate and success of such aryne reactions.

This review is focused on the construction of heterocycles using Kobayashi's silylaryl triflate aryne precursors. It is organized according to the nature of the final heterocycle.

2. Synthesis of 5-membered ring-containing heterocycles

2.1. Benzotriazoles

Benzynes are well known to participate in cycloaddition reactions with 1,3-dipoles. In 2008, Larock and co-workers reported the so-called "aryne click" reaction, a cycloaddition between azides **4** and arynes generated *in situ* (Scheme 2).[12]

The reaction proceeds at room temperature and gives rise to the benzotriazoles **5** in 51–100% yields. Aryl, benzyl, and allyl azides provide excellent (83–100%) yields regardless of the substitution pattern. Alkyl and heteroaryl azides give slightly lower (51–93%) yields with ester, alkynyl, and hydroxyl groups being tolerated under the reaction conditions. Sulfonyl and alkenyl azides react poorly or not at all. Substituted

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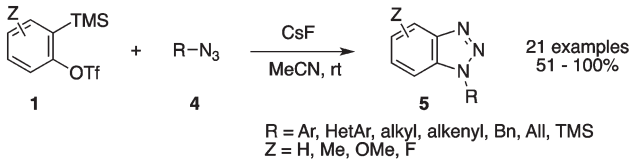
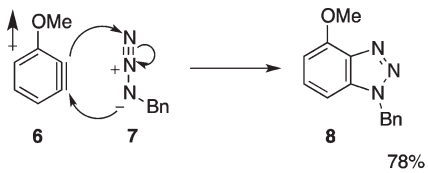


Scheme 2 Synthesis of benzotriazoles developed by Larock.



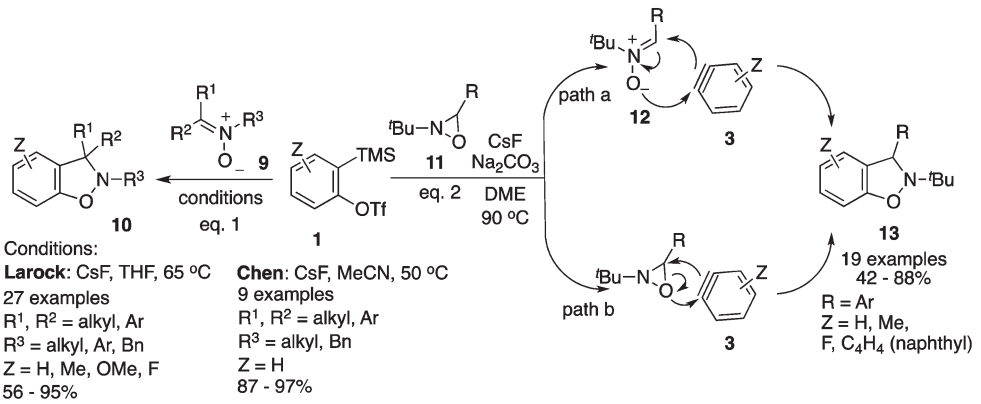
Scheme 3 The transition state for coupling with 3-methoxybenzyne.

benzynes provide the corresponding products in 56–78% yields. It is noteworthy that the unsymmetrical benzyne **6** provides the corresponding product **8** as a single regioisomer, a result of the expected[13] transition state (Scheme 3) in which the nucleophilic portion of the azide moiety adds to the more electron-deficient and more sterically accessible pseudo *meta*-position of the 3-methoxybenzyne **6**. Noteworthy, in most methodologies described in this review, the reaction with 3-methoxybenzyne is highly regioselective, allowing one to predict the initial steps of the reaction's mechanism.

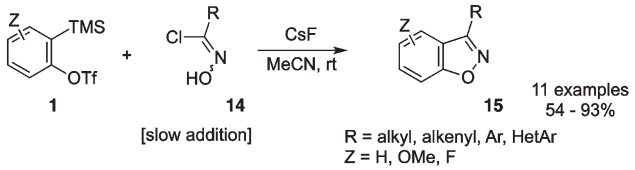
2.2. Benzisoxazolines

Since nitrones constitute another class of readily available, stable and isolable 1,3-dipoles, one should expect the analogous cycloaddition reaction of benzynes generated *in situ* with nitrones **9** to lead to the benzisoxazoline moiety. Indeed, under two different sets of reaction conditions (CsF/MeCN at 50 °C and CsF/THF at 65 °C), the Chen[14] and Larock[15] groups have independently reported successful one-pot syntheses of benzisoxazolines **10** in 87–97% and 56–95% yields respectively (Scheme 4, eqn (1)). While only unsubstituted alkyl-, aryl-, and benzyl-substituted nitrones were studied under the first set of reaction conditions, the reaction using CsF/THF tolerates a wide range of functional groups, including halide, thio ether, ester, amine, alkenyl, nitrile, and nitro functional groups.

The Larock group has also recently reported that oxaziridines react with arynes with formation of the C–O insertion products, benzisoxazolines (Scheme 4, eqn (2)).[16] In this case, the bulky *tert*-butyl substituent present on the nitrogen atom seems to be required to achieve high yields. Adding stoichiometric amounts of Na_2CO_3, whose role is not obvious, and running the reaction in DME at 90 °C allows one to obtain the desired benzisoxazolines **13** in 42–88% yields. The substrates that failed to provide the expected products contained a nitro group, a pyridine moiety, or an alkyl substituent on the carbon of the starting oxaziridine. The authors considered two possible mechanisms for this coupling reaction: (a) formation of the nitrone intermediate **12**, followed by a [3 + 2] cycloaddition with the benzyne intermediate **3**; or (b) a



Scheme 4 Synthesis of benzisoxazolines.



Scheme 5 Synthesis of benzisoxazoles.

concerted mechanism with the oxygen atom of the oxaziridine ring attacking the electrophilic benzyne **3**.[17]

2.3. Benzisoxazoles

Benzisoxazoles are the expected product of a formal cycloaddition between nitrile oxides and arynes. Unfortunately, the majority of nitrile oxides are not stable and isolable and they tend to dimerize.[18] One of the convenient ways to generate nitrile oxides is by the dehydrohalogenation of chlorooximes.[19] The Larock group found that CsF cannot only induce the generation of benzyne from a silylaryl triflate, but can also act as a base to generate the unstable nitrile oxide from the parent chlorooxime (Scheme 5).[20] Both intermediates are highly reactive, *e.g.* nitrile oxides are known to form different types of dimerization products.[18] Therefore, the challenge of this methodology was to find reaction conditions where the rates of benzyne and nitrile oxide generation match each other, thereby favoring the cycloaddition process over dimerization and other side reactions. Indeed, slow addition of the chlorooxime **14** to a mixture of the benzyne precursor **1** and CsF in MeCN at room temperature allows one to isolate the desired aryl, alkyl, alkenyl, and heterocyclic 3-substituted benzisoxazoles **15** in 54–93% yields (Scheme 5).

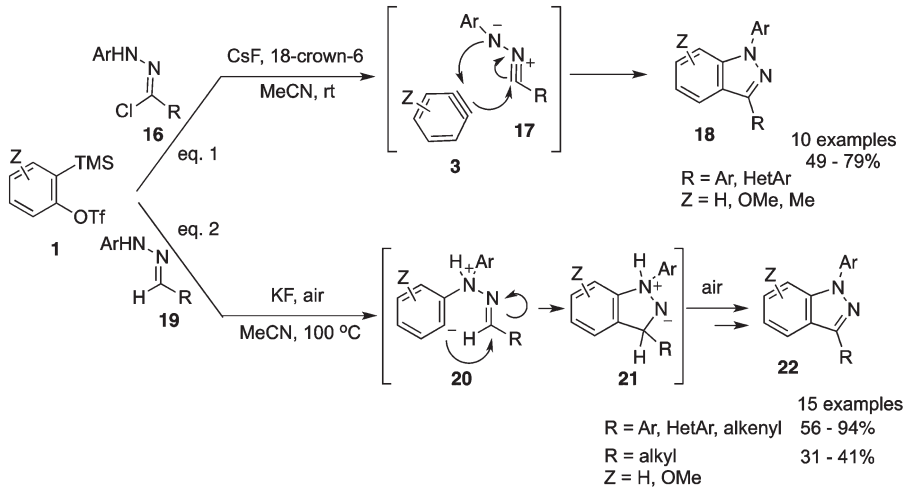
About the same time, two complementary methodologies for the synthesis of benzisoxazoles appeared, developed by the research groups of Browne[21] and Moses.[22] The Browne methodology allows one to obtain aryl, alkenyl, and heteroaryl-substituted benzisoxazoles in 73–99% yields, utilizing TBAF and a 3-fold excess of the chlorooxime **14** in THF. In this case, slow addition of the reagents to the reaction mixture is not necessary. Moses' approach utilizes only a 1.5 fold excess of the chlorooxime **14** and TBAF in THF and affords the desired benzisoxazoles in 50–99% yields. Only aryl- and benzyl-containing chlorooximes were examined using this latter approach.

2.4. 1*H*-Indazoles

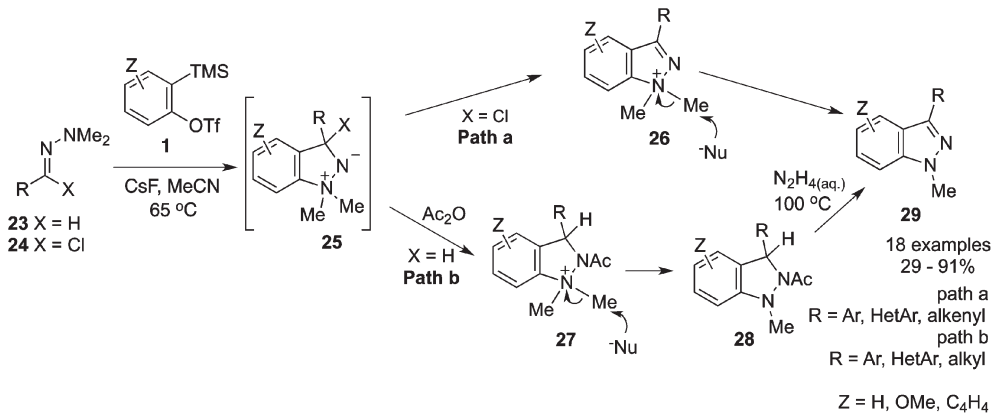
An aza-analogue of a nitrile oxide, namely a nitrile imine **17**, can be generated *in situ* from hydrazonoyl chlorides **16** by a based-induced dehydrohalogenation. In fact, Moses and co-workers have shown that hydrazonoyl chlorides derived from chlorinated *N*-phenyl hydrazones of aryl and heteroaryl aldehydes afford the corresponding *N*-aryl substituted 1*H*-indazoles **18** after a [3 + 2] cycloaddition process with benzyne **3** (Scheme 6, eqn (1)).[23] The yields of the products **18** range from 49% to 79%. Optimal conditions were found to use CsF in the presence of stoichiometric amounts of 18-crown-6 in MeCN at room temperature. This unusual combination of reagents suppressed formation of the undesired self-dimerization products of the highly reactive nitrile imine intermediates.

Shi has found that one can start from the *N*-phenyl hydrazones of aldehydes **19** and obtain the aforementioned 1*H*-indazole moiety upon reaction with a benzyne.[24] Apparently, the reaction goes through an ionic annulation pathway, followed by an aromatization step (Scheme 6, eqn (2)). In this protocol, 3-alkyl-containing indazoles are obtained in poorer (31–41%) yields than the products bearing aryl, heteroaryl, and alkenyl substituents (56–94%). The reaction proceeds at 100 °C in the presence of KF as the fluoride source.

The Larock group has found[25] that the corresponding indazoline cationic intermediate of type **25** (compare with **21**), generated from the reaction of *N*,*N*-disubstituted hydrazones **23** and benzyne **3**, can be conveniently transformed into the desired indazole structure by one of the following modifications (Scheme 7): (a) NCS-mediated chlorination of the starting hydrazone; or (b) trapping the anion of type **21** by Ac_2O and subsequently cleaving the protecting group, followed by aromatization to generate the desired indazoles **29** in 29–91% yields. The Ac_2O-mediated pathway (path b) allows one to conveniently synthesize 3-alkyl-substituted indazoles. Both methods tolerate ester, nitrile, terminal alkynyl, and halide functional groups, and some heteroaryl moieties. Using an



Scheme 6 Synthesis of *N*-aryl 1*H*-indazoles.



Scheme 7 Two complementary pathways leading to indazoles.

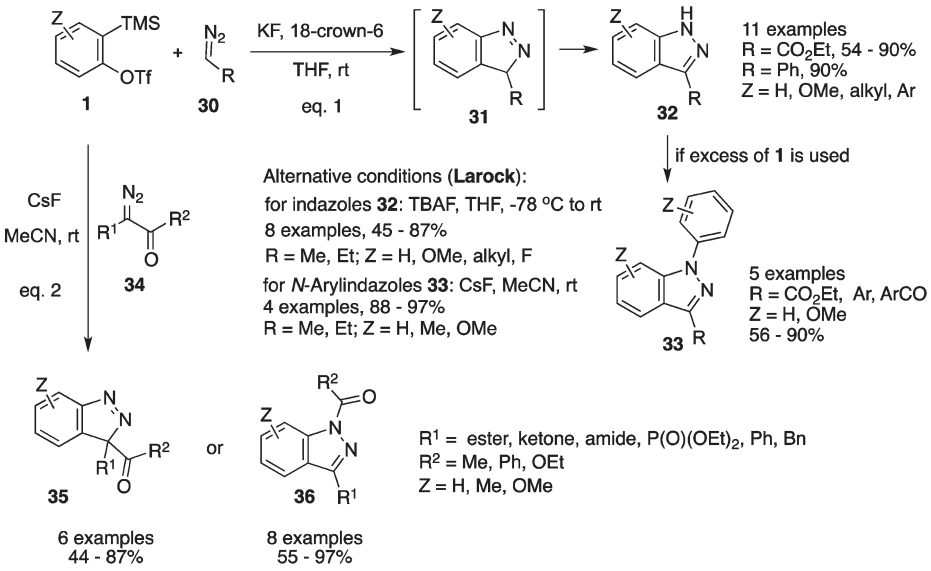
alkenyl-containing hydrazone afforded the corresponding indazole in only a 32% yield.

Diazo compounds also engage in a cycloaddition reaction with a benzyne with the formation of 1*H*-indazoles. Yamamoto has shown[26] that the reaction of ethyl diazoacetate and the silylaryl triflates **1** in the presence of KF/18-crown-6 in THF at room temperature leads to formation of the corresponding unsubstituted or *N*-arylated (depending on the benzyne/substrate ratio) indazoles **32** in 54–90% yields (Scheme 8, eqn (1)). Phenyldiazomethane successfully provided the corresponding products in 90% and 56% yields.

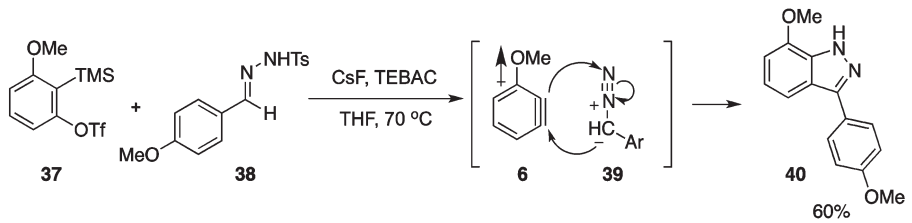
The Larock group found that the yield of the unsubstituted indazole **32** can be improved to 85% if the reaction is run in the presence of TBAF in THF at −78 °C (Scheme 8, eqn (1)).[27] They also found that running the reaction with 2.4 equiv. of the benzyne precursor in the presence of CsF in MeCN affords the *N*-arylated product **33** in a 97% yield.

The disubstituted stabilized diazomethane derivatives **34** in an analogous reaction provide the direct coupling products, 3,3-disubstituted 3*H*-indazoles **35**, in 44–87% yields (Scheme 8, eqn (2)). However, in many cases the carbonyl-containing functional group further undergoes a 1,3-migration from the carbon to the nitrogen atom with formation of the *N*-substituted 1*H*-indazoles **36** in 55–97% yields. In this rearrangement, a ketone group migrates in preference to an ester or amide group.

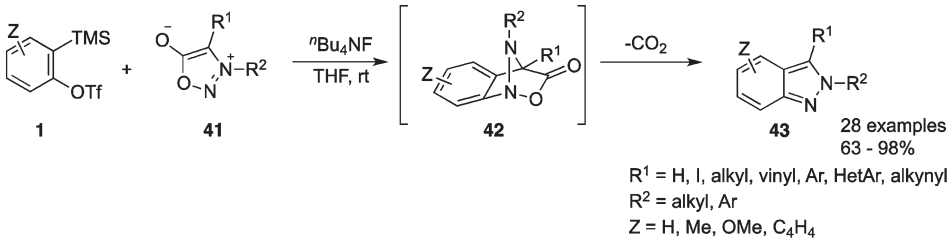
Shi has demonstrated that the diazo substrates **30** can also be generated *in situ* from the corresponding *N*-tosylhydrazones.[24,28] The optimal conditions for this transformation were found to be CsF/THF at reflux temperatures with the addition of sub-stoichiometric amounts of a common phase transfer catalyst, $[Et_3NBn]^+Cl^-$ (TEBAC). As opposed to the method with pre-prepared diazo compounds,[27] formation of the undesired *N*-arylated indazole **33** was minimal. Hydrazones derived from aromatic and heteroaromatic aldehydes afford the unsubstituted 1*H*-indazoles in 36–85% yields. The regioselectivity of the reaction of the tosyl hydrazone **38** with the unsymmetrical benzyne **37** (Scheme 9), as well as the detection of the characteristic absorption of diazo functionality in the IR spectrum of the reaction mixture of **38** with CsF, has been presented as evidence for the formation of the diazo intermediate **39**.



Scheme 8 Reaction of benzyne with diazo compounds.



Scheme 9 Reaction of an *N*-tosyl hydrazone with 3-methoxybenzyne.



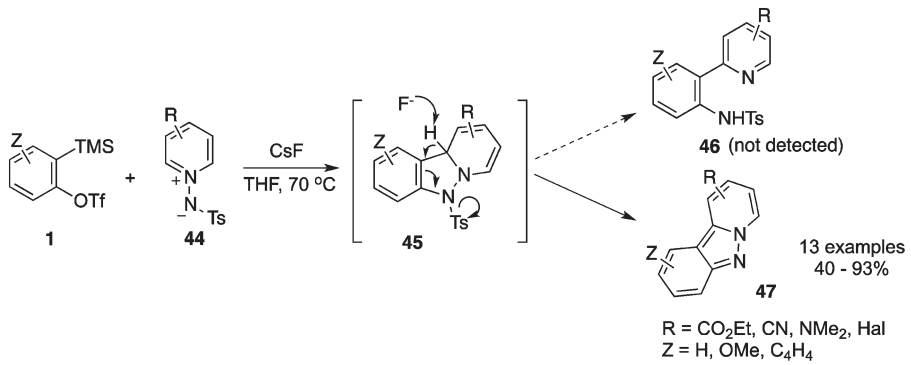
Scheme 10 Reaction of sydnones and arynes.

2.5. 2*H*-Indazoles

2*H*-Indazoles have been successfully prepared by Shi and Larock using the [2 + 3] cycloaddition reaction between arynes and sydnones (**41**), which are stable mesoionic cyclic compounds, followed by CO_2 extrusion (Scheme 10).[29] The reaction is most efficient in THF at room temperature using TBAF as the fluoride source, and affords the desired 2*H*-indazoles **43** in 63–98% yields. A wide range of functional groups is tolerated: alkyl, vinylic, benzylic, aryl, heteroaryl, alkynyl, halide, dioxolane and ketone functionalities among others. The limitations of this methodology include nitro-substituted substrates and acylated sydnones (Scheme 10, R^1 = Ac), which apparently are completely unreactive towards the benzyne.

2.6. Pyrido[1,2-*b*]indazoles

The cycloaddition between pyridinium imide derivatives and benzyne has been reported decades ago.[30] However, the imides studied, which were stabilized by PhC(O)- and EtOC(O)-groups, afforded only 3–13% yields of the corresponding [3 + 2] cycloaddition products with the benzyne. It has recently been found that using the Ts-stabilized pyridinium imide **44** and the Kobayashi benzyne precursor **1** produces the desired coupling reaction in much higher yields.[31] The reaction presumably starts with a cycloaddition process leading to the intermediate **45** (Scheme 11). The base-promoted elimination of the tosyl anion furnishes the tricyclic moiety **47**. The excellent leaving ability of the tosyl group (and, in some cases,



Scheme 11 Reaction of pyridinium imides and arynes.

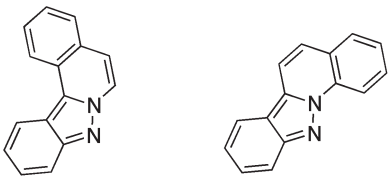


Fig. 1 Products of the reaction of quinolinium and isoquinolinium imides and benzyne.

a nosyl group) prevents formation of the side product **46** observed in the case of the other leaving groups (*e.g.* Ac, Boc).

Thus, reacting the imide **44** with *o*-(trimethylsilyl)aryl triflates at 70 °C in the presence of CsF in THF affords the tricyclic pyrido[1,2-*b*]indazoles **47** in 40–93% yields. A variety of functional groups are tolerated under the reaction conditions, such as ester, nitrile, halo, and amino functionalities. Unsymmetrical pyridinium imines result in the formation of mixtures of regioisomers with only poor to modest selectivities. Employing isoquinolinium and quinolinium imides in the same transformation allows one to obtain the tetracyclic heterocycles **48** and **49** in 87% and 92% yields respectively (Fig. 1).[32]

2.7. Pyrido[2,1-*a*]isoindoles, pyrido[1,2-*a*]indoles and related heterocycles

Azomethine ylides are carbon analogues of the pyridinium imide **44**. The Huang[33] and Zhang[34] groups have independently reported the cycloaddition reaction of azomethine ylides **51** and arynes leading to the formation of pyrido[2,1-*a*]-isoindoles **53** (Scheme 12). The reactive intermediates **51** have been generated *in situ* from pyridine/isoquinoline and α-haloketones (**50**). Running the reaction with CsF/DME at 85 °C in the presence of stoichiometric amounts of Na_2CO_3 or using CsF/MeCN at 80 °C provided the desired products in 31–60% and 37–60% yields respectively.

A convenient methodology for the synthesis of various 10-substituted pyrido[1,2-*a*]indoles by the reaction of readily prepared 2-substituted pyridines and arynes has been recently reported (Scheme 13).[35] After initial attack of the nitrogen atom onto the benzyne, the resulting aryl anion attacks the neighboring imine or Michael acceptor to generate the intermediate **55**, which rearranges to form the pyridoindoles **56**. Thus, the pyridoindole malonates have been obtained in 32–75% yields. In the case of the imines, subsequent arylation was unavoidable and *N*-arylated compounds **57** were isolated in 22–80% yields.

Another example of the reaction of an azomethine imine with an aryne has been demonstrated in the Larock group (Scheme 14).[36] In this case, the stable and isolable azomethine imines **58** were prepared by the condensation of 3-pyrazolidinones with various aldehydes. Upon cycloaddition with the benzyne generated in the presence of the organic-soluble tetrabutylammonium difluorotriphenylsilicate (TBAT) in MeCN at room temperature, tricyclic 1,2-dihydropyrazolo[1,2-*a*]indazol-3(9*H*)-ones **59** were formed in 20–85% yields.

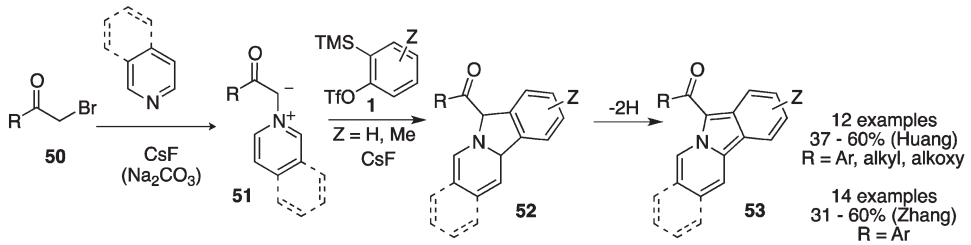
A related heterocycle, indolizino[3,4,5-*ab*]isoindole, can be prepared by the [3 + 2] cycloaddition reaction of indolizine **60** with benzyne. Running the reaction in the presence of CsF in MeCN at 90 °C allows one to obtain the desired products **61** in 23–75% yields (Scheme 15).[37] The indolizine core can have multiple substituents, such as hydrogens, alkyl and aryl groups, and nitrile and ketone functionality.

Running an analogous reaction with benzo-fused or heterocycle-fused indolizines provides polycyclic aromatic heterocycles, such as **63**, in 52–93% yields (Scheme 16).

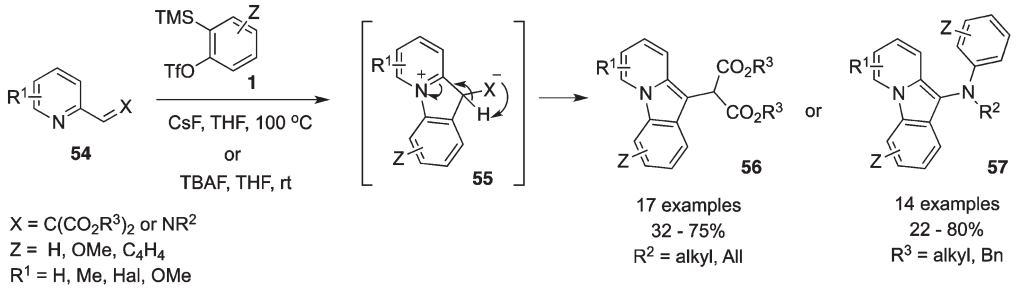
2.8. Benzofurans and dihydrobenzofurans

Benzofuran derivatives have been obtained in a coupling reaction between stabilized iodonium ylides **64** and arynes (Scheme 17).[38] This reaction appears to proceed by enolate oxygen attack on the aryne ring. The resulting aryl anion **65** forms a 5- or 6-membered ring intermediate that, after extrusion of phenyl iodide, forms the observed benzofuran moiety.[39] Running the reaction in the presence of CsF in MeCN at ambient temperatures allows one to obtain the desired benzofuran products **66** in 43–91% yields.

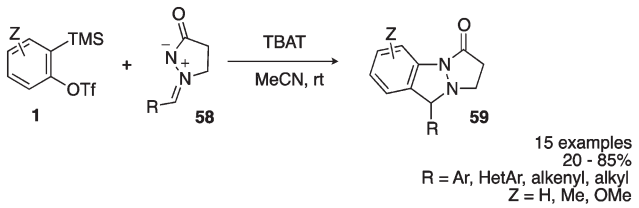
Dihydrobenzofurans can be formed by the insertion of a benzyne into the C–O bond of an epoxide, albeit in low yields. Thus, the reaction of styrene oxide (**67**) with the benzyne precursor **1** in the presence of CsF in MeCN affords the heterocyclic product **71** in a 32% yield as a single regioisomer



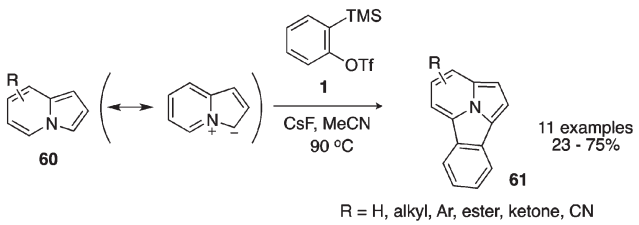
Scheme 12 Reaction of azomethine ylides with arynes.



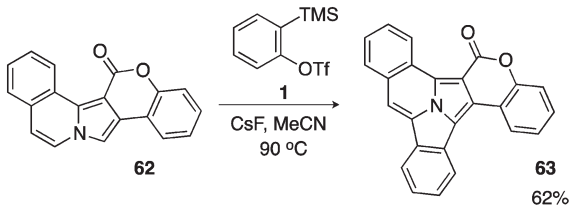
Scheme 13 Synthesis of pyrido[1,2-*a*]indoles through aryne annulation.



Scheme 14 Synthesis of 1,2-dihydropyrazolo[1,2-*a*]indazol-3(9*H*)-ones.



Scheme 15 Reaction of indolizine with benzyne.



Scheme 16 Reaction of a fused indolizine with an aryne.

(Scheme 18).[40] The regioselectivity of the reaction can be rationalized by the relative stability of the cationic resonance structure **70** as opposed to the structure **69**, which lacks the additional benzylic stabilization.

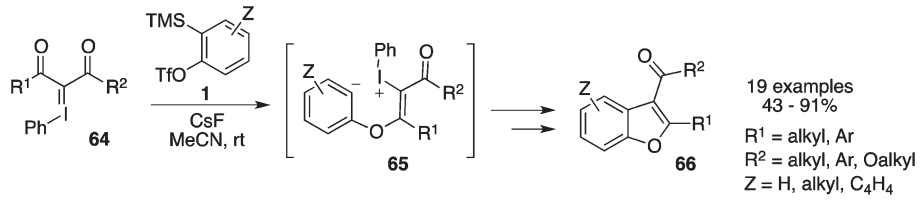
2.9. Indoles, indole–indolones, pyrroloindolones, isatins, indolines, and indolin-3-ones

An interesting route to the indole scaffold has been developed by Greaney (Scheme 19).[41] In a two step procedure, *N*-tosylhydrazones of ketones **72** are first arylated by an aryne with formation of the *N*-aryl-*N*-tosylhydrazones **73**.[42] The latter species is a convenient intermediate for an acid-catalyzed Fischer indole synthesis. Under the optimized conditions, running the *N*-arylation step using CsF/MeCN at room temperature and further subjecting the reaction mixture to stoichiometric amounts of $BF_3{\cdot}Et_2O$, leads to formation of the corresponding indoles **74** in 51–80% yields.

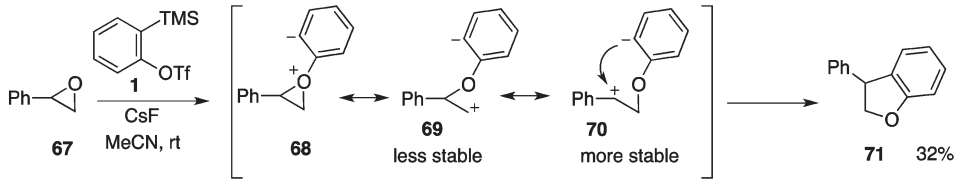
An alternative route to the indole ring system has been developed by Wang, which involves the coupling of azo-ylides with arynes (Scheme 20).[43] Azo-ylides **76** are generated *in situ* from the corresponding alkenyl azides **75** and PPh_3. Double cyclization leads to the formation of intermediate **77**, which after hydrolysis and elimination of triphenylphosphine oxide is transformed into the indoline structure **78** (Scheme 28). Aerobic oxidation of the latter furnishes the desired indoles **79** in 64–89% overall yields when the reaction is run in the presence of CsF and PPh_3 in a Tol–MeCN mixture at 50 °C under aerobic conditions.

The indole products **79** can be used as starting materials in annulation reactions with arynes. After nucleophilic attack of the indole nitrogen on the benzyne, the resulting anion attacks the ester group with formation of the indole–indolone structure **80** (Scheme 21).

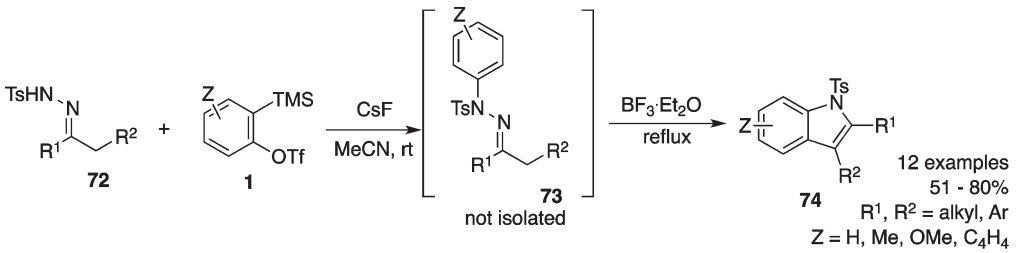
The Ramtohul[44] and Larock[45] groups have independently studied this system and found that using tetramethylammonium fluoride (TMAF) in THF at room temperature (Ramtohul) or CsF in DME in the presence of Cs_2CO_3 at 90 °C



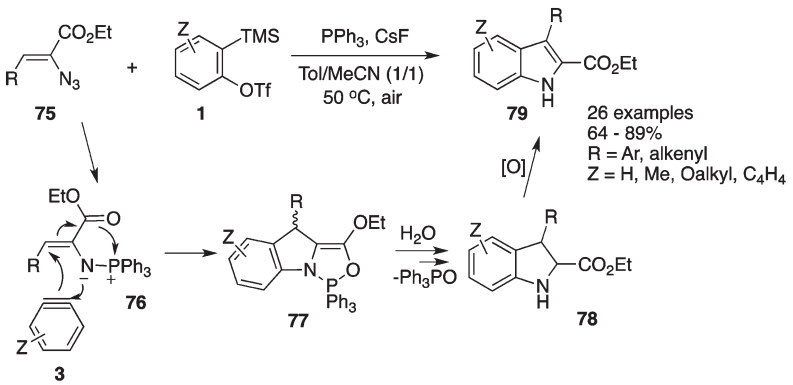
Scheme 17 Reaction of iodonium ylides and arynes.



Scheme 18 Reaction of styrene oxide and benzyne.



Scheme 19 Synthesis of indoles developed by Greaney.



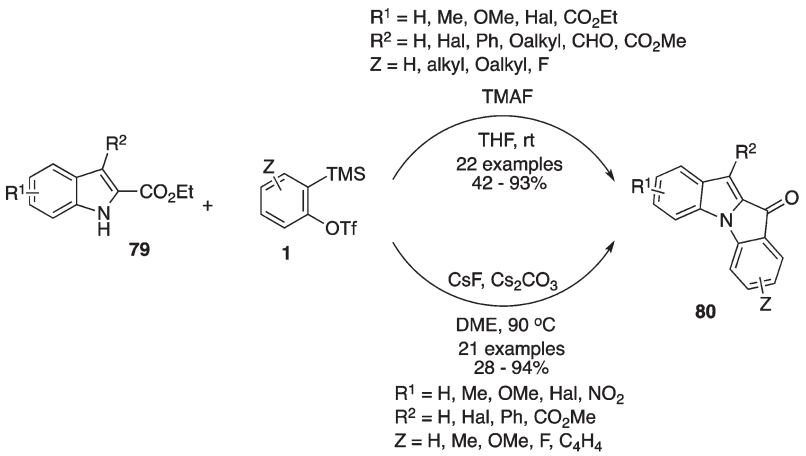
Scheme 20 Synthesis of indoles developed by Wang.

(Larock) provides the desired tetracyclic heterocycles in 42–93% and 28–94% yields respectively.

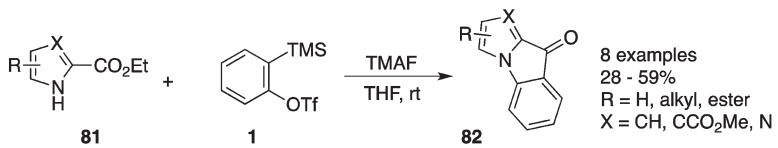
The analogous reaction of the pyrrole-2-carboxylate ester **81** (X = CH) leads to the formation of the pyrroloindolone structure **82** (X = CH) (Scheme 22).[44] Interestingly, the use of the aza-analogue of the starting material (**81**, X = N) allows one to obtain tricyclic imidazoloindolones in 44–59% yields (Scheme 22).

Using a similar annulation strategy, nucleophilic attack of the nitrogen of the methyl 2-oxo-2-(arylamino)acetate system **83** on a benzyne, followed by intramolecular attack of the resulting aryl anion onto the ester group, results in ring closure and formation of an isatin (**84**) in 51–92% yields (Scheme 23).[46] The optimal conditions were found to employ CsF/MeCN in the presence of stoichiometric amounts of $NaHCO_3$ at room temperature.

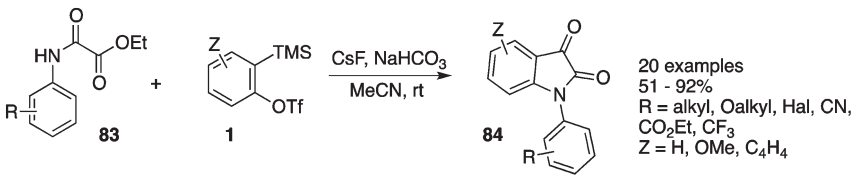
The Stoltz group has reported an annulation approach to indolines starting from ene carbamates.[47] When reacting *N*-Boc enamines **85** with benzyne in the presence of TBAT in THF at ambient temperatures, the desired heterocycles **86** were obtained in 39–61% yields (Scheme 24). Interestingly, the Boc group is crucial to the reaction's success. Acyl-substituted



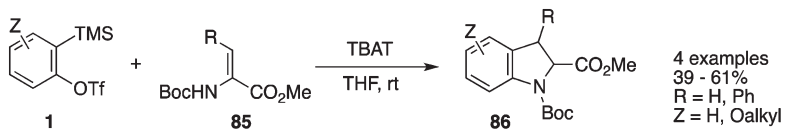
Scheme 21 Synthesis of indole–indolones.



Scheme 22 Synthesis of pyrroloindolones and imidazoloindolones.



Scheme 23 Synthesis of isatins.

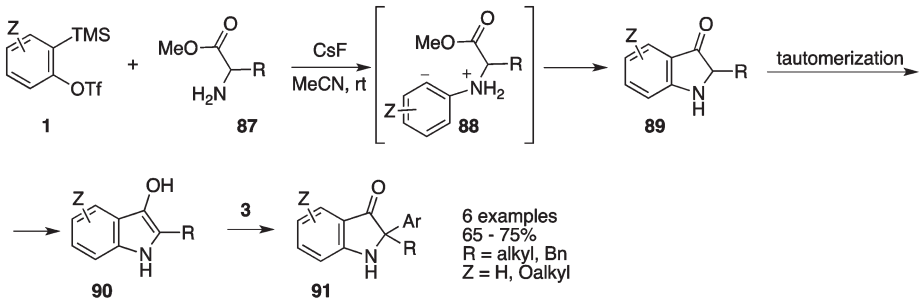


Scheme 24 Synthesis of indolines.

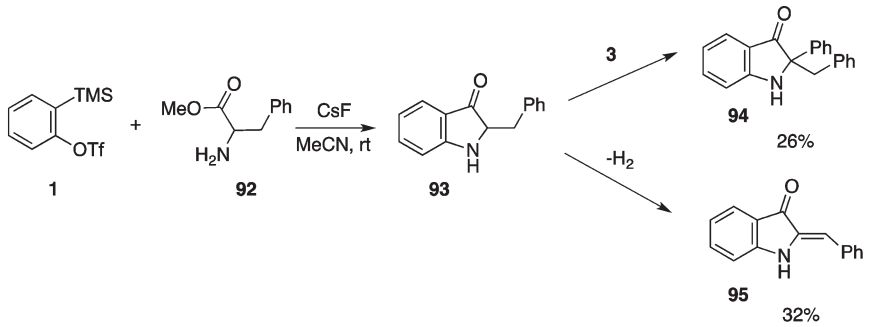
enamines alter the reaction pathway and lead to the formation of isoquinolines (see Section 3.1). The reaction with *N*-Boc enamines presumably occurs through the following pathway. The stabilized ambident nucleophile attacks the electrophilic aryne intermediate through its nitrogen atom, and the resulting aryl anion undergoes an intramolecular Michael reaction to form the final indolines (Scheme 24).

2-Arylindolin-3-ones can be prepared from the methyl esters of α-amino acids **95** using a similar aryne annulation strategy (Scheme 25).[48] The unprotected amino group attacks the benzyne and the resulting aryl anion **88** intramolecularly reacts with the nearby ester group. The reaction does not stop, however, since the resulting (after tautomerization) 3-hydroxyindole **89** is more reactive towards the benzyne than the starting material. The reaction stops only after *C*-arylation of the latter (presumably by an ene-reaction). The corresponding products **91** were isolated in 65–72% yields (Scheme 25).

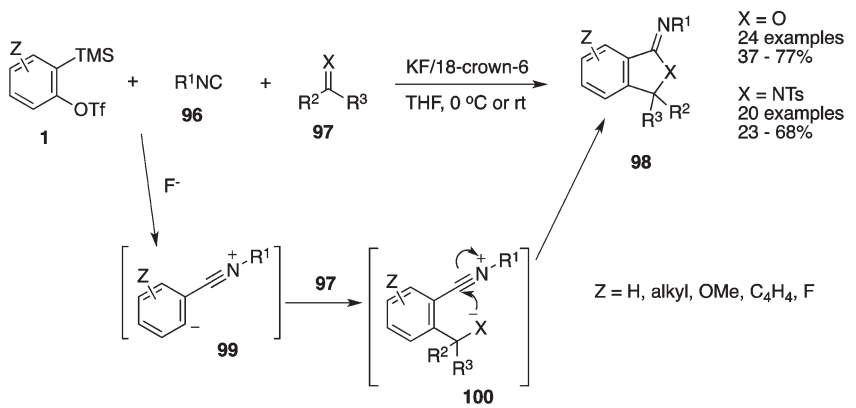
The optimized reaction conditions employed CsF/MeCN at ambient temperatures. It is noteworthy that not all amino esters undergo the desired cyclization. For instance, the methyl esters of alanine and proline provided only the



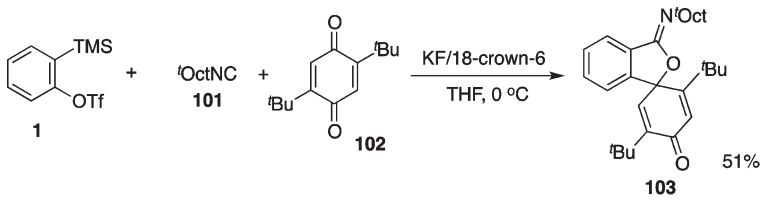
Scheme 25 Synthesis of indolin-3-ones.



Scheme 26 Reaction of phenylalanine and benzyne.



Scheme 27 Synthesis of iminoisobenzofurans and iminoisoindolines.



Scheme 28 Synthesis of spiroheterocycles.

corresponding *N*-arylation products. In the case of phenylalanine (**92**), along with a 26% yield of the expected product **94**, the dehydrogenated product **95** was isolated in a 32% yield (Scheme 26).

2.10. Iminoisobenzofurans and iminoisoindolines

An interesting route to iminoisobenzofurans and iminoisoindolines has been developed by Kunai and Yoshida.[49] In this

multicomponent process, the isocyanide **96** reacts with the benzyne intermediate with formation of the intermediate **99**. The latter attacks an aldehyde/ketone or a *N*-tosyl imine and subsequent intramolecular cyclization leads to formation of the desired heterocycles **98** (Scheme 27). Running the reaction in the presence of KF/18-crown-6 in THF at 0 °C (X = O) or room temperature (X = NTs) allows one to isolate the desired iminoisobenzofurans **98** (X = O) and iminoisoindolines **98** (X = NTs) in 37–77% and 23–68% yields respectively.

It is noteworthy that this methodology works well with a quinone and some alkyl-substituted derivatives, providing the spiroheterocycles **103** in 32–52% yields (Scheme 28).

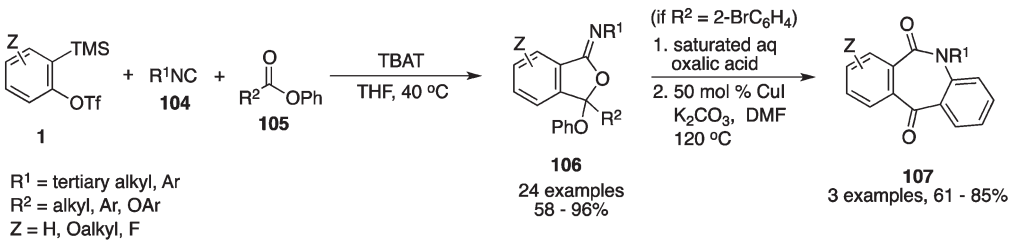
An analogous reaction with esters, instead of aldehydes/ketones/imines, has been studied by Stoltz and co-workers.[50] While alkyl esters, such as ethyl acetate, are not electrophilic enough to react with the intermediate **99**, aryl esters lead to the formation of the heterocyclic products **106** (Scheme 29). Running the reaction in the presence of TBAT in THF at 40 °C affords the final products in 58–96% yields.

It is noteworthy that these iminoisobenzofurans can be hydrolyzed under acidic conditions into the corresponding *o*-ketobenzamides. Employing the phenyl *o*-halobenzoate **106** (R^2 = 2-Br–C_6H_4) in this 2-step route leads to the formation of the hydrolyzed substrate, which can be further cyclized under copper-mediated conditions into the 7-membered dibenzoketocaprolactams **107** in 61–85% yields (Scheme 29).

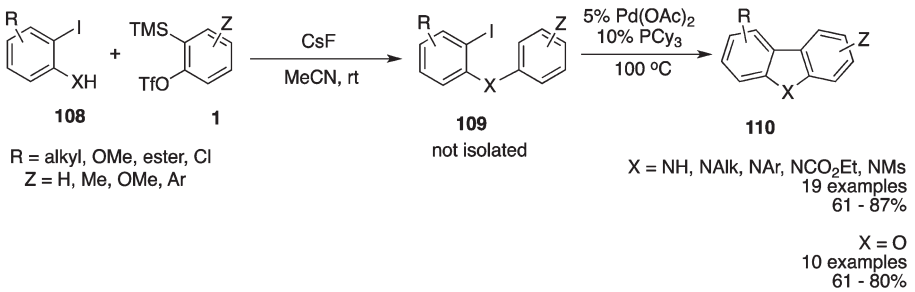
2.11. Carbazoles and dibenzofurans

A two-step approach to carbazoles and dibenzofurans has been developed by Larock and co-workers.[51] In their earlier work,[52] the Larock group developed conditions for the formal insertion of arynes into the N–H bond of amines and the O–H bond of phenols. The optimal conditions were found to be CsF/MeCN at ambient temperatures. Employing *o*-iodoanilines and *o*-iodophenols in this transformation leads to the formation of the corresponding arylation products in 90–97% yields. After Pd-catalyzed intramolecular arylation (the Pd catalyst is added to the reaction mixture without isolation of the arylation products **109**), the corresponding carbazoles and dibenzofurans **110** can be obtained in 61–87% and 61–80% yields respectively (Scheme 30).

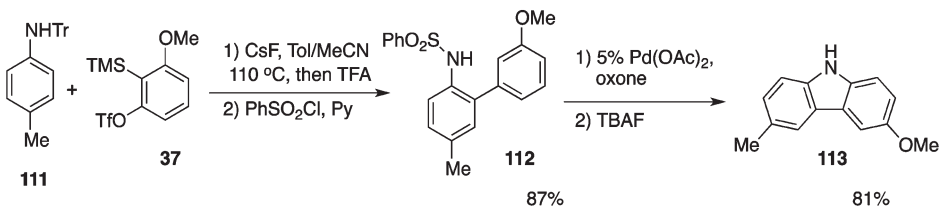
Both methodologies tolerate a wide range of functional groups: ketones, halides, esters, and alkoxy groups. Unsubstituted anilines, monoalkyl, monoaryl and *N*-mesyl anilines, as



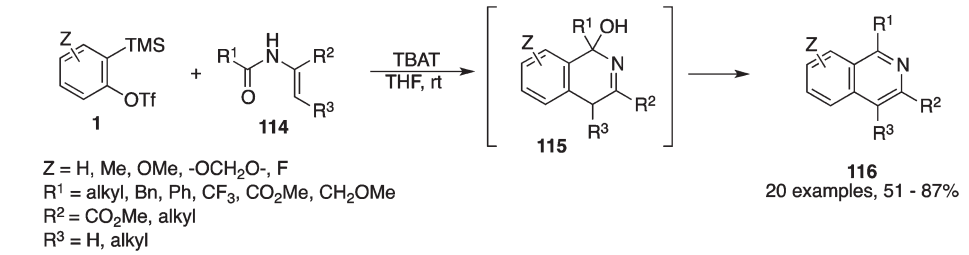
Scheme 29 Reaction with aryl esters.



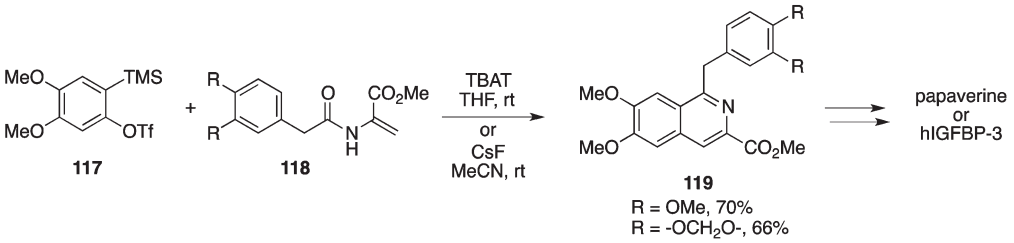
Scheme 30 Synthesis of carbazoles and dibenzofurans.



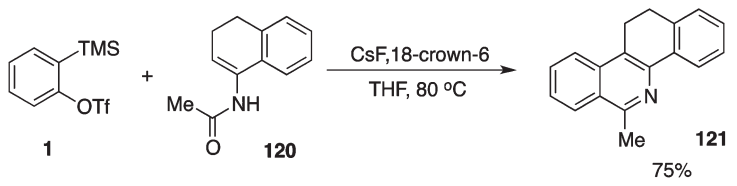
Scheme 31 Synthesis of a biologically important carbazole.



Scheme 32 Coupling of enamides with benzyne.



Scheme 33 Applications towards the total syntheses of papaverine and hIGFPB-3.



Scheme 34 Transformation of enacetamides into isoquinolines.

well as urethanes, all undergo the desired one-pot transformation with high efficiency. Interestingly, the use of homologues of substrates **108** leads to formation of a number of 6-membered ring heterocycles, such as 5,6-dihydrophenanthridines and 6*H*-dibenzo[*b*,*d*]pyran-6-ones.[51]

Greaney reported a four-step synthesis of the antibiotic and antifungal carbazole-containing product **113** using aryne chemistry (Scheme 31).[53] The trityl-substituted aniline **111** was allowed to undergo an ene-reaction with 3-methoxybenzyne. The trityl group was then removed under acidic conditions and the nitrogen sulfonylated. Thus, the 2-arylaniline **112** was isolated in an 87% yield. A Pd-catalyzed cyclization, followed by removal of the sulfonyl group, resulted in the formation of the cyclic carbazole natural product **113** in an 81% yield.

3. Synthesis of 6-membered ring-containing heterocycles

3.1. Isoquinolines, quinolines, phenanthridines, phenanthridinones and related heterocycles

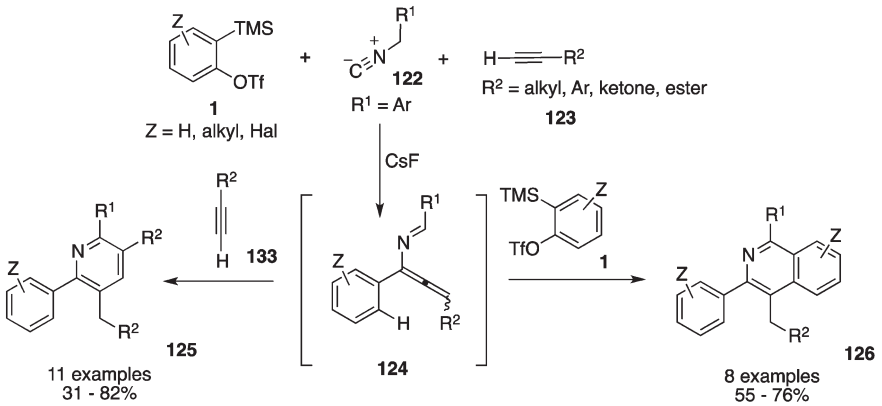
In 2008, Stoltz and co-workers reported that the enamides **114** react with benzyne at the carbon atom of the enamide (compare the corresponding reaction of *N*-Boc carbamates in section 2.9) resulting in the formation of the isoquinolines **116** after cyclization and dehydration.[47] Running the reaction using TBAT in THF at room temperature allows one to obtain isoquinolines in 51–87% yields (Scheme 32).

An alternative set of reaction conditions has been developed by Ramtohul and co-workers.[54] Their process employs CsF in MeCN at room temperature, followed by the addition of TFA to facilitate dehydration. A variety of alkyl and aryl, halide, ether, and dioxalano-containing isoquinolines **116** has been isolated in 42–69% yields along with the undesired [2 + 2] cycloaddition products (11–25%).

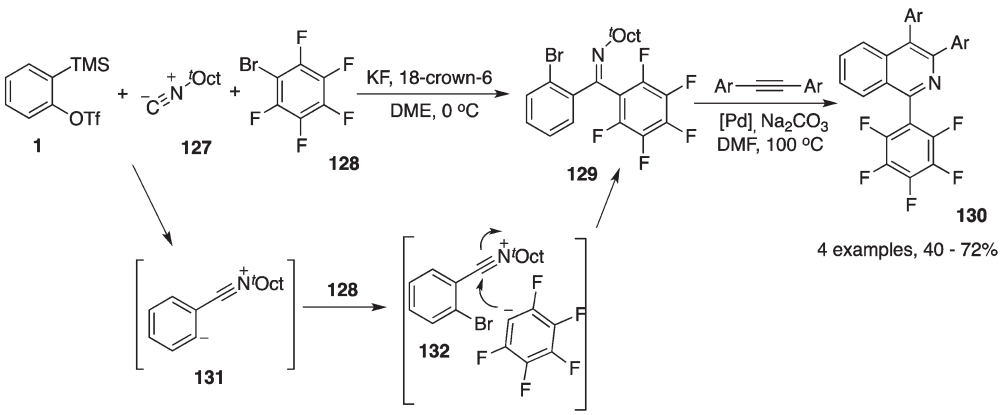
Stoltz's and Ramtohul's methodologies have been successfully applied to the synthesis of a natural alkaloid papaverine and the insulin-like growth-factor inhibitor hIGFPB-3 respectively (Scheme 33).

Guan developed yet another set of reaction conditions for the transformation of enacetamides into isoquinolines.[55] Running the reaction in THF in the presence of CsF/18-crown-6 at 80 °C allows one to obtain the desired products **116** in 60–75% yields. Using this methodology, an interesting tetracyclic product **121** was obtained in a 75% yield starting from the cyclic enamide **120** (Scheme 34).

Huang has developed an interesting route to isoquinolines and pyridines using aryne methodology (Scheme 35).[56] First,



Scheme 35 Isocyanide-based route to isoquinolines and pyridines.



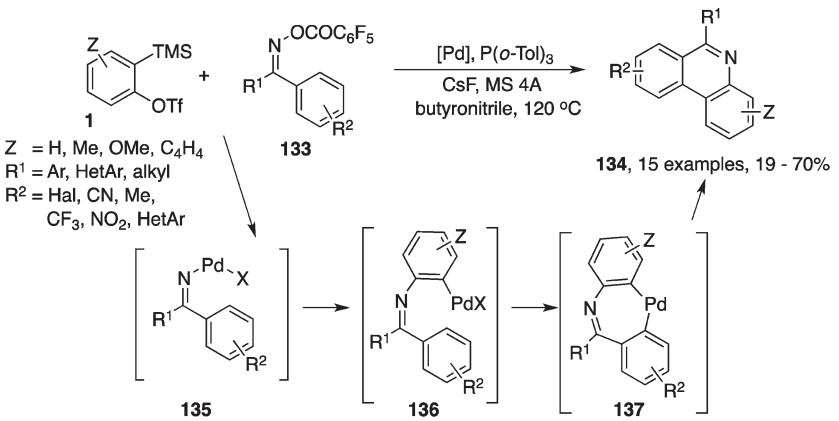
Scheme 36 Reaction of benzyne with isocyanides and perfluorinated bromoarenes.

the isocyanide **122** adds to the benzyne. Then, the resulting aryl anion deprotonates the terminal alkyne in the reaction mixture, followed by the addition of the resulting alkynyl anion to the cationic iminium species. An imide intermediate is formed which undergoes a 1,5-hydride shift to produce an allenyl imine **124**. The latter undergoes a [4 + 2] cycloaddition process with an excess of benzyne or an alkyne (depending on the ratios of starting materials) to produce the final isoquinolines **126** (55–79% yields) or pyridines **125** (31–82%) respectively (Scheme 35). The formation of isoquinolines is favored at 40 °C in a Tol–MeCN (1 : 3) mixture using CsF as the fluoride source. The formation of pyridines is favored at 75 °C in a Tol–MeCN (4 : 1) mixture in the presence of CsF. In both methodologies, aryl-, alkyl- and ester-substituted terminal alkynes are tolerated, and benzylic isocyanides are required.

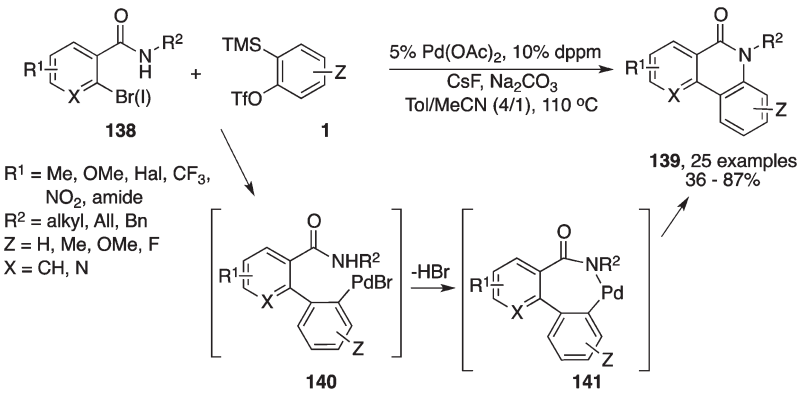
The reaction of benzyne with nonbenzylic isocyanides and perfluorinated bromoarenes has been developed by Yoshida (Scheme 36).[57] After the addition of the isocyanide **127** to the benzyne, the aryl anion **131** substitutes a bromide of the perfluorinated bromoarene, and the addition of an anion to the activated iminium ion **132** furnishes the target ketimines **130** (Scheme 36). In the case of perfluorinated arenes, the resulting *o*-bromoaryl ketimines **129** can be further reacted with diarylalkynes in a Pd-catalyzed annulation process to yield isoquinolines **130** in 40–72% yields.

A related palladium-catalyzed pathway to phenanthridines has been recently reported by Neuville and Zhu (Scheme 37).[58] Therein, the perfluorobenzoyl esters of the benzophenone oximes **133** react with the silylaryl triflate in the presence of CsF, a palladium catalyst, P(*o*-Tol)$_3$, and molecular sieves in butyronitrile at 120 °C to generate the phenanthridines **134**. First, the palladium inserts into the N–O bond of the acyl oxime. Then the resulting Pd(II) intermediate **135** adds to the benzyne present in the reaction mixture. A C–H activation process and reductive elimination follows, furnishing the final phenanthridine products in 30–70% yields. Acetophenone derivatives produce the corresponding phenanthridines as well, albeit in poor (19–29%) yields. Fluoro, chloro, nitrile, nitro, and methoxy groups, as well as several heterocycles, are well tolerated in this methodology.

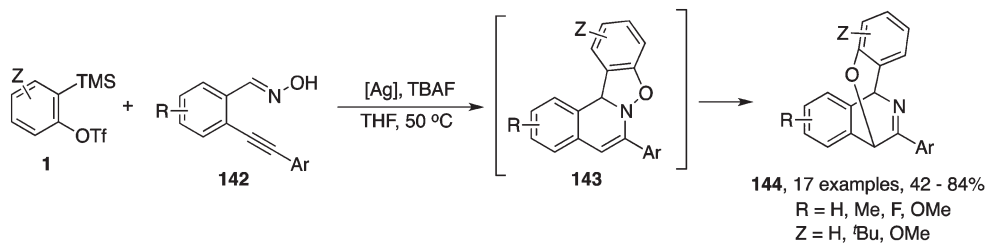
Another palladium-catalyzed aryne annulation approach has been recently reported by Larock.[59] The coupling of *o*-bromobenzamides **138** and arynes proceeds efficiently in the presence of CsF, Na_2CO_3, a Pd catalyst and a ligand in Tol–MeCN (4 : 1) at 110 °C to afford the phenanthridinones **139** in 36–87% yields (Scheme 38). A great variety of functional



Scheme 37 Palladium-catalyzed pathway to phenanthridines.



Scheme 38 Palladium-catalyzed aryne annulation to phenanthridinones.

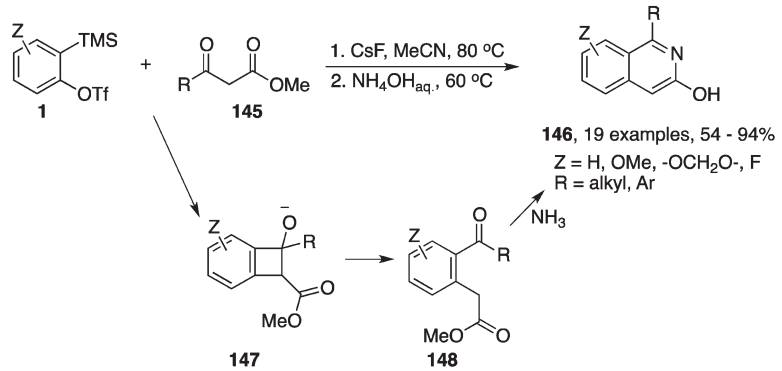


Scheme 39 Silver-catalyzed reaction of 2-(1-alkynyl)benzaldoximes with arynes.

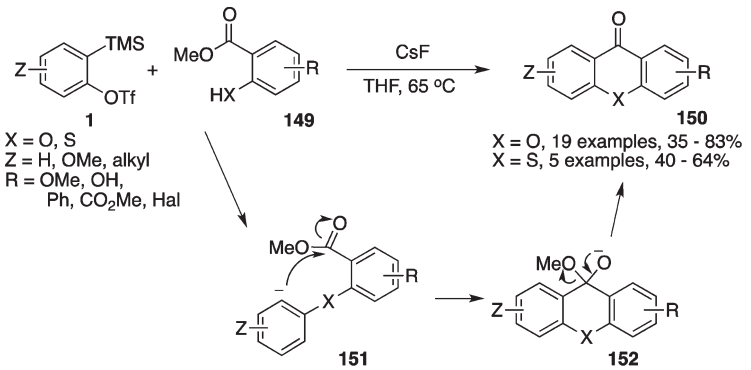
groups is well tolerated under the reaction conditions employed: alkyl, benzyl, allyl, methoxy, nitro, chloro, fluoro, trifluoromethyl, ester, and pyridine substituents.

A silver-catalyzed domino process leading from 2-(1-alkynyl)-benzaldoximes to tetracyclic derivatives of the 1,4-dihydroisoquinolines **144** has been discovered by Wu (Scheme 39).[60] As expected, the silver-catalyzed intramolecular cyclization of the starting oximes **142** leads to isoquinoline-*N*-oxides,[61] which are trapped *in situ* in a [3 + 2] process by a benzyne intermediate. Unexpectedly, the addition products **143** that are formed are not stable and rearrange to tetracyclic derivatives **144**, possibly through a radical pathway. The transformation proceeds in the presence of TBAF and catalytic amounts of AgOTf in THF at 50 °C yielding the final products in 41–84% yields.

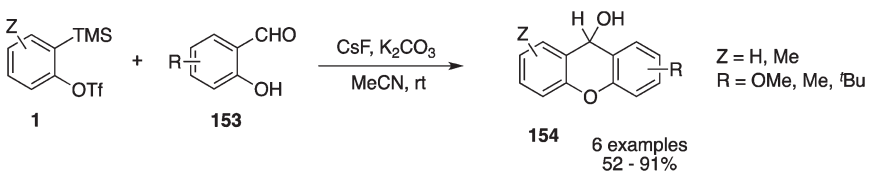
Stoltz has reported that arynes can insert into the C–C bond of β-keto esters through a 4-membered ring intermediate **147** (Scheme 40).[62] Based on this transformation, a one-pot route to 3-hydroxyisoquinolines **146** has been reported. Therein, β-keto esters **145** react with silylaryl triflates **1** in the presence of CsF in MeCN at 80 °C, followed by the addition of aqueous ammonia at 60 °C. Plausibly, an imine is formed that cyclizes onto the ester group, and subsequent enolization furnishes the desired isoquinoline core **146**. Electron-rich and electron-poor benzyne precursors proved to be efficient in this transformation, yielding products in 73–81% yields.



Scheme 40 One-pot route to 3-hydroxyisoquinolines by an aryne reaction with β-keto esters.



Scheme 41 Aryne annulation approach to xanthones.



Scheme 42 Aryne annulation route to 9-hydroxyxanthenes.

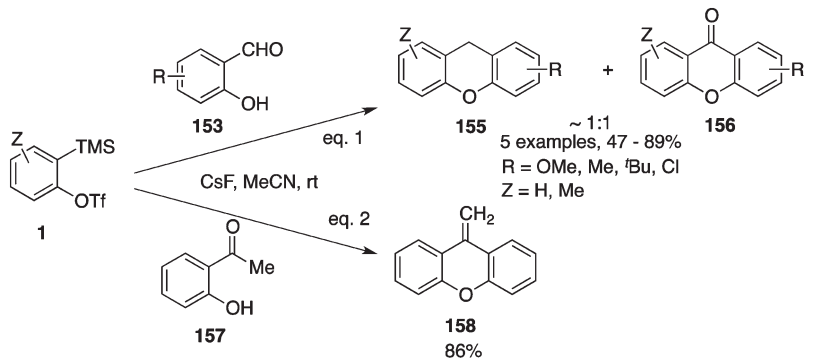
Interestingly, this methodology was successfully applied to the synthesis of an important chiral ligand QUINAP.

3.2. Xanthenes, xanthones, and xanthols

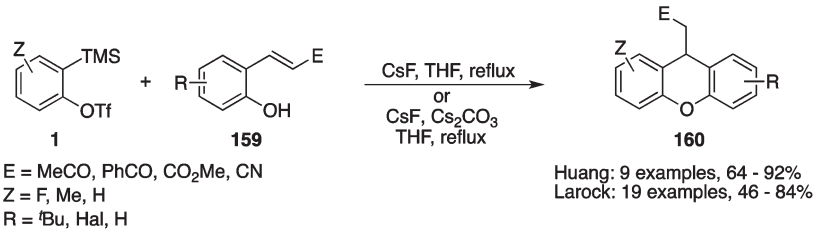
An annulation approach to xanthones has been developed by the Larock group starting from methyl salicylates **149** (X = O) (Scheme 41).[63] After nucleophilic attack of the hydroxyl group on the benzyne intermediate, the resulting aryl anion **151** intramolecularly attacks the *ortho*-situated ester group resulting in the formation of the desired xanthone core **150**. The solvent choice plays a crucial role in this transformation. In the relatively acidic solvents acetone or MeCN, the benzyne's formal insertion into the O–H bond is the major pathway for this reaction. Running the reaction in THF, however, allows one to obtain the desired xanthones **150** (X = O) as the dominant products in the reaction mixture. Running the reaction in the presence of CsF in THF at 65 °C allows one to obtain xanthones in 35–83% yields with a variety of functional groups tolerated: alkyl, aryl, methoxy, halo, and ester groups. Additionally, thioxanthones **150** (X = S) can be prepared in moderate (40–64%) yields utilizing this methodology, if one starts from methyl thiosalicylates.

Changing the substrate to salicylaldehyde **153** results in the formation of the expected 9-hydroxyxanthenes **154** (xanthols) as reported by Okuma.[64] It is interesting that the presence of stoichiometric amounts of K_2CO_3 is crucial for the successful isolation of these products. Thus, performing the reaction in the presence of CsF and K_2CO_3 in MeCN at room temperature allows one to obtain the desired xanthols **154** in 52–91% yields (Scheme 42).

In contrast, running the reaction in the absence of K_2CO_3 resulted in the formation of ~1 : 1 mixtures of xanthene **155** and xanthone **156** in 47–89% overall yields (Scheme 43, eqn (1)). Apparently, the preformed xanthols are not stable and disproportionate into the final reaction products. When a methyl ketone **157** is used instead of a carbaldehyde, the xanthene



Scheme 43 Xanthene and xanthone formation in the absence of K_2CO_3.



Scheme 44 Synthesis of 9-functionalized xanthenes.

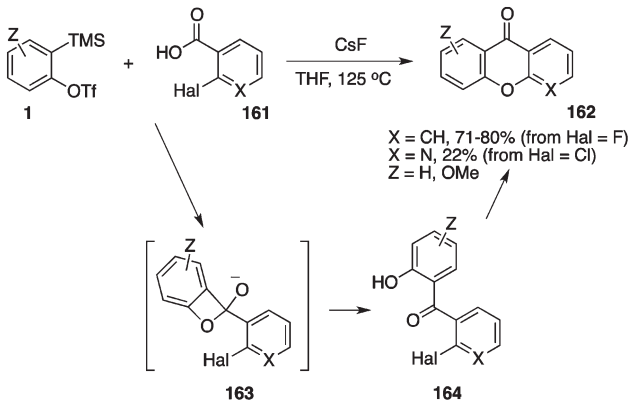
158 is obtained in an 86% yield, even in the absence of K_2CO_3 (Scheme 43, eqn (2)).[65]

Instead of the aryl anion **151** attacking a neighboring carbonyl group, a Michael acceptor can be employed as a trap. Huang[66] and Larock[67] have independently reported such processes leading to the formation of 9-functionalized xanthenes **160** (Scheme 44). Huang's protocol uses CsF in THF at reflux temperatures, allowing one to obtain the desired products in 64–92% yields, while Larock's protocol utilizes the same reaction conditions, but with the addition of an inorganic base, Cs_2CO_3.[68] The yields in the Larock methodology vary from 46 to 84%.

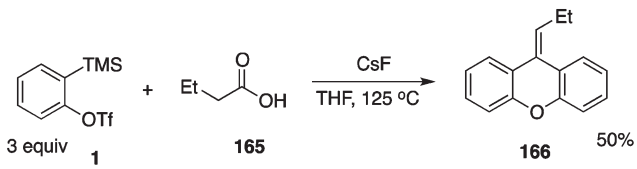
An alternative route to xanthones has been developed in the Larock group starting from *o*-haloarenecarboxylic acids **161** (Scheme 45).[69] Running the aryne reaction in THF at 125 °C (sealed tube) in the presence of CsF results in an initial insertion of the benzyne into the C–O bond of the acid through a 4-membered ring intermediate **163**. The *o*-hydroxyaryl ketone **164** thus formed apparently undergoes an intramolecular S_NAr process, furnishing the xanthones **162** in 22–80% yields.

Starting with an alkyl carboxylic acid **165** leads to the formation of the corresponding *o*-hydroxyaryl ketone, but running the reaction with an excess of the benzyne precursor allows one to convert the latter substrate into substrates analogous to those prepared by the process described above for salicylaldehydes.[64] Thus, the xanthene **166** was obtained in a 50% yield using this one-pot method, starting from butyric acid and using an excess of the benzyne precursor **1** (Scheme 46).

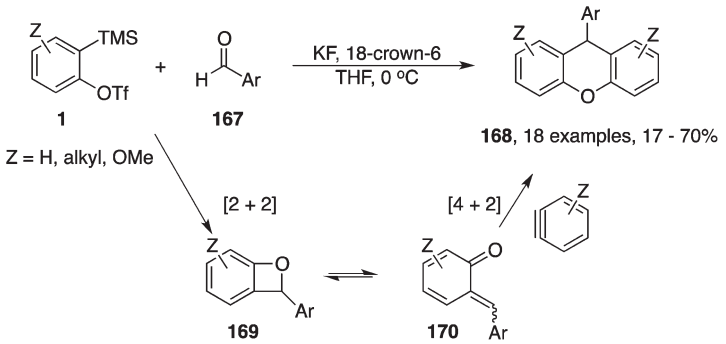
An alternative pathway to 9-substituted xanthenes has been developed by Yoshida and Kunai (Scheme 47).[70] Aromatic aldehydes **167** and the benzyne precursor **1** in the presence of KF/18-crown-6 in THF at 0 °C undergo a formal [2 + 2] cycloaddition forming the benzoxete **169**. The latter rearranges to the *o*-quinone methide intermediate **170**, which is further trapped by an aryne molecule through a [4 + 2] cycloaddition, furnishing the final 9-arylxanthenes **168**. The yields of the final products range from 17% to 70%. Electron-rich methoxy-



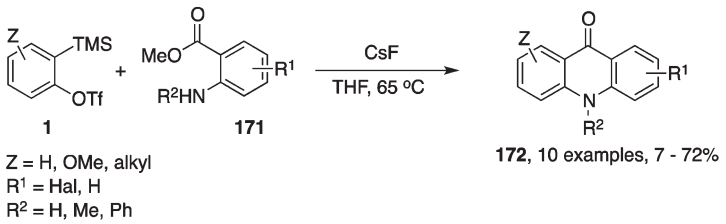
Scheme 45 Reaction of *o*-haloarenecarboxylic acids with arynes.



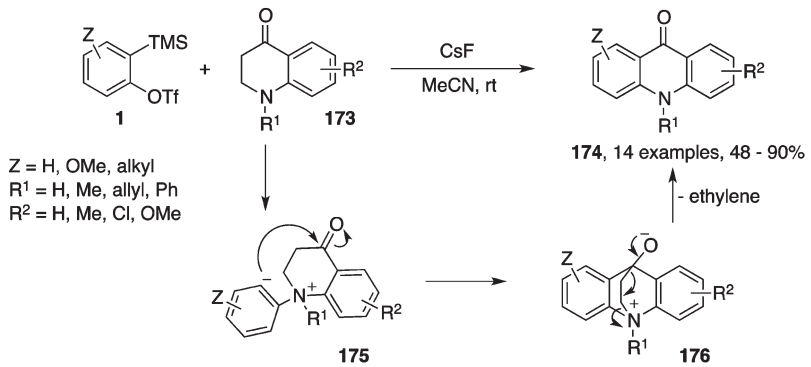
Scheme 46 Reaction of butyric acid with an excess of the benzyne precursor.



Scheme 47 Synthesis of 9-substituted xanthenes.



Scheme 48 Reaction of 2-aminobenzoates and benzyne.



Scheme 49 Reaction of 2,3-dihydroquinolin-4(1*H*)-ones with benzyne.

substituted benzaldehydes are substantially more efficient in this transformation than the parent benzaldehyde.

3.3. Acridones and acridines

Similar to the reaction of methyl salicylates and benzyne yielding xanthones (see Section 3.2), 2-aminobenzoates **171** engage in a analogous annulation process with formation of the acridones **172** as discovered by Larock.[63b] Herein, the nucleophilic attack of the nitrogen of the amino group onto the benzyne, followed by intramolecular attack of the resulting aryl anion onto the neighboring ester group, leads to formation of the final acridone products (Scheme 48).

Simple anilines, as well as *N*-methyl and even *N*,*N*-dimethyl anilines readily engage in the desired process in the presence of CsF in THF at reflux temperatures, allowing one to obtain the final acridones **172** in 50–72% yields. *N*-Phenyl anilines are substantially less reactive, resulting in the formation of *N*-phenylacridone in only a 7% yield.

An interesting extension of this methodology has been recently developed in a collaboration between the Larock and Shi groups (Scheme 49).[71] The reaction between 2,3-dihydroquinolin-4(1*H*)-ones **173** and benzyne yields *N*-arylacridones **174** in high (69–90%) yields under mild (CsF/MeCN at room temperature) reaction conditions. Similar to the reaction of 2-aminoaryl esters noted above, the nitrogen of the amino group attacks the benzyne with formation of the aryl anion **175**. The latter intramolecularly adds to the ketone by a favorable 6-membered ring formation. The subsequent elimination of ethylene leads to the formation of the N–H acridone, which is further *N*-arylated to provide the observed heterocycle **174** (R^2 = Ar). Starting with *N*-alkyl or *N*-allyl 2,3-dihydroquinolin-4(1*H*)-ones allows one to avoid the final *N*-arylation step and to

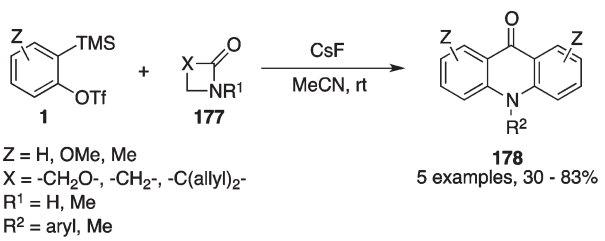
obtain the *N*-substituted acridones **174** (R^2 = H, Me, Ar) in 48–63% yields.

As shown by Greaney[72] and Yoshida,[73] benzyne can insert into the C–N bond of amides and ureas (see Schemes 53 and 64 for the synthesis of heterocycles using this methodology). Larock and Shi have further shown that starting from the β-lactams **177** (X = CR_2) affords 2,3-dihydroquinolin-4(1*H*)-ones **173**, which react further with the excess of benzyne (Scheme 50). Thus, three molecules of benzyne are incorporated into the structure of the resulting *N*-arylacridones **178**. The final compounds are obtained in 30–83% yields starting from the free β-lactams, and in only trace amounts starting from *N*-substituted β-lactams. Starting from 3-methyl-2-oxazolidinone **177** (X = –CH_2O–) leads to the formation of *N*-methylacridone though a similar mechanistic pathway, but with the extrusion of ethylene oxide, albeit in only a low 33% yield.

Starting from a 2-aminoaryl aryl or alkyl ketone **179**, instead of a 2-aminoaryl ester **171**, alters the reaction mechanism and results in dehydration and formation of the acridine scaffold **180** (Scheme 51).[74] Optimization revealed two alternative sets of suitable reaction conditions: MeCN in the presence of CsF at 65 °C, and DME in the presence of TBAT at room temperature. These complementary protocols afford acridines **180** in 51–80% yields. Alkyl, alkoxy, and halide functional groups are tolerated. The reaction failed in the case of a nitro-substituted substrate.

The interesting polycycles **181** and **182** have been obtained starting from anthraquinone and fluorenone substrates using this aryne chemistry (Fig. 2).

The scope of Larock's acridone methodology has been extended to alkyl, hydroxyl-containing alkyl, and benzyl 2-aminoaryl ketones by Okuma.[65] Running the reaction using the CsF/MeCN system at ambient temperatures produces 9-substituted acridines in 73–91% yields.



Scheme 50 Reaction of β-lactams with arynes.

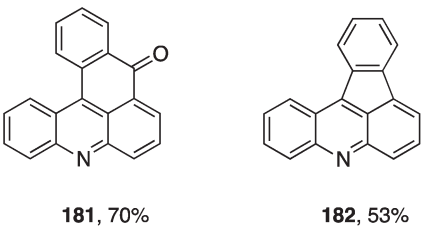
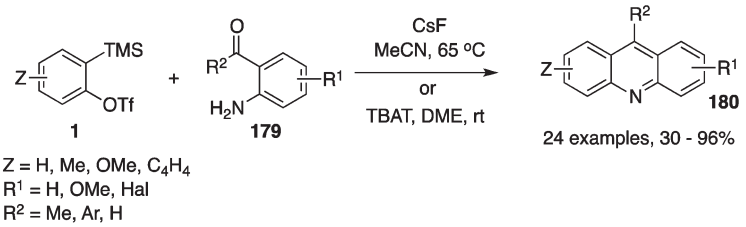


Fig. 2 Products from anthraquinone and fluorenone substrates.

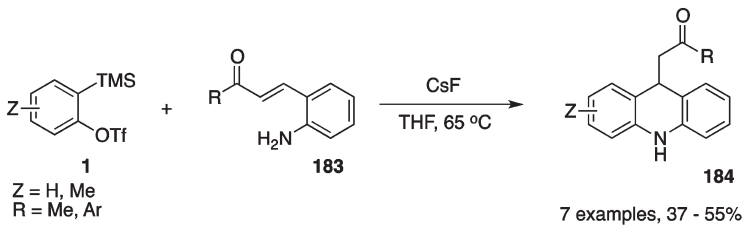
Starting from a Michael acceptor-containing aniline **183**, instead of a ketone or ester-containing aniline **179**, alters the reaction pathway and results in conjugate addition of the aryl anion in the final step of the mechanism. Thus, 9,10-dehydroacridines **184** can be produced as shown by Huang (Scheme 52).[66] Running the reaction in THF in the presence of CsF at reflux temperatures affords the final products in 37–54% yields. Acetyl- and benzoyl-substituted styrenes are both tolerated in this transformation. Interestingly, the products from the expected *N*-arylation process can be completely suppressed using the optimized reaction conditions.

Greaney has utilized conditions for the insertion of arynes into the C–N bond of *N*-aryl amides for the one-pot synthesis of acridones and acridines (Scheme 53).[72] The reaction proceeds through the formation of a strained 4-membered ring intermediate (see Schemes 40 and 45 for related processes). Starting from the *o*-halobenzamides **185** allows for a subsequent S_NAr step, resulting in the formation of the acridones **186** (Scheme 53, eqn (1)). The optimal conditions for the overall transformation, TBAT in toluene under microwave irradiation at 120 °C, provides the *N*-arylacridones **186** in 62–92% yields. Allowing *N*-arylbenzamides to react with benzyne, followed by the addition of $BF_3{\cdot}Et_2O$ at 80 °C, results in an S_EAr process and subsequent dehydration, resulting in a one-pot formation of acridines **187** (Scheme 53, eqn (2)). Products containing ester, methoxy, and halo functional groups have been obtained in 62–78% yields.

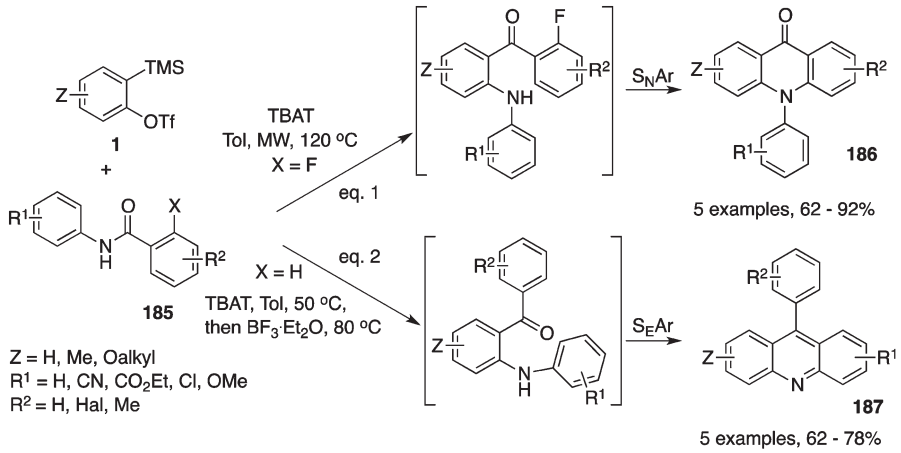
The reaction of benzyne and hydrazones derived from aldehydes leads to the formation of *o*-(*N*,*N*-dimethylamino)aryl ketimines under mild conditions (CsF in MeCN at 65 °C) as reported by Larock (Scheme 54).[75] The presence of halide functionality allows for a favorable ring-closure and a one-pot synthesis of *N*-methylacridones. Thus, the reaction between *o*-chloro- or *o*-fluorobenzaldehyde hydrazones **188** and benzyne, followed by an S_NAr process (induced by running the



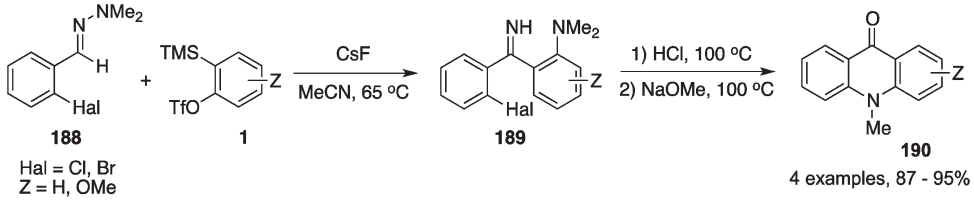
Scheme 51 Synthesis of acridines by aryne annulation.



Scheme 52 Synthesis of 9,10-dehydroacridines.



Scheme 53 One-pot synthesis of acridones and acridines from amides.



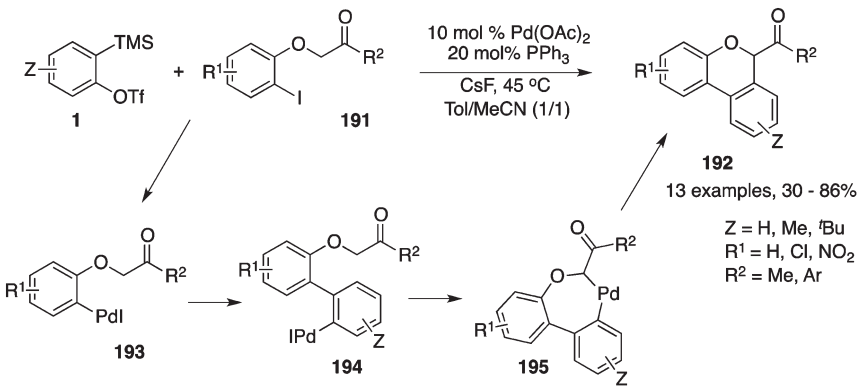
Scheme 54 Reaction of benzyne and hydrazones for the synthesis of acridones.

reaction at 100 °C), leads to the formation of the desired *N*-methylacridones **190** in 87–95% yields.

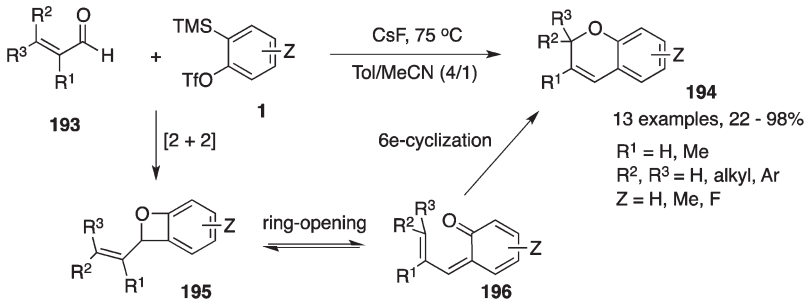
3.4. Chromenes and benzochromenes

Li reported a Pd-catalyzed annulation methodology that generates benzochromenes **192** starting from 2-(2-iodo-phenoxy)-1-substituted ethanones **191** and silylaryl triflates **1** (Scheme 55).[76] Running the reaction in the presence of CsF, catalytic amounts of $Pd(OAc)_2$ and PPh_3 in 1 : 1 Tol–MeCN at 45 °C produces the final heterocyclic products **192** in 30–86% yields. Aryl ketones with electron-withdrawing substituents generally provide higher yields, while electron-rich aryl ketones and alkyl ketones provide lower yields of the desired products. Alkyl, aryl, chloro, and nitro groups are well tolerated. The authors propose the following pathway for this transformation. Insertion of Pd into the C–I bond, followed by addition to the benzyne molecule and base-mediated deprotonation/insertion, leads to the 7-membered ring palladacycle **195**, which upon reductive elimination of Pd(0) furnishes the desired products.

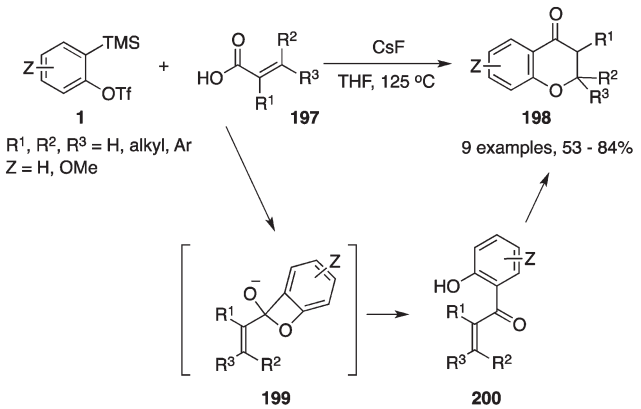
Another method leading to chromenes has been reported by Huang and Wu.[77] Upon reaction of α,β-unsaturated enals **193** with benzynes, the *in situ* formed [2 + 2] adducts **195** undergo a ring opening/6-e electrocyclization sequence to yield 2*H*-chromenes **194** (Scheme 56). The optimal reaction conditions employ slow addition of the benzyne precursor **1** to the reaction mixture in 4 : 1 Tol–MeCN in the presence of CsF at 75 °C. The products **194** were obtained in 22–98% yields. The reaction works most efficiently with electron-rich aryl substituents at the β-position of the enal system. Interestingly, the reaction with ketones/esters/nitriles/nitro derivatives, instead of the aldehydes, under similar reaction conditions proceeds through a different route, not yielding the desired heterocyclic system.



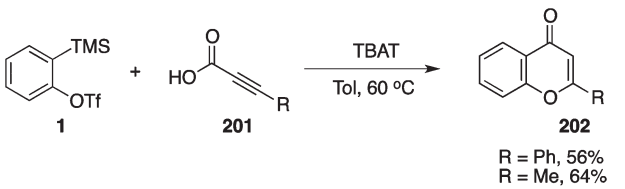
Scheme 55 Synthesis of benzochromenes by Pd-catalyzed annulation.



Scheme 56 Reaction of α,β-unsaturated enals with benzynes.



Scheme 57 Reaction of alkenoic acids with arynes.



Scheme 58 Reaction of alkynoic acids with arynes.

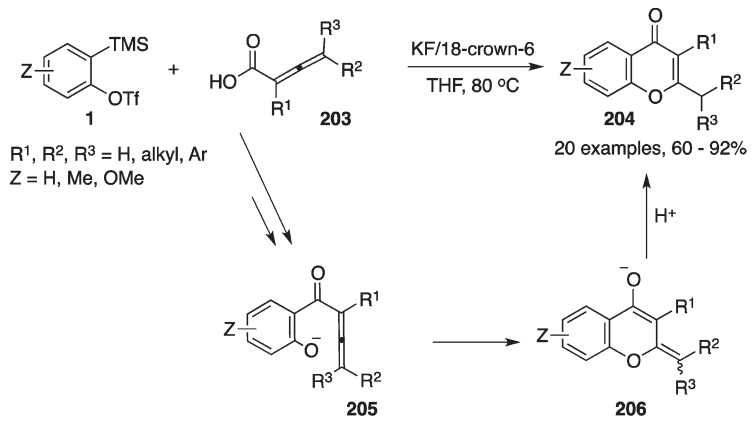
3.5. Chromones and flavanones

Larock discovered that the reaction of carboxylic acids with arynes in THF proceeds through the formation of the 4-membered ring intermediate **199** and yields *o*-hydroxyaryl ketones.[69] Starting from alkenoic acids **197** generates *o*-hydroxyaryl ketones **200**, which undergo a subsequent intramolecular Michael reaction furnishing the 4-chromanones **198** in 53–84% yields (Scheme 57). The optimized reaction conditions involve the addition of the benzyne precursor and CsF in two portions to the reaction mixture in overheated THF. The optimized reaction conditions for the analogous reaction with alkynoic acids **201** employ TBAT in toluene at 60 °C.[78] The latter reaction successfully yields chromones **202** in 56–64% yields (Scheme 58).

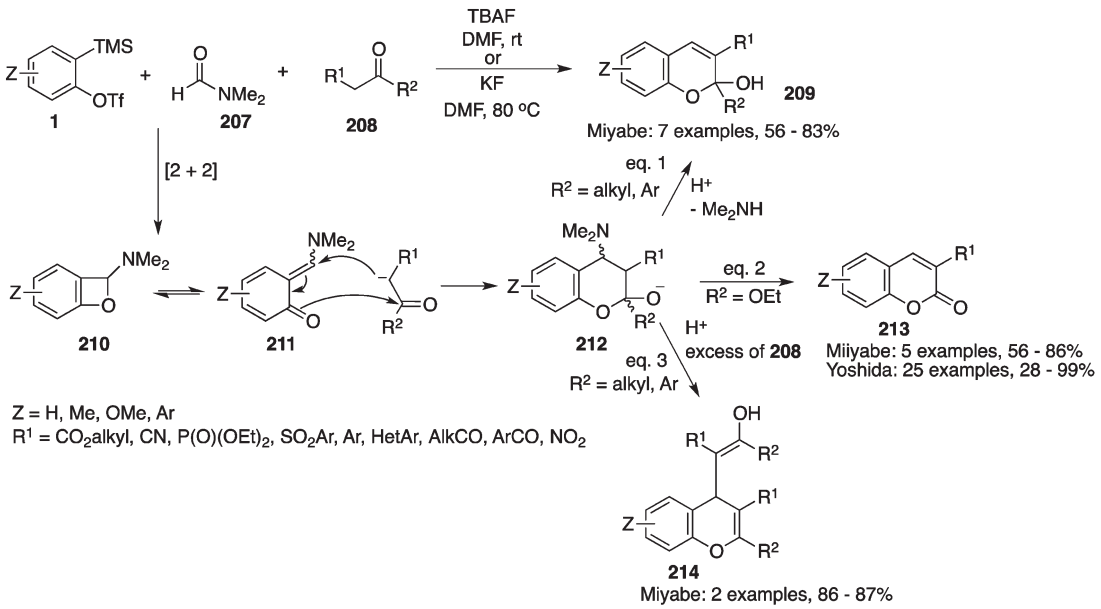
Ma has studied the analogous reaction of 2,3-allenoic acids **203** with benzyne (Scheme 59).[79] After the expected insertion of the benzyne into the C–O bond of the starting acid, the phenoxide ion **205** apparently attacks the allenoic system with formation of the intermediate **206**, which rearranges to the chromone system **204**. The optimized reaction conditions, KF/18-crown-6 in THF at 80 °C, allow the isolation of the desired products in 60–92% yields.

3.6. Coumarins

Miyabe has discovered an interesting three-component coupling of arynes, DMF, and active methylene compounds[80] based on his prior work (Scheme 60).[81] The [2 + 2] coupling product **210** of an aryne and DMF apparently coexists with its open *o*-quinone methide form **211**. The latter is highly unstable and reacts with 1,3-diketones **208** in a cyclization/dehydroamination process yielding the 2-hydroxy-2*H*-chromenes **209** in



Scheme 59 Reaction of 2,3-allenoic acids with arynes.



Scheme 60 Three-component coupling of arynes, DMF, and methylene compounds.

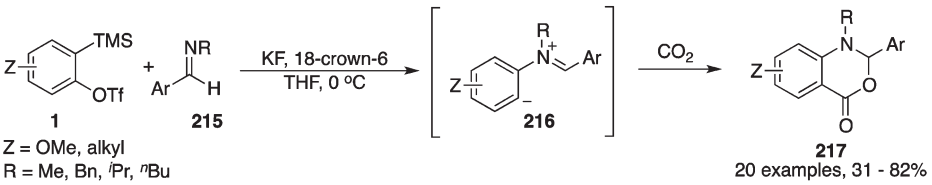
56–83% yields (Scheme 60, eqn (1)). The optimized conditions involve running the reaction in presence of TBAF in DMF as a solvent at ambient temperatures. Interestingly, if the excess of the 1,3-diketone **208** is employed, the extra enolate participates in an S_N2' process yielding derivatives **214** in 86–87% yields (Scheme 60, eqn (3)). The same transformation may occur with a different enolate if to run the reaction in a sequential manner.

When β-keto esters, 1,3-diesters, or α-nitro esters are employed in an analogous transformation, coumarins **213** are produced in 56–86% yields after the loss of the alkoxy group and dehydroamination (Scheme 60, eqn (2)).

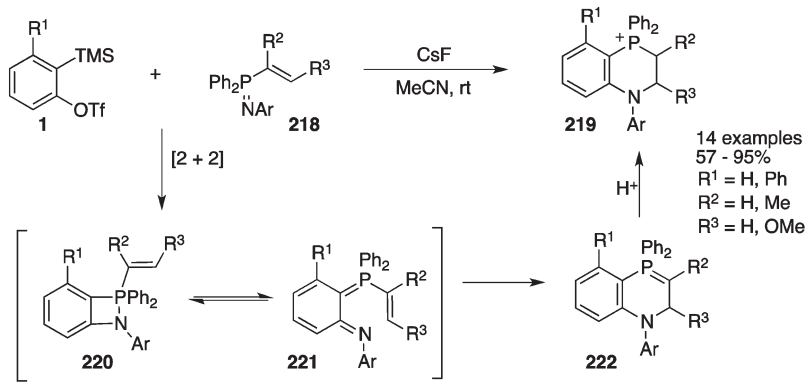
An analogous transformation has been reported by Yoshida.[82] Running the reaction of arynes and β-keto esters and 1,3-diesters with DMF at 80 °C affords coumarins **213** in moderate to high (55–87%) yields (Scheme 60, eqn (2)). Analogous products have been obtained from malononitriles and diethylphosphoryl- and arylsulfonyl-containing methylene donors in 39–74% yields. Even benzyl esters and benzyl nitriles participate as active methylene compounds in this transformation, affording the desired 3-arylcoumarins **213** in 28–99% yields.

3.7. Benzoxazinones

An interesting example of a three-component coupling has been reported by Yoshida and Kunai. The aromatic imines **215** react with arynes under a CO_2 atmosphere to form the aryl anion **216**, which reacts with CO_2 leading to the formation of the 6-membered ring benzoxazinones **217** (Scheme 61).[83] Under the optimal conditions, KF/18-crown-6 in THF at 0 °C, the desired products can be obtained in 31–82% yields. Primary and secondary alkyl imines are tolerated, but not tertiary or aryl imines.



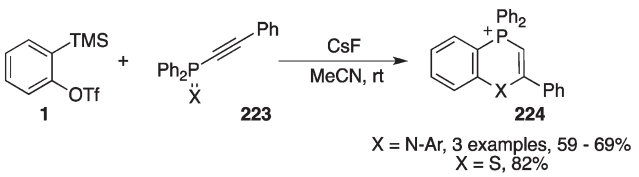
Scheme 61 Reaction of aromatic imines with arynes under a CO_2 atmosphere.



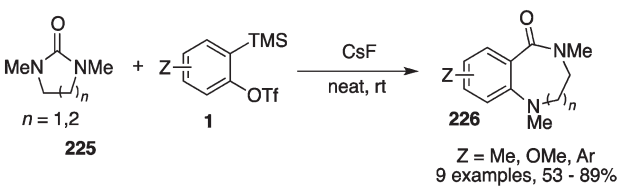
Scheme 62 Reaction of *P*-alkenyl-λ5-phosphazenes and silylaryl triflates.

3.8. Benzazaphosphorinium triflates

An unusual heterocyclic system has been prepared starting from *P*-alkenyl-λ5-phosphazenes **218** and silylaryl triflates as reported by Alajarin and Lopez-Leonardo (Scheme 62).[84] The P═N bond of the starting aza-ylides undergoes a [2 + 2] cycloaddition with the arynes, followed by a retro [2 + 2] cycloaddition with formation of the triene system **221**. This is followed by ring-closure, which furnishes the final compounds **219** after a proton shift. The reaction proceeds under very mild conditions, CsF in MeCN at room temperature. The products have been obtained in 57–95% yields. Interestingly, employing alkynyl derivatives of these aza-ylides results in formation of the heterocycles **224**, albeit in lower (59–69%) yields (Scheme 63). The sulfur-analogue **223** (X = S) results in formation of a derivative **224** (X = S) in an 82% yield.



Scheme 63 Reaction of alkynyl derivatives.



Scheme 64 Insertion of arynes into the N–CO bond of cyclic ureas.

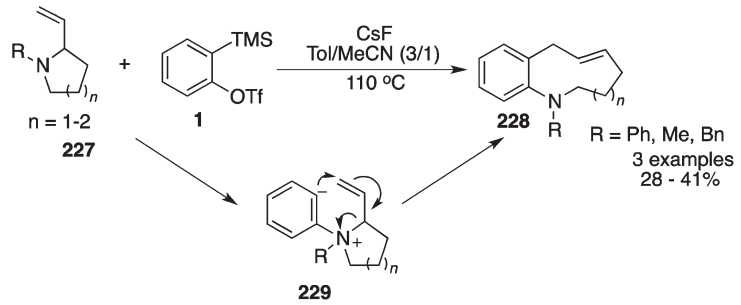
4. Synthesis of larger ring heterocycles

4.1. Benzodiazepines and benzodiazocines

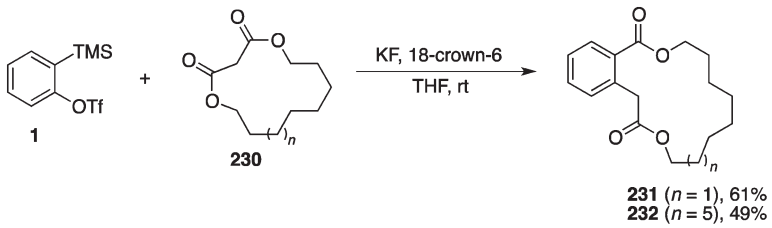
A variety of 1,4-benzodiazepine and 1,5-benzodiazocine derivatives **226** have been obtained through the insertion of arynes into the N–CO bond of cyclic 5- and 6-membered ring ureas **225** (Scheme 64).[73] The reaction occurs in the urea as the solvent in the presence of CsF at room temperature and affords the desired products in 53–89% yields. The reaction presumably occurs through the formation and subsequent ring-opening of a four-membered ring intermediate (see Schemes 40 and 45).

In 2009, Greaney and co-workers reported a benzyne-mediated aza-Claisen reaction.[85] Along with the number of tertiary allyl amines that were shown to react with aryne precursors, the benzyne aza-Claisen reaction has been extended to cyclic tertiary amines **227** to afford benzannulated medium-ring amines **228** in a single step (Scheme 65). Five- and six-membered ring precursors have successfully produced the corresponding 9- and 10-membered ring compounds **228** in moderate (28–41%) yields. The use of a secondary proline derivative was also possible when an excess of the benzyne precursor is used to ensure prior phenylation of the nitrogen atom.

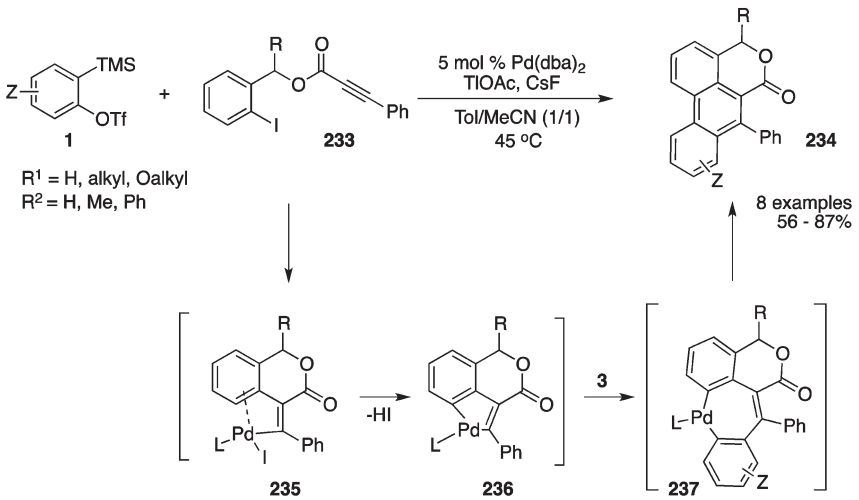
In 2005, Kunai reported a procedure for the insertion of arynes into the C–C bonds of various β-dicarbonyl compounds (see Scheme 40 for a mechanism).[86] The mild reaction conditions (KF/18-crown-6, THF, rt) successfully afford aryne insertion products in good to excellent (56–82%) yields. When the



Scheme 65 Benzyne aza-Claisen reaction.



Scheme 66 Reaction of arynes with β-dicarbonyl compounds.



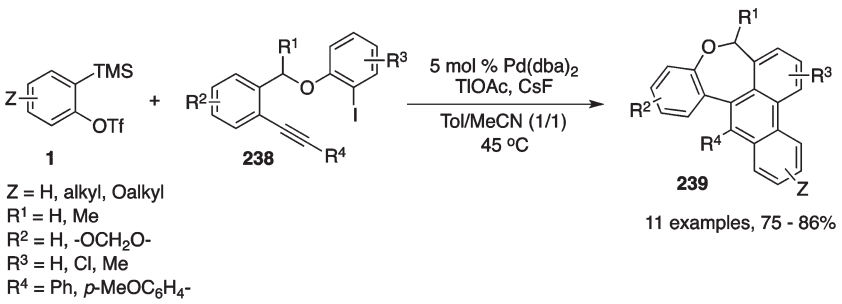
Scheme 67 Pd-catalyzed cascade cyclization of alkynes and benzynes.

cyclic malonates **230** were employed, the compounds **231** (n = 1) and **232** (n = 5) were obtained in 61% and 49% yields respectively (Scheme 66).

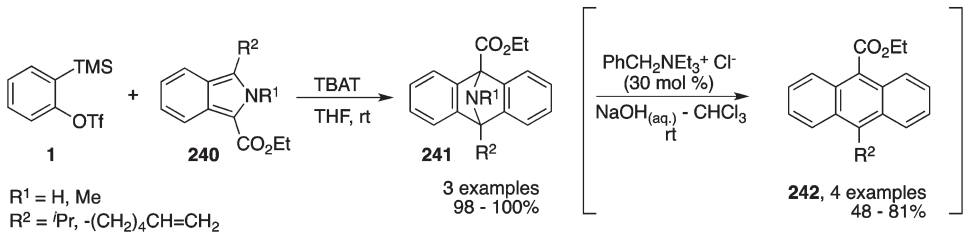
5. Heterocycles not a result of direct benzyne addition

Very recently, Cheng reported a novel Pd-catalyzed cascade cyclization of alkynes **233** and benzynes for the synthesis of isochromenones **234** (Scheme 67).[87]

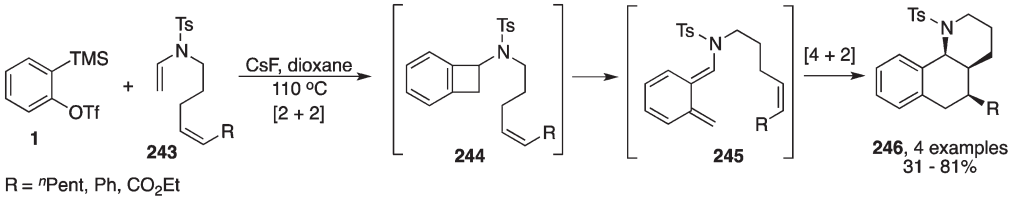
The mechanism presumably involves initial oxidative addition of the C–I bond of the starting material **233** to Pd(0), intramolecular insertion into the alkyne triple bond to generate the organopalladium species **235**, intramolecular C–H bond activation to provide the palladacycle **236**, which reacts with benzyne and undergoes subsequent reductive elimination to afford product **234** (Scheme 67). The reaction is most efficient in the presence of CsF, catalytic amounts of $Pd(dba)_2$ and stoichiometric amounts of TlOAc (the role of which is not certain) in 1 : 1 Tol–MeCN at 85 °C. The desired heterocycles were obtained in 75–86% yields. Running the analogous coupling on the iodobenzenes **238** bearing remote alkyne functionality produces the 7-membered ring oxepines **239**, or its aza-analogues, in 75–86% yields (Scheme 68).



Scheme 68 Aryne annulation route to oxepines.



Scheme 69 Reaction of isoindoles and arynes.



Scheme 70 Reaction of benzynes and *N*-tosyl enamides bearing a remote alkene.

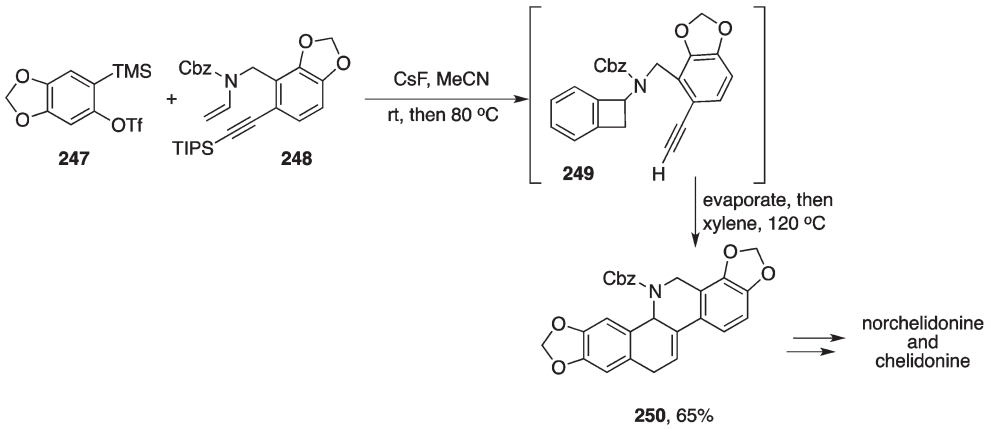
An interesting reaction of isoindoles **240** and arynes has been reported by Chiba (Scheme 69).[88] Running the reaction in the presence of TBAT in THF at room temperature affords nearly quantitative yields of the desired [4 + 2] adducts **241**. In addition, the compounds obtained have been subsequently converted to anthracenes **242** after a dichlorocarbene-induced deaminative aromatization.

Hsung has reported a tandem process involving benzynes and the *N*-tosyl enamides **243** bearing a remote alkene moiety (Scheme 70).[89] The process involves a [2 + 2] cycloaddition, followed by ring opening to provide the *o*-quinodimethane intermediate **245**, which undergoes an intramolecular [4 + 2] cycloaddition with the remote C=C bond. Running the reaction in the presence of CsF in 1,4-dioxane at 110 °C provides the tricyclic (starting from cyclic substrates leads to tetracyclic) products **246** in 31–81% yields with excellent stereoselectivity.

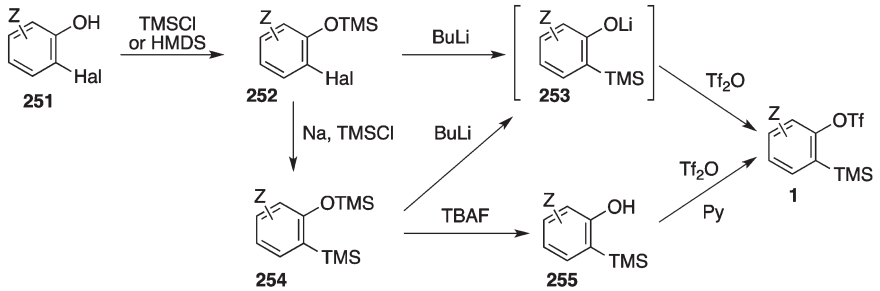
Later, this methodology was adapted for the synthesis of two alkaloids (Scheme 71).[90] Reacting the dioxolane-containing aryne with a remote alkyne-containing enamide under mild reaction conditions lead to formation of the [2 + 2] cycloaddition product **249**. Substituting MeCN with xylene and running the reaction at 120 °C allowed the remaining steps of the tandem process to proceed, providing the common precursor **250** for the two alkaloids in a 65% overall yield.

6. Availability and synthesis of benzyne precursors

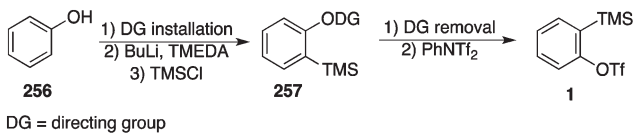
Several conceptually unique pathways has been designed for the synthesis of substituted *o*-(trimethylsilyl)aryl triflates. One of the most common approaches utilizes an *o*-halophenol (**251**) as a starting material (Hal = Cl, Br) (Scheme 72).[5,91] After *O*-silylation of the phenol moiety, the intact halide in intermediate **252** is exchanged for lithium by treatment with *n*-BuLi.[91a–d] Subsequently, migration of the TMS group from oxygen to carbon occurs to provide the phenoxide **253**. The latter is quenched *in situ* with a triflating reagent to provide the desired benzyne precursor **1**.[91a–d] Alternatively, the halide in **252** can be exchanged for a TMS silyl group in a sodium-mediated coupling reaction with formation[5,91e] of the derivative **254**. The TMS group on the oxygen atom in compound **254** can be cleaved with *n*-BuLi[5] or TBAF,[91e] followed by triflation of the liberated phenol group to provide the final product **1**.



Scheme 71 Aryne synthesis of alkaloids.



Scheme 72 Synthesis of benzyne precursors from *o*-halophenols.



Scheme 73 Synthesis of benzyne precursors from phenols.

A variety of symmetrical and unsymmetrical benzyne precursors containing condensed aromatic rings and various halides, silyl, alkyl and alkoxy substituents have been prepared utilizing this methodology.

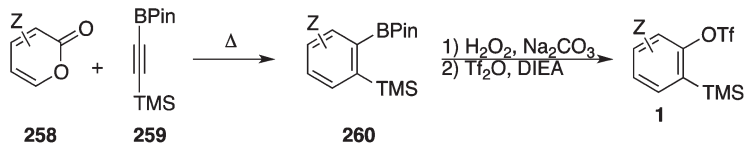
Another approach to the benzyne precursors **1** has recently been developed by Garg.[92] It takes the advantage of directed-metalation chemistry and, thus, starts from readily available phenols (Scheme 73). The hydroxyl group in phenol (**256**) is transformed into an *N*-silylcarbamate *via* two simple steps, *o*-metalation occurs upon treatment with chelated *n*-BuLi and this is followed by the addition of a silylating agent, which leads to formation of the silyl derivative **257**. The urethane is subsequently cleaved under basic conditions and the deliberated hydroxyl group is triflated with the formation of **1**. Although this method utilizes six chemical transformations, it requires only one chromatographic purification and has so far been applied to the synthesis of an unsymmetrical alkyl- and alkoxy-containing benzyne precursor and an indolyne precursor.

Lastly, a Diels–Alder based approach to benzyne precursors has been reported by Harrity (Scheme 74).[93] Substituted 2-pyrones **258** undergo cycloaddition with trimethylsilyl alkynyl boronates **259** to afford the benzene skeleton **260** after the extrusion of CO_2. Oxidation of the boron moiety and triflation of the resulting hydroxyl group leads to the formation of the benzyne precursors **1**. This approach has been utilized to prepare regioisomeric mixtures of halo-, ester-, and cyano-containing benzyne precursors **1** in moderate to high yields.

To assist the synthetic organic community, a number of benzyne precursors have recently become commercially available (Fig. 3).[94]

7. Late additions

During the peer-review process, several articles have been published that are pertinent to the scope of the present review. Kaliappan has reported a [3 + 2] cycloaddition between sugar-derived chiral nitrones and arynes leading to the formation of benzisoxazolines (see Section 2.2).[95] Enacetamides have been found to react with benzynes with the formation of isoquinolines (see Section 3.1).[96] Stoltz has reported a method leading to *N*-aryl acridones starting from β-lactams (see Section 3.3).[97] Saito has reported a formal [6 + 2] cycloaddition between 2-vinylazetidines and arynes leading to 8-membered nitrogen-containing heterocycles (see Section 4.1).[98] Shi has reported an



Scheme 74 Synthesis of benzyne precursors utilizing a [4 + 2] cycloaddition.

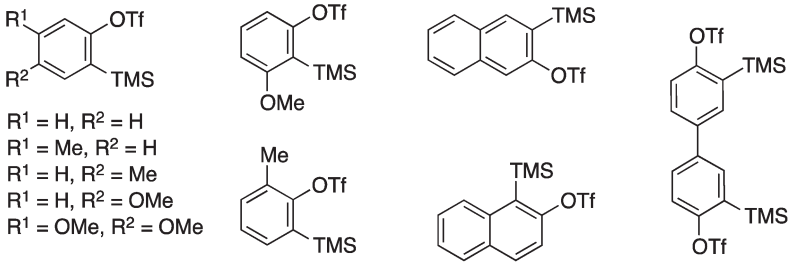


Fig. 3 Commercially available benzyne precursors from major vendors.

unusual [3 + 2] cycloaddition between 3-oxidopyridinium salts and benzynes (see Section 5).[99] Finally, Li and Jia have reported a successful Diels–Alder reaction between arynes and methyleneindolinones leading to naphtho-fused oxindoles (see Section 5).[100]

8. Conclusions

In recent years, aryne intermediates have continued their journey from objects of purely theoretical interest to indispensable tools in the synthesis of pharmaceutically and biologically interesting small molecules, as well as complex natural products. The major breakthrough in synthetic aryne chemistry has been the development of a mild, controlled method for generating the highly reactive benzyne intermediate from silylaryl triflates, which was first reported by Kobayashi in 1983. However, not until the mid-2000's did aryne methodologies start flourishing in the literature. A great variety of heterocycles can now be prepared from cheap and readily available starting materials by simple one-step or one-pot processes with high regioselectivities and in high yields. A broad variety of functional groups are tolerated under the mild reaction conditions used. However, the poor atom economy of Kobayashi's precursor and its relatively high price continue to remain a major drawback to even wider application of this fascinating chemistry. Solutions to this problem and broader applications of the existing aryne precursors are currently being sought by many research groups. One can expect new, more efficient, more regio- and stereoselective aryne methodologies to appear in the near future.

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