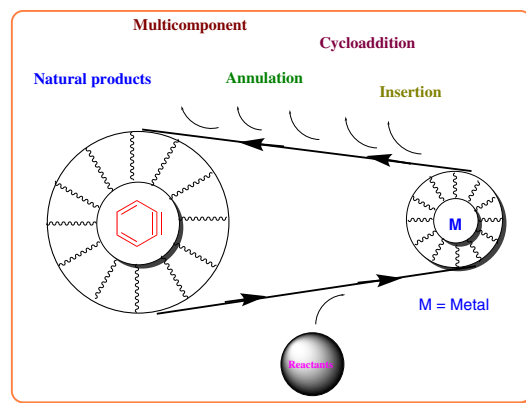R. A. Dhokale, S. B. Mhaske

Transition-Metal-Catalyzed Reactions Involving Arynes

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Abstract The plethora of transformations attainable by the transition-metal-catalyzed reactions of arynes has found immense contemporary interest in the scientific community. This review highlights the scope and importance of transition-metal-catalyzed aryne reactions in the field of synthetic organic chemistry reported to date. It covers transformations achieved by the combination of arynes and various transition metals, which provide a facile access to a biaryl motif, fused polycyclic aromatic compounds, different novel carbocycles, various heterocycles, and complex natural products.

1   Introduction

Arynes find prime applications in organic synthesis due to the presence of a highly electrophilic strained triple bond.[1–15] The energy gap between the HOMO and the LUMO of arynes is less compared to that of unstrained alkynes, which makes them superior electrophiles, hence arynes smoothly react even with weak nucleophiles under milder reaction conditions.[12] The existence of aryne intermediates was first indicated after experiments performed by Stoermer and Kahlert in 1902.[16] Wittig observed the formation of biphenyl by reacting fluorobenzene and phenyllithium via a zwitterionic intermediate.[17] Furthermore, Roberts and co-workers confirmed the formation of an aryne by a classical ^{14}C-labeling experiment.[18] Several methods to generate arynes from varyingly substituted aromatics or alkynes have been well documented in the literature.[5,19–25] However, the generation of arynes from *o*-(trimethylsilyl)aryl triflate developed by Kobayashi and co-workers[26] remains the most convenient and one of the most highly utilized methods, which enables various carbon–carbon and carbon–heteroatom bond-forming processes. This mild method of aryne generation is also compatible with transition metals, thus enabling enhanced reactivity giving rise to novel transformations. Such transformations of arynes to multifunctionalized arenes, heteroarenes, and polycyclic rings in the presence of transition metals have found immense contemporary interest in the scientific community. Transition-metal-catalyzed reactions of arynes have also been found useful in the total synthesis of bioactive natural products. Reactions involving an aryne, a nucleophile, and an electrophile, referred as a multicomponent reaction, provide diverse 1,2-difunctionalized arenes and heteroarenes in the presence of a transition metal. Polyaromatic rings, which find prime applications in materials chemistry, are constructed by transition-metal-catalyzed cyclotrimerization and cocyclotrimerization reactions of arynes. The transition-metal-catalyzed annulation of arynes with substituted aromatic rings bearing heteroatoms provides varyingly substituted heterocycles. The general chemistry of arynes has been covered in many reviews.[1–15] Larock and co-workers have reviewed Pd-catalyzed aryne reactions reported until 2011.[27] Yoshida has a book chapter that highlights transition-metal-catalyzed aryne reactions reported until 2013.[28a] The present review focuses on transition-metal-catalyzed reactions of arynes reported to date that are not covered in these previous reports. Interestingly, a review on a similar topic appeared online after submission of this review.[28b]

2 Insertion of Arynes

Insertion of arynes into an element–element bond is a facile and very well explored reaction of high synthetic importance.[7] The reactants, which otherwise would be unreactive/less reactive with arynes are further activated by transition-metal catalysis.[27,28]

The first reported example of the coupling of an alkyne and an aryne in the presence CuI under microwave-assisted conditions was in 2009 by Biehl and Akubathini; this was the first example of aryne chemistry under microwave conditions. The reaction was performed under microwave heating in acetonitrile/toluene (1:1) solvent. Various symmetric and unsymmetric disubstituted alkynes were synthesized (Scheme 1).[29]
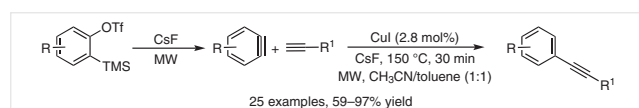
Scheme 1 Cu-catalyzed alkyne–aryne coupling

The insertion of an aryne into an ArS–CN bond to give substituted 2-(arylthio)benzonitriles **1** was successfully carried out by Werz and co-workers using a Pd catalyst. The reaction did not work in the absence of a Pd(II) catalyst because the sulfur in thiocyanate is positively polarized to undergo nucleophilic attack, therefore, the activation of aryl thiocyanates by Pd(OAc)$_2$ was necessary. The active [Pd(0)] catalyst generated by the combination of Pd(OAc)$_2$ and

Xantphos undergoes oxidative addition to the ArS–CN bond to give intermediate **1a**. The Pd complex **1a** coordinates with in situ generated aryne affording **1b**. Further, thiometalation and reductive elimination of **1b** affords substituted 2-(arylthio)benzonitrile **1**. It was observed that an oxygen atmosphere was crucial to obtain high yields of the expected products. Differently substituted aryl thiocyanates and aryne precursors were utilized (Scheme 2).[30]
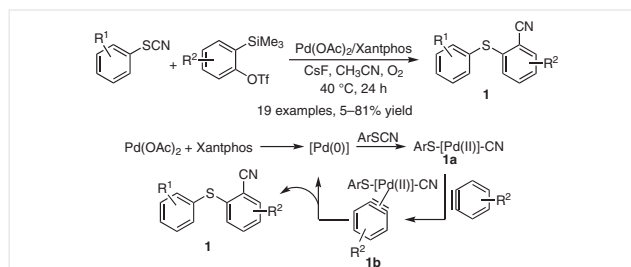
Scheme 2 2-(Arylthio)benzonitriles from insertion of arynes into aryl thiocyanates catalyzed by Pd(OAc)$_2$

The insertion of indolynes **2** into a symmetrically substituted B–B bond was successfully achieved by the Oestreich group in 2015 by employing the catalyst Pt(dba)$_2$ and the ligand tBuNC (Scheme 3).[31] The resulting diborane products **3** were utilized in further C–C bond forming organometallic Suzuki–Miyaura coupling reactions. Excellent regioselectivity was achieved with the first Suzuki–Miyaura coupling reaction occurring unexpectedly at C7 to give **4**. Further,

Biographical Sketches

Mr. Ranjeet A. Dhokale obtained his B.Sc. and M.Sc. (Nowrosjee Wadia College, Pune) degrees from the University of Pune, India. After completing his M.Sc. in organic chemistry he worked at Sai Life Sciences Ltd. as a research chemist (2008–2010).

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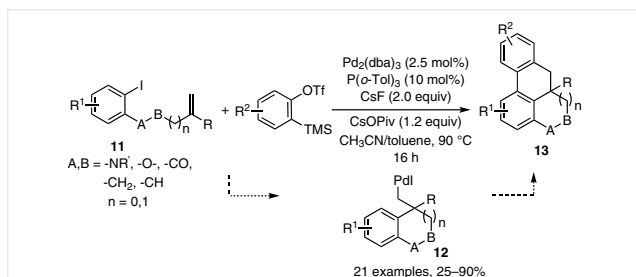
Dr. Santosh B. Mhaske completed his Ph.D. from CSIR-National Chemical Laboratory, Pune India in February 2005. He completed his postdoctoral studies in the USA followed by Humboldt Postdoctoral studies at University of Hannover, Germany. He joined CSIR-NCL as a Ramanujan Fellow

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and drugs, synthesis and biological evaluation of computationally designed molecules, interdisciplinary research directed towards novel, efficient and affordable treatment of diseases.

Suzuki–Miyaura coupling was carried out on monocoupled product **4** with bulky aryl iodides at C6 position giving very good yields of the 6,7-difunctionalized indoles **5**.

Scheme 3　Pt(0)-catalyzed indolyne insertion into bis(pinacolato)diboron

In 2016, García-López and Pérez-Gómez synthesized spirobiaryls by reacting *N*-(2-phenylallyl)sulfonamide **6** (X = NTs) with an in situ generated aryne in the presence of Pd(OAc)$_2$ catalyst and PPh$_3$ ligand in toluene/acetonitrile (1:1) solvent (Scheme 4).[32]

Scheme 4　Spirobiaryls through a Pd-catalyzed cascade reaction

Mechanistically, the intramolecular Heck arylation of complex **6a** affords the intermediate **6b**. Path A suggests C–H activation of **6b** furnishing five-membered palladacycle **7**. The insertion of the aryne into complex **7** produces intermediate **7a** and further reductive elimination furnishes spiro product **8**. Alternatively, substrates with a longer tethering chain undergo C–H activation producing palladacycles of type **6f**, which undergo insertion with the aryne and finally reductive elimination providing the product **6g**. In alternative path B, the formation of intermediate **6e** via trapping of the aryne by intermediate **6b** is suggested, followed by C–H activation and C–C coupling to afford the spirocyclic compound **8**. The compatibility of the optimized protocol was tested on various substrates containing alkene, aryl, and heteroaryl moieties and different aryne precursors.

Chen and co-workers reported the insertion of an aryne into the H–P(O) bond of a secondary phosphine oxide using catalytic CuI (Scheme 5). The optimized protocol was tested on various aryne precursors and afforded a diverse range of arylphosphine oxides. These arylphosphine oxides are a useful source of ligands that also find prime applications in medicinal chemistry and material science.[33]

Scheme 5　Insertion of an aryne into a H–P(O) bond through a Cu-catalyzed reaction

The synthesis of spirodehydrobenzofuran **10a** and spirooxindoles **10b** from alkene **9** via Pd-catalyzed domino Heck reaction was established by Lautens and co-workers (Scheme 6). The reaction consists of a Pd-catalyzed domino-Heck spirocyclization via C–H activation and benzyne insertion sequence. A wide range of spirooxindoles and spirodihydrobenzofurans were synthesized in good to excellent yields.[34]

Scheme 6　Pd-catalyzed spirocyclization

The synthesis of heterocycle-fused 9,10-dihydrophenanthrenes **13** from 1-iodo-2-[(2-methylallyl)oxy]benzene **11** and in situ generated aryne was demonstrated by Yao and He (Scheme 7).[35] Intramolecular Heck reaction of 1-iodo-2-[(2-methylallyl)oxy]benzene generates σ-alkyl–palladium(II) intermediate **12**, which is intercepted by the aryne followed by C–H activation to afford the product **13**. This protocol involves the formation of three new C–C bonds and the generation of a quaternary

carbon center. Overall 26 different substituted heterocycle-fused 9,10-dihydrophenanthrenes including regioisomers were synthesized in moderate to excellent yields.

**Scheme 7** Synthesis of heterocycle-fused 9,10-dihydrophenanthrenes

The above-mentioned examples demonstrate the importance of transition metals for controlled reactivity of the substrates in the expected transformation utilizing highly reactive aryne species.
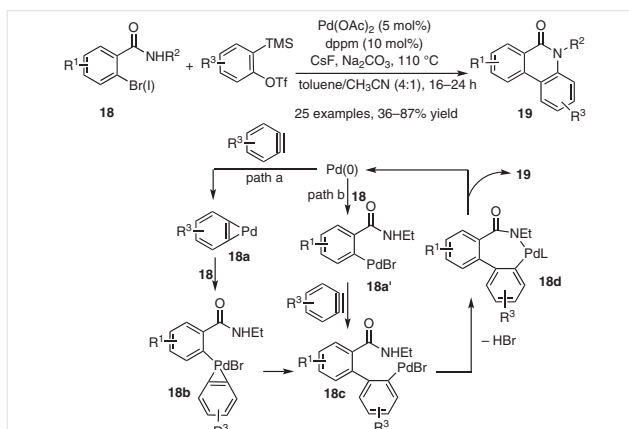
3 Annulation of Arynes

The annulation reaction of arynes catalyzed by transition metals is an important reaction in organic synthesis. Syntheses of various novel heterocycles, which find prime application in the pharmaceutical field, have been achieved by the annulation of arynes in a single-step transformation. The annulation process has been efficiently used for the synthesis of various bioactive natural products.[36]

In 2010, Huang and co-workers reported the carboannulation of arynes with vinyl iodides in the presence of a Pd catalyst. The substrate scope of the optimized protocol was studied on various allyl-substituted iodocycloalkenones **14** and iodofuranones **15** with substituted aryne precursors for the synthesis of dihydrophenanthren-1(2H)-ones **16** and naphtho[2,1-c]furan-3(1H)-ones **17**, respectively. Methyl- and fluorine-substituted aryne precursors gave a mixture of regioisomers in ~1:1 ratio, whereas the methoxy-substituted aryne precursor gave high regioselectivity (Scheme 8).[37]

The mechanism in path A suggests the formation of palladacycle **15a** by coordination of Pd(0) with benzyne. The oxidative addition of vinyl iodide **15** to palladacycle **15a** leads to arylpalladium(IV) complex **15b**, which on reductive elimination generates arylpalladium intermediate **15c**. However, alternatively in path B, the complex **15a′** formed via oxidative addition undergoes insertion with the aryne to generate intermediate **15c**. Intramolecular Heck coupling of intermediate **15c** furnishes **15d**, which on subsequent β-hydride elimination and aromatization affords the product **17**. A similar mechanism is proposed for **16**.
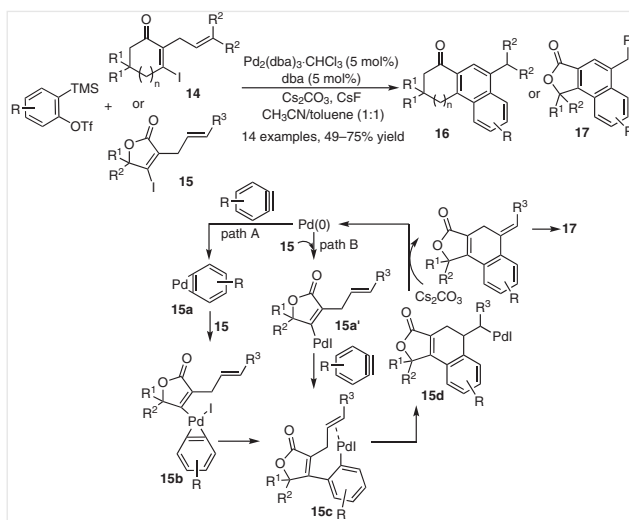
Scheme 8 Pd-catalyzed synthesis of dihydrophenanthren-1(2H)-ones and naphtho[2,1-c]furan-3(1H)-ones from arynes

Scheme 9 Phenanthridinones by annulation of o-halobenzamides with arynes

Larock and co-workers introduced a novel protocol for the synthesis of diverse phenanthridinones **19** by simultaneous C–C and C–N bond formation. The reaction involved an aryne precursor, o-halobenzamides **18**, a Pd catalyst, CsF, and a base in toluene/acetonitrile (4:1) solvent. Mechanistically, the palladacycle **18a** (path a) undergoes oxidative addition with **18** to generate Pd(IV) intermediate **18b**. Further reductive elimination affords the arylpalladium(II) intermediate **18c**. Alternatively, in path b the oxidative addition of Pd(0) with **18**, followed by carbopalladation of the aryne produces intermediate **18c**. The intermediate **18c**, under basic condition cyclizes to **18d**, which undergoes reductive elimination affording the product **19**. A total of 25 phenanthridinones were obtained in moderate to good yields (Scheme 9).[36]

The highly electrophilic nature of arynes has been used for the construction of diverse carbazoles **21** by annulation with 2-haloacetanilides **20** in the presence of Pd(dba)$_2$ catalyst, dppf ligand, CsF, and toluene/acetonitrile (4:1) as the solvent. Both C–C and C–N bonds were formed simultaneously. A diverse range of carbazoles was prepared from inexpensive starting materials using this methodology (Scheme 10).[38]
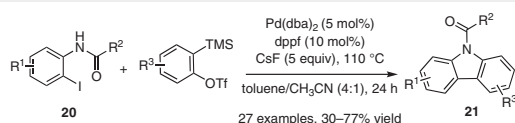
Scheme 10 Carbazoles by annulation of *o*-haloacetanilides with arynes

Wang and co-workers demonstrated insertion of arynes into the C–S bond of α-carbamoyl ketene dithioacetals **22** catalyzed by Pd(OAc)$_2$ and dppf as the ligand. Mechanistically, the palladacycle **22a** undergoes insertion into the C–S bond to afford intermediate **22c** via **22b**. The seven-membered palladacycle **22d** is formed at the expense of the thioanisole derivative through intramolecular substitution of **22c**; reductive elimination of **22d** offers the expected product **23**. The alternative path B suggests the oxidative addition of the Pd complex to one of the C–SR bonds, followed by aryne insertion leading to palladacycle **22c**, which finally provides product **23**. Various alkylthio-substituted quinolines **23** were synthesized in moderate to good yields (Scheme 11).[39]
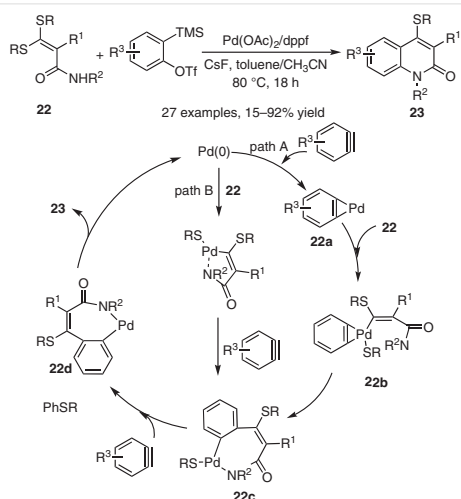
Scheme 11 The reaction of α-carbamoyl ketene dithioacetals with arynes in the presence of Pd(OAc)$_2$

Ma and Yuan developed an efficient method for the synthesis of 2,3-disubstituted benzofuran derivatives **25** containing a trisubstituted alkene functional group from the

preinstalled alkyne in **24**. In the proposed mechanism, intramolecular ene reaction of the preinstalled alkyne with the aryne precursor in the presence of Pd(PPh$_3$)$_4$ catalyst and CsF leads to the formation of allene intermediate **24a**. In situ formed ArPdI undergoes insertion with **24a** furnishing π-allyl–palladium complex **24b**. Finally β-H elimination affords the isomeric benzofuran derivative **25** in moderate yields (Scheme 12).[40]
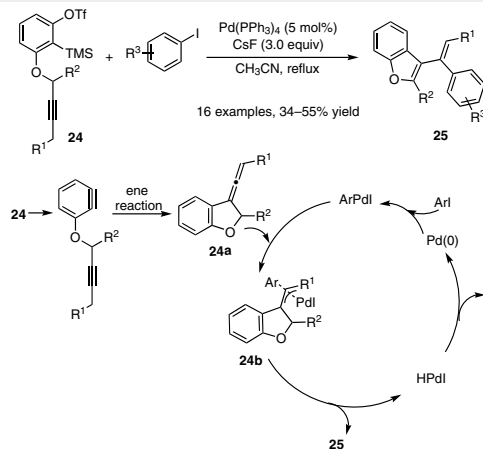
Scheme 12 2,3-Disubstituted benzofurans from the reaction of aryl iodide with arynes in the presence of Pd(PPh$_3$)$_4$

A novel protocol was developed by Liang and co-workers in 2014 for the synthesis of various substituted phenanthridinones **27** by Pd-catalyzed annulation of a benzyne with an *N*-substituted *N*-(2-halophenyl)formamide **26**. Pd(OAc)$_2$ was the most successful catalyst for this reaction along with P(*o*-Tol)$_3$ as the ligand. This protocol was general and various substituted *N*-(2-halophenyl)formamides as well as arynes were tolerated. Regioisomeric products in the ratio 1.6:1 were observed for an unsymmetrical chloroaryne precursor (Scheme 13).[41]
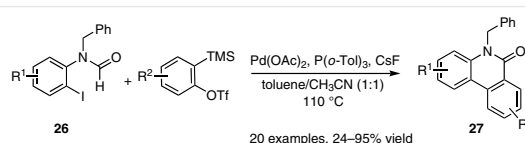
Scheme 13 Phenanthridinones from Pd-catalyzed annulation of *N*-substituted *N*-(2-halophenyl)formamides with arynes

In 2014, Sha and co-workers reported the synthesis of phenanthridines **29** via Pd-catalyzed C–H activation from aryl ketone *O*-acetyloximes **28** and arynes (Scheme 14).[42] In general, preactivated substrates are used for the synthesis of such heterocycles using aryne chemistry, but in this case, the synthesis of phenanthridines was carried out through C–H bond activation involving a directing group. The protocol was established successfully using Pd catalyst, CuCl$_2$ as

an oxidant, and Cs_2CO_3 as the base. The reaction worked well for different combinations of substituted *O*-acetyloximes and substituted aryne precursors.
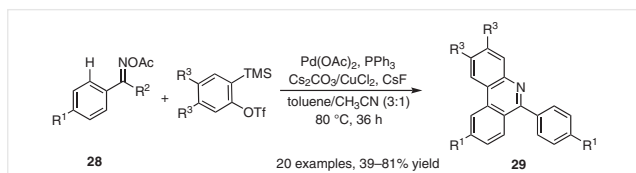

Scheme 14 Phenanthridines from ketoximes and aryne precursors

Transition-metal-catalyzed C–H functionalization is a very powerful synthetic strategy in building complex molecules. The Xu group[43] and Jeganmohan and Pimparkar[44] both reported this concept in aryne chemistry independently in 2014. This methodology involves the Pd N–H/C–H activation of amides **30**, aryne insertion, and cyclization in the presence of catalytic $Pd(OAc)_2$ to provide a tricyclic phenanthridinone core **31**. The Xu group used $Pd(OAc)_2$ as the catalyst, $Cu(OAc)_2$ as the oxidant, and DMSO/dioxane solvent,[43] whereas Jeganmohan and Pimparkar optimized the protocol using $Pd(OAc)_2$ as the catalyst in combination with adamantane-1-carboxylic acid as the ligand and $K_2S_2O_8$ as the oxidant.[44] The Xu group extended the methodology to cyclooctynes, which also yielded the expected products in good yields (Scheme 15).[43] Mechanistically, the five-membered palladacycle intermediate **30a** is formed via coordination of nitrogen with Pd followed by orthometalation. The in situ generated aryne undergoes insertion to form a seven-membered palladacycle intermediate **30b**. The reductive elimination of complex **30b** furnishes the product **31** (Scheme 15).[44]
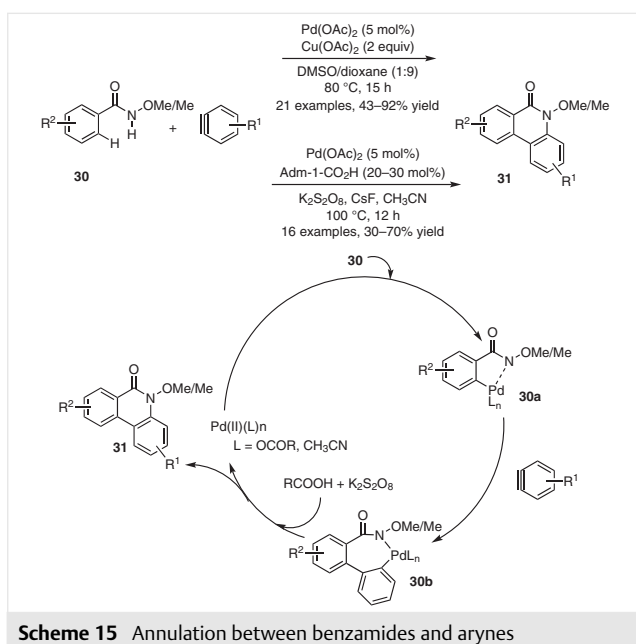
Scheme 15 Annulation between benzamides and arynes

In 2015, the Xu group extended (Scheme 15)[43] their methodology by reacting acrylamides **32** with arynes delivering diverse quinolinones **33**. The optimized protocol was developed in which $Pd(OAc)_2$, $Cu(OAc)_2$, and tetrabutylammonium bromide (TBAB) in DMSO/dioxane (1:9) was used to give quinolinones **33** in moderate to good yields. A variety of quinolinones were synthesized using substituted aryne precursors (Scheme 16).[45]
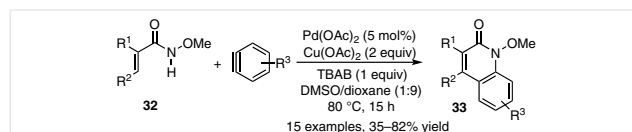
Scheme 16 Quinolinones from annulation between acrylamides and arynes

In 2016, Yao and co-workers developed a protocol for the synthesis of substituted 9,10-disubstituted phenanthrenes by annulation of *o*-halostyrenes with an aryne in the presence of a Pd catalyst. Various substituted *o*-halostyrenes **34** reacted with simple aryne precursors giving moderate to good yields of 9,10-disubstituted phenanthrenes **35**. The substrate scope for variously substituted aryne precursors was also examined (Scheme 17).[46]
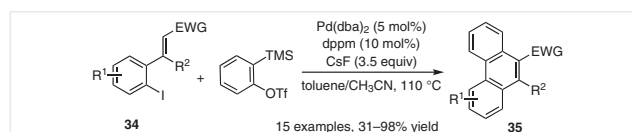
**Scheme 17** 9,10-Disubstituted phenanthrenes by Pd-catalyzed aryne annulation by *o*-halostyrenes

Gogoi and co-workers reported the synthesis of biologically important diverse coumestans **37** from arynes and 4-hydroxycoumarins **36** (Scheme 18). The reaction proceeds through C–H activation of the 4-hydroxycoumarin. Mechanistically, the anion species **36a** undergoes C–H activation at 3-position to give intermediate **36b**, which undergoes carbopalladation with the aryne precursor to give intermediate **36c** that converts into **37** in the presence of a base. The catalyst was regenerated by $Cu(OAc)_2$, which acts as an oxidant (Scheme 18).[47] In total, 20 substituted coumestans were synthesized in moderate to good yields. Moreover, the protocol was compatible with halo-substituted 4-hydroxycoumarins.[47]

In 2017, Zhang and co-workers reported the annulation of directing group containing benzamides **38** by benzynes in the presence of $Cu(OAc)_2$ catalyst. The resulting *ortho*-C–H/N–H annulations afforded the biologically important phenanthridinone compounds **39**. The reaction was performed using TBAI in DMF/CH_3CN solvent under an oxygen atmosphere. The optimized protocol was tested on a wide
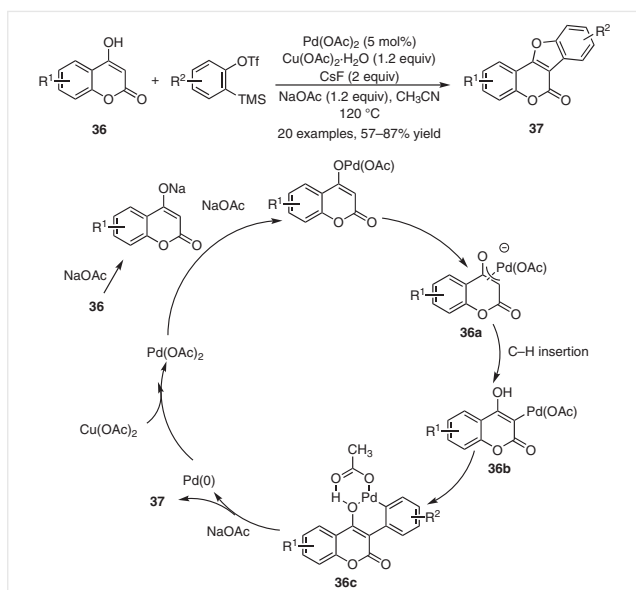
Scheme 18 Coumestans via Pd-catalyzed C–H activation/C–C and C–O bond formation

range of benzamides and substituted aryne precursors to afford 44 substituted phenanthridinone compounds (Scheme 19).[48]
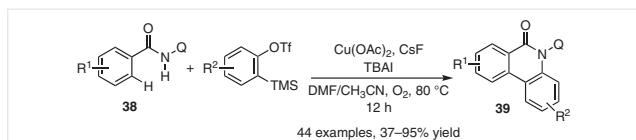
**Scheme 19** Phenanthridinone by Cu-catalyzed annulations of aryne, and benzamides; Q = 8-quinolinyl

Several reports[36–48] on the synthesis of biologically relevant heterocycles such as naphthofurans, phenanthridinones, carbazoles, using the aryne annulation process suggest its importance for their construction and structure–activity relationship studies.

4   Cycloaddition of Arynes

The cycloaddition of arynes is a well-known reaction that furnishes scaffolds of biological interest, however, the control of both regio- and chemoselectivity remained a great challenge. Transition-metal catalysis has advantages over traditional methods as it improves these important aspects of the reaction. The cyclotrimerization of arynes and alkynes/alkenes/allenes has been reviewed reviewed in detail by Peña and co-workers.[49]

In 2005, Cheng and Hsieh reported the first Ni-catalyzed [2+2+2] cocyclotrimerization of arynes with diynes **40** providing substituted naphthalenes **41** containing five- to sev-

en-membered rings (Scheme 20).[50] NiBr$_2$(dppe) was the most appropriate catalyst for this transformation, while zinc promoted the reduction of the Ni(II) species to a Ni(0) species, which initiates the reaction. In the proposed mechanism, the complex **40a** formed by the coordination of both C≡C bonds of the diyne to the Ni(0) center, undergoes cyclometalation furnishing **40b**. The in situ generated aryne is inserted into complex **40b** affording nickelacycloheptatriene intermediate **40c**, which on reductive elimination generates **41** and regenerates the Ni(0) catalyst. The established protocol was sensitive to substituents on both the diyne and aryne.
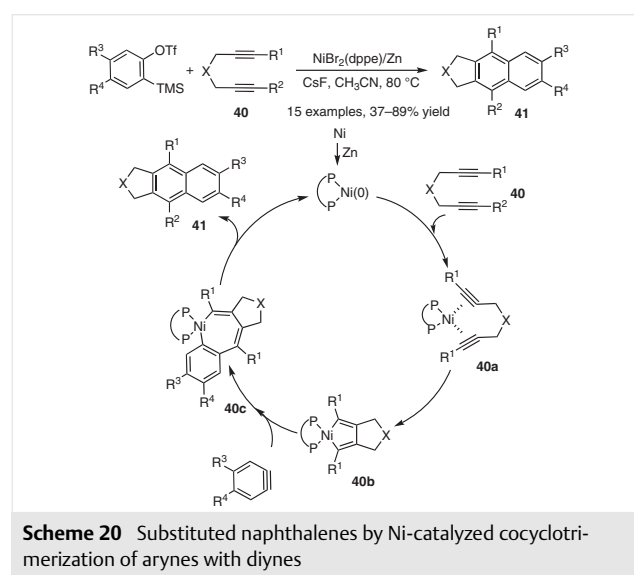

Scheme 20 Substituted naphthalenes by Ni-catalyzed cocyclotrimerization of arynes with diynes

In 2008, Cheng and Hsieh employed o-dihaloarenes as aryne precursors for the Ni-catalyzed [2+2+2] cycloaddition with alkynes or dialkynes **40a** and nitriles to give substituted naphthalene, phenanthridine **29a**, or triphenylene derivatives (Scheme 21).[51] The key step of this transformation is the Ni-assisted generation of the aryne. The cycloaddition reaction also worked well with various diynes, nitriles, disubstituted acetylenes, and o-diiodoarenes.
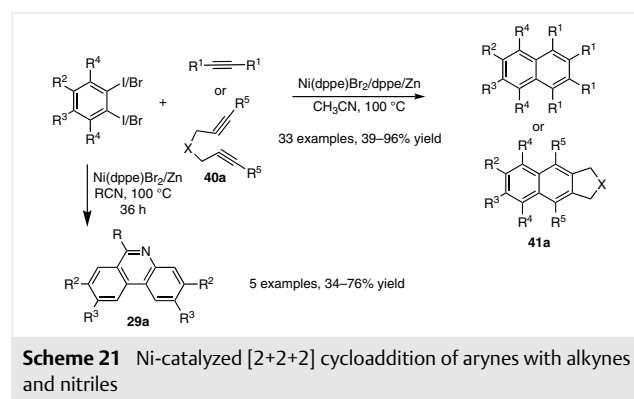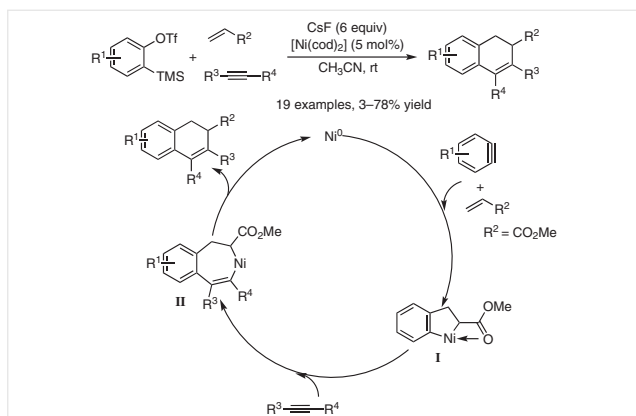

Scheme 21 Ni-catalyzed [2+2+2] cycloaddition of arynes with alkynes and nitriles

Review

There are few reports on the [2+2+2] cycloaddition of arynes and activated alkene moieties. Sato and co-workers were the first to report the [2+2+2] cycloaddition of an aryne and unactivated alkene catalyzed by a Ni catalyst. The aim of the [2+2+2] cycloaddition of an aryne and α,ω-diene **42** was to synthesize the 1,2,3,4-tetrahydronaphthalene skeleton, but it afforded 9,10-dihydrophenanthrene derivatives **43** in good yield together with a low yield of the dienyl-substituted biphenyl **44** (Scheme 22).[52] Reaction of various dienes with the unsubstituted aryne precursor gave moderate yields of 9,10-dihydrophenanthrenes. Good yields were obtained when a diene (X = cyclic acetal) was reacted with an aryne precursor bearing an electron-donating group.
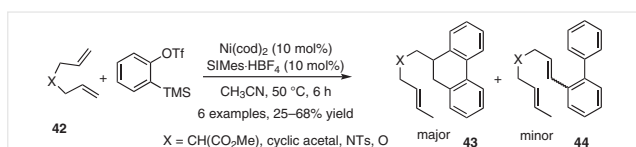
Scheme 22 9,10-Dihydrophenanthrenes by Ni-catalyzed [2+2+2] cycloaddition of arynes and unactivated alkenes

The transition-metal-mediated [2+2+2] cycloaddition of alkynes and alkenes is an asset for building complex structures. Prior to aryne methodology, Xie and Qiu reported the Ni-mediated [2+2+2] cycloaddition of carboryne (1,2-dehydro-*o*-carborane), alkynes, and alkenes.[53] Due to the similar reactivity pattern between carboryne and aryne, they extended it to afford diverse dihydronaphthalenes that are difficult to prepare from simple starting materials. After optimization of the reaction conditions, the use of Ni(cod)$_2$ (5 mol%) and CsF (6 equiv) in acetonitrile at room temperature afforded the dihydronaphthalenes in very good yield together with trace amounts of a regioisomer. Using different substituted aryne, alkynes, and alkenes gave a total of 19 differently substituted dihydronaphthalenes (Scheme 23).[54]

Scheme 23 Dihydronaphthalenes by Ni-catalyzed cycloaddition of arynes, activated alkenes, and alkynes

Mechanistically, the five-membered Ni complex **I** is formed by co-ordination of Ni(0) with the benzyne and alkene through oxidative coupling. Further alkyne insertion with complex **I** produces the seven-membered intermediate **II** followed by reductive elimination affording the dihydronaphthalenes (Scheme 23).[54]

The use of arynes in stereoselective reactions is very rare. In 2011, Lautens and Candito reported the stereoselective Ni-catalyzed [2+2+2] cycloaddition of arynes and 1,6-enynes **45**. The substituent near to the C=C bond proved to be a crucial factor for diastereoselectivity. The proposed mechanism involves the formation of an enyne complex by coordination with the Ni(0) catalyst followed by oxidative addition. The complex then coordinates with the aryne by insertion into one of the carbon–metal bonds followed by reductive elimination resulting in **46**. The *trans* stereochemistry is set at the stage where enyne complex is formed with the Ni(0) catalyst. A model study suggests two diastereotopic complexes, which can cyclize in an irreversible step, but the transition step having lower 1,3-allylic strain favors the *trans* product (Scheme 24).[55]
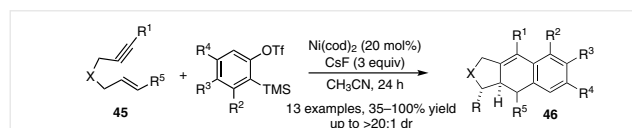
Scheme 24 Ni-catalyzed [2+2+2] cycloaddition of enynes and arynes
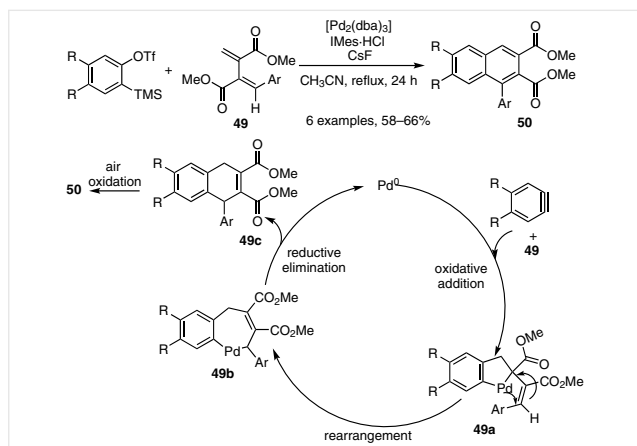
In 2011, Wu and co-workers reported the [3+2] cycloaddition of an aryne with (diarylmethylene)cyclopropa[*b*]naphthalenes **47** in the presence of a Pd catalyst (Scheme 25);[56] isopropylidenecyclopropa[*b*]naphthalenes (replacement of Ar in **47** by Me) gave geometrical isomers in 1:1 ratio. The synthetic utility of the obtained 11-(diarylmethylene)-11*H*-benzo[*b*]fluorenes **48** was demonstrated by treating them further under different transition-metal-catalyzed reaction conditions.
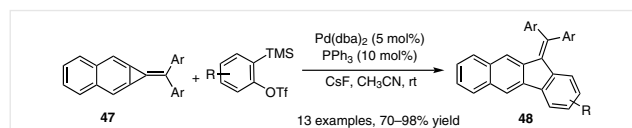
Scheme 25 Pd-catalyzed [3+2] cycloaddition reaction of (diarylmethylene)cyclopropa[*b*]naphthalenes with arynes

Argade and Patel reported the synthesis of differently substituted arylnaphthalenes **50** by metal-catalyzed [2+2+2] cocyclization of arynes with unsymmetrical conjugated dienes **49** in the presence of Pd$_2$(dba)$_3$ catalyst and a N-heterocyclic carbene ligand (Scheme 26).[57] In the mechanism, the oxidative insertion of the Pd catalyst with aryne and diene affords five-membered palladacycle **49a** which rearranges to **49b** via insertion of a double bond into the Pd–C (alkyl bond). Finally, reductive elimination of the Pd catalyst gives intermediate **49c** which is oxidized, produc-

ing arylnaphthalene **50**. Six different substituted arylnaphthalenes were synthesized in good yields by reaction of variously substituted aryne precursors with unsymmetrical dienes.


Scheme 26 Arylnaphthalenes by Pd-promoted [2+2+2] cocyclization of arynes and unsymmetrical conjugated dienes

In 2012, Cheng and co-workers reported the synthesis of isochromenones **53** and oxepines **54** by reacting 2-iodobenzyl 3-phenylpropynoates **51** and 1-iodo-2-[2-(phenylethynyl)benzyloxy]benzenes **52**, respectively, with arynes in the presence of Pd(dba)$_2$ catalyst and Tl(OAc) (Scheme 27).[58] The reaction proceeds by Pd insertion into the iodo compound followed by C–H activation and then insertion of benzyne leading to the expected product. Mechanistically, intermediate **51b** is formed via Pd(0) oxidative addition and insertion into the C≡C bond through palladium complex **51a**. Intermediate **51b** undergoes C–H activation to form a palladacycle **51c**. Further insertion of aryne with palladacycle **51c** gives the seven-membered intermediate **51d**, which undergoes reductive elimination producing **53**. This protocol produces two new rings. Various substituted iodo compounds and aryne precursors were compatible with the optimized protocol.

Ma and co-workers reported the synthesis of 9-vinylphenanthrenes **56** by reacting two molecules of benzyne with propargylic carbonate **55** in the presence of Pd(OAc)$_2$ catalyst and tris(2-furyl)phosphine (TFP) ligand (Scheme 28).[59] Mechanistically, it is proposed that an intermolecular reaction takes place between benzyne and an allenylpalladium complex. The allenylpalladium complex **55a**, formed via oxidative addition of Pd with intermediate **55**, is inserted into the aryne leading to **55b**, subsequently another aryne insertion with **55b** and carbopalladation of intermediate **55c** furnishes intermediate **55d**. Finally, β-hydride elimination from **55d** produces the expected phenanthrene products **56**.
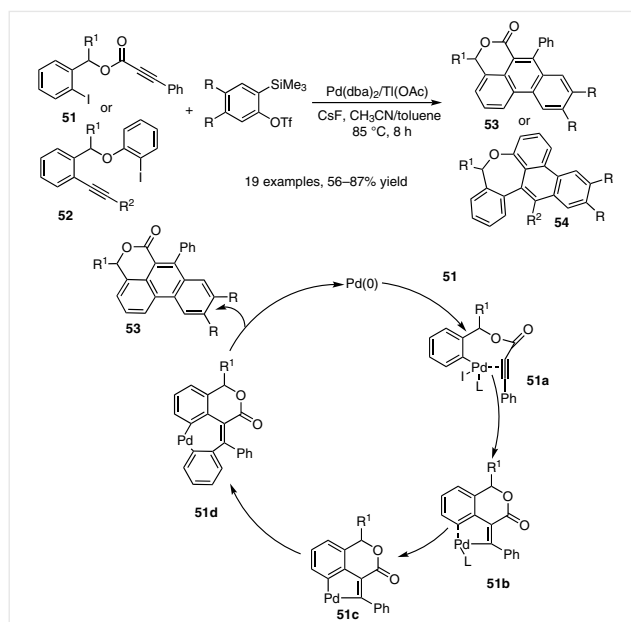

**Scheme 27** Cascade cyclization of alkynes and arynes in the presence of Pd(dba)$_2$
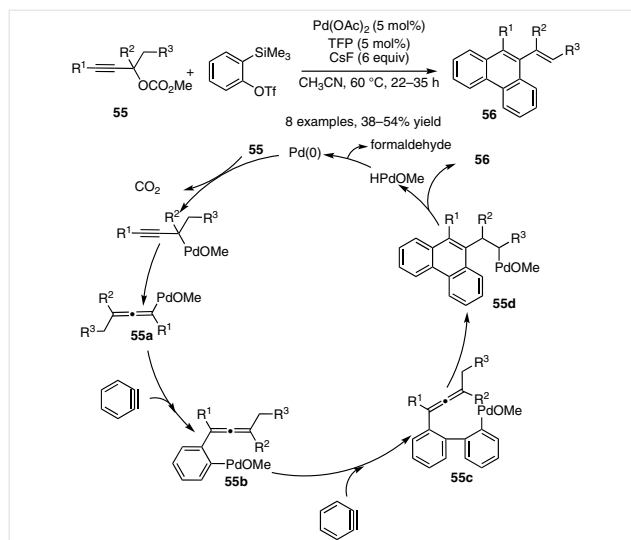
Scheme 28 9-Vinylphenanthrenes by Pd(OAc)$_2$-catalyzed reaction of a propargylic carbonate with an aryne

Greaney and co-workers reported the synthesis of triphenylenes by trimerization of arynes, which were derived from *ortho*-substituted arylboronates **57**. The reaction was carried out in the presence of Pd(dba)$_2$ catalyst, DPEphos ligand, and potassium *tert*-butoxide in toluene as a solvent at 100 °C; various substituents were tolerated (Scheme 29).[23] The metal-bound aryne intermediates are formed and these undergo trimerization.
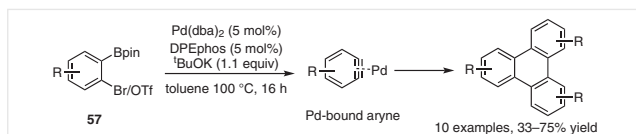
Scheme 29　Triphenylenes by Pd-catalyzed trimerization of arynes

In 2015, Chen and co-workers were the first to report the cyclotrimerization of arynes using (Ph₃P)AuCl. The mechanism for this reaction is very similar to Pd(0)-catalyzed cyclotrimerization. These results provide an efficient protocol for the synthesis of triphenylene derivatives by gold catalysis, which should also lead to the discovery of new applications of gold complexes in aryne chemistry (Scheme 30).[60a]
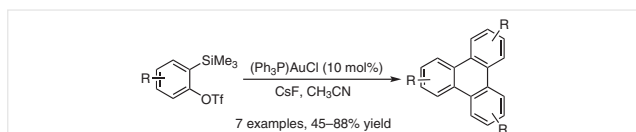

Scheme 30　Triphenylenes by Au(I)-catalyzed cyclotrimerization of arynes

In 2014, Peña and co-workers elegantly applied the Pd-catalyzed [2+2+2] cycloaddition trimerization concept of arynes to the synthesis of the 22-ring fused aromatic ring hydrocarbon nanographene (Scheme 31). The synthesis of nanographene was achieved by cyclotrimerization of a polycyclic aryne, which was synthesized from perylene. This example shows the application of arynes in materials chemistry.[60b]
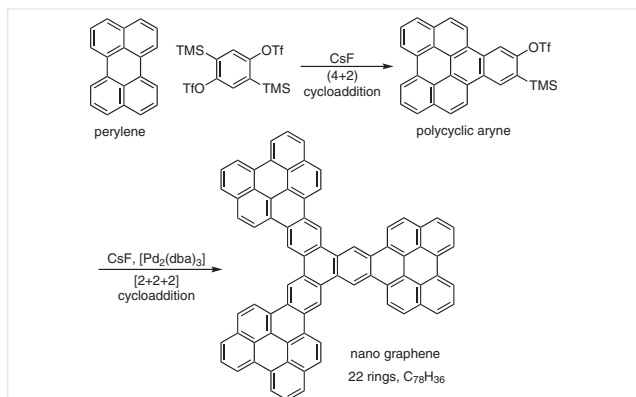
Scheme 31　Synthesis of nanographene from a polycyclic aryne

Garg and co-workers reported a novel class of heteroatomic indole-based trimers (Scheme 32). The synthesis of these unique scaffolds was achieved by reacting in situ generated indolyne intermediates in the presence of a Pd catalyst. Further computational studies were performed for structural and photophysical properties of the conjugated trimeric scaffolds.[60c]
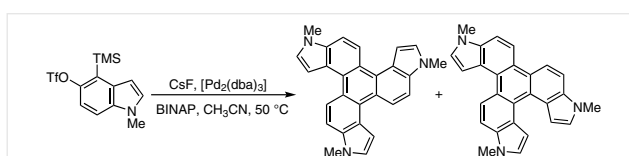

Scheme 32　Conjugated trimeric scaffolds accessible from indolyne

It is evident from the above examples that the scope of the simple cycloaddition reaction of arynes has been tremendously enhanced by transition-metal catalysis to obtain the desired scaffolds more efficiently.

5　Multicomponent Reactions of Arynes

Multicomponent reactions (MCR) of arynes in the presence of a transition metal provide easy access to 1,2-difunctionalized arenes. The two new bonds are constructed simultaneously on the aryne intermediate. The resulting product of the MCR can further be used for the construction of natural products or bioactive pharmaceuticals.

Snowden and Ganta elegantly carried out the difunctionalization of substituted arynes by reaction of in situ generated lithium bis[3-(trimethylsilyl)prop-1-enyl]cuprate and appropriate electrophiles, such as allyl bromide and ethyl chloroformate. Three equivalents of the lithiated allyltrimethylsilane were generated in situ, one equivalent was utilized to generate the aryne from the 1-iodo-3-(triflyloxy)arene. The aryl anion generated was trapped with ethyl chloroformate and various alkyl or allyl halides. This protocol afforded exclusively *E*-diastereoselective functionalized homobenzylic vinylsilanes **58** (Scheme 33).[61]
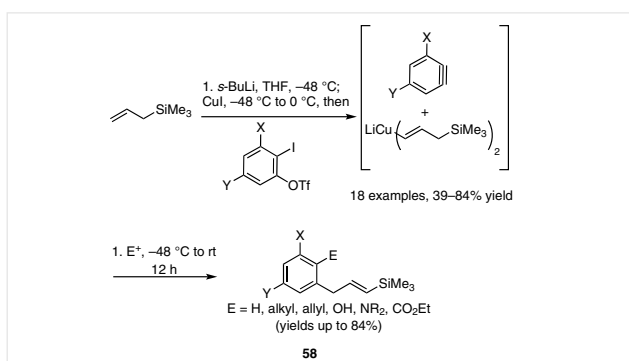
**Scheme 33**　One-pot preparation of *ortho*-substituted [(*E*)-3-phenyl-prop-1-enyl]silanes

Pineshi and co-workers successfully carried out the arylation of vinylaziridines by using an aryne and a terminal alkyne in the presence of CuI–PPh₃. The reaction is initiated by attack of the terminal alkyne onto the aryne to generate an arylcopper(I) species, which opens the vinylaziridine to provide allylic amines such as **59**. The reaction was SN2′ re-

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gioselective in the case of acyclic vinylaziridines. Various vinylaziridines reacted with benzyne to give the product allylic amines (8 examples) in moderate to good yields (Scheme 34).[62]
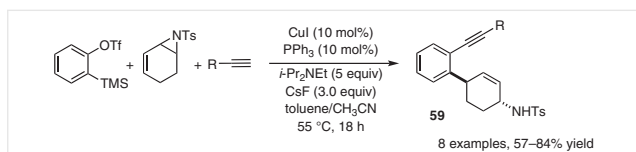
Scheme 34 Three-component coupling of benzyne, terminal alkyne, and vinylaziridine in the presence of CuI

The introduction of the CF_3 group into an aromatic ring is a challenging and highly desired transformation. The vicinal difunctionalization of arenes using trifluoromethylated reagents was first reported by Hu and co-workers in 2013, who ingeniously reacted an aryne with 1-iodophenylacetylene, 2,2,6,6-tetramethylpiperidine (TMP) and $AgCF_3$ (Scheme 35).[63] The TMP plays an important role in the difunctionalization of the aryne. Mechanistically, intermediate **I** is formed via the reaction between the aryne and $AgCF_3$·TMP; **I** further hydrogen bonds with another TMP molecule to provide **II**. Abstraction of a proton from **II** and coordination with iodophenylacetylene produces **III**. The 'ate' complex **IV** is formed by intramolecular nucleophilic attack, which rearranges to afford the expected product, a 1-iodo-2-(trifluoromethyl)benzene. Methyl- and phenyl-substituted aryne precursors gave product mixtures of regioisomers in 1:1 ratio. However, excellent regioselectivity was observed for the methoxy-substituted aryne precursor.
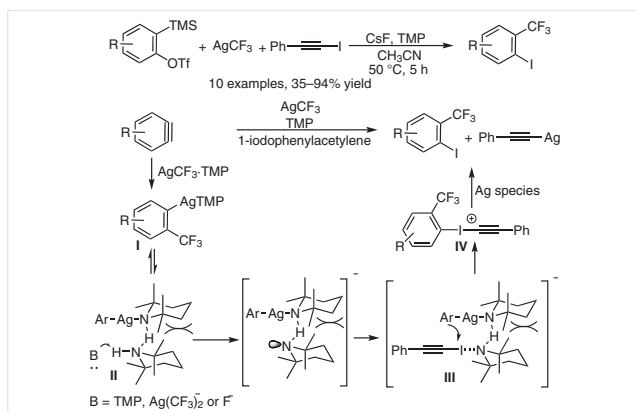
**Scheme 35** Ag-mediated trifluoromethylation–iodination of arynes

Isocoumarins are basic key structures found in various natural products. Kobayashi and co-workers synthesized substituted isocoumarins **60** in a single-step transformation using arynes (Scheme 36).[64] The in situ generated aryne reacts with copper acetylide, generated from phenylacetylene and NHC–copper hydroxide or carbonate. Mechanistically, the intermediate **60a** is intercepted by CO_2 producing cop-

per carboxylate **60b**; the copper heterocycle **60c** is formed via 6-*endo-dig* cyclization of **60b**. Finally, transmetalation with a cesium salt furnishes **60d**, which is then converted into the isocoumarin. The substrate scope was demonstrated on substituted aryne precursors as well as on aryl/alkyl-substituted terminal alkynes.
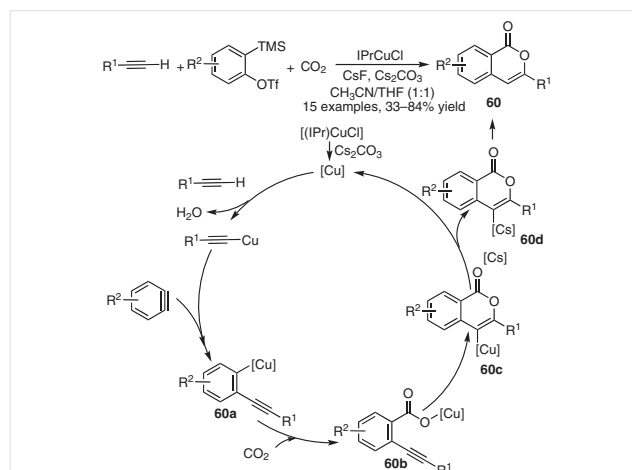

Scheme 36 NHC–copper complex catalyzed three-component coupling of aryne, terminal alkyne, and carbon dioxide

Nishihara and co-workers reported the synthesis of cyano-substituted iminoisobenzofurans by one-pot reaction of arynes, isocyanides, and cyanoformates in the presence of catalytic $[Pd(NCPh)_2(dppf)](BF_4)_2$ (Scheme 37).[65] Along with iminoisobenzofurans **61**, minor amount of α-iminonitriles **62** were also formed. The iminoisobenzofurans were then converted into α-iminonitriles using DIBAL-H or the Lewis acid $AlMe_3$. In these reactions, the formation of three new C–C bonds at the expense of one C–C bond cleavage and migration of a cyano group was observed.
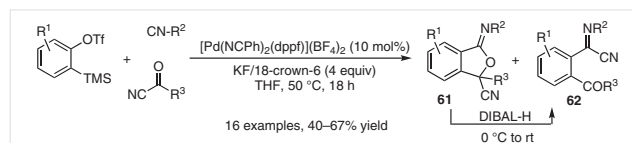

Scheme 37 Iminoisobenzofurans by Pd-catalyzed three-component coupling of aryne, isocyanide, and cyanoformate

Wu and co-workers synthesized various substituted pyrazolo[5,1-*a*]isoquinolines **64** by reaction of 2-alkynyl-benzaldehyde **63**, sulfonylhydrazine, and benzyne in the presence of silver triflate (Scheme 38).[66] An intermediate isoquinolium-2-ylamide, generated from the 2-alkynyl-benzaldehyde and sulfonylhydrazine in the presence of Lewis acid, undergoes [3+2] cycloaddition with the aryne to give the pyrazolo[5,1-*a*]isoquinoline.

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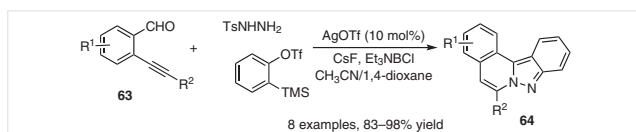
Scheme 38 Pyrazolo[5,1-*a*]isoquinolines by three-component coupling of aryne, benzaldehyde, and sulfonylhydrazine

2-Vinylcyclopropane-1,1-dicarboxylate was utilized as an electrophile for the first time in a three-component coupling reaction with an aryne; a terminal alkyne was employed as the nucleophile (Scheme 39).[67] The reaction conditions utilized catalytic Pd(dba)$_2$, with dppp as the ligand, and CuI for the synthesis of difunctionalized arenes **65**. The terminal alkyne undergoes addition to the aryne to generate a carbocopper intermediate, which then attacks the cyclopropanedicarboxylate ring activated by the transition metal. Regioisomers were observed in the case of unsymmetrical aryne precursors.
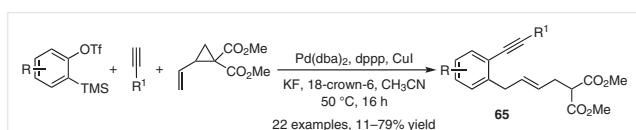

Scheme 39 Pd-catalyzed three-component coupling of aryne, terminal alkyne, and 2-vinylcyclopropane-1,1-dicarboxylate

Jiang and co-workers reported the construction of variously substituted phenanthridinones **19a** and acridone alkaloids **66** by Pd-catalyzed and ligand-controlled regiodivergent C1 insertion involving an aryne, CO, and a 2-iodoaniline (Scheme 40).[68]. Mechanistically, the Pd catalyst without a bulky ligand undergoes oxidative addition with iodoaniline. The in situ generated aryne co-ordinates with the complex **19a′** followed by insertion to provide the intermediate **19c′**. The insertion of CO provides acyl–Pd species **19d′**, which on reductive elimination delivers the phenanthridinone product **19a**. When the bidentate phosphine ligand bis(diphenylphosphino)methane (dppm) was employed, complex **66a′** coordinates with CO instead of the aryne due to steric hindrance, giving intermediate **66c′**. Further interception of **66c′** with aryne followed by reductive elimination of Pd affords the acridone product **66**. Optimization showed that for phenanthridinone synthesis the conditions required were Pd(OAc)$_2$ as catalyst and TBAI as the additive; to avoid the formation of the minor product acridone 10% H$_2$O was added to the acetonitrile solvent. The optimized synthesis of acridones also used Pd(OAc)$_2$ as catalyst, but the addition of the ligand dppm was crucial; the slow release of aryne was also important, and was achieved by using KF.
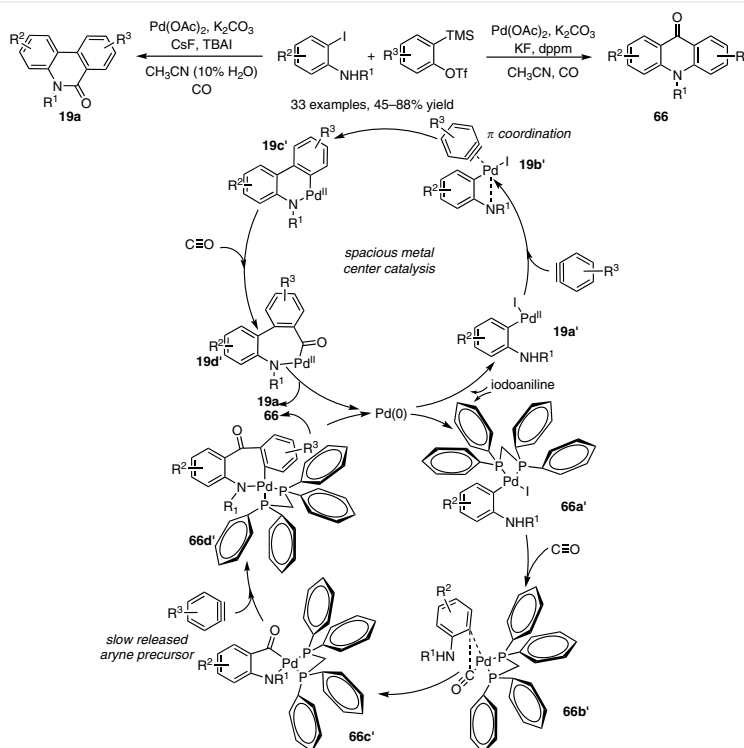

Scheme 40 Ligand-controlled regiodivergent C$_1$ insertion of an aryne for the construction of phenanthridinones and acridones

Jiang and co-workers extended their previous methodology (Scheme 40) to the synthesis of phenanthridinone **19b** through C–H activation. The reaction was carried out in the presence of unactivated anilines, aryne, and CO. The use of CuF$_2$·2H$_2$O for the slow release of aryne was found to be crucial to obtain high yields of products. Diverse phenanthridinones were synthesized in moderate to good yields (Scheme 41).[69]
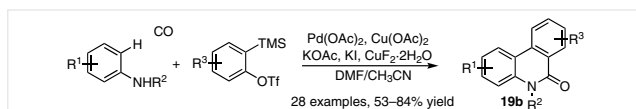

Scheme 41 Phenanthridinones from arynes, anilines, and carbon monoxide

Xu and co-workers successfully carried out a one-pot difunctionalization of arynes via C–C and C–S bond formation by reacting terminal alkynes, arynes, and benzenesulfonothioates in the presence of catalytic CuI to give 1-alkynyl-2-(arylthio)benzenes **67** (Scheme 42).[70] Various substituents on the aryne precursors, terminal alkynes, and benzenesulfonothioates were tolerated.
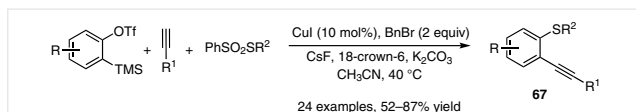
Scheme 42 Cu-catalyzed three-component coupling of aryne, terminal alkyne, and benzenesulfonothioate

Hu and Zeng extended their previous methodology (Scheme 35) for the one-pot trifluoromethylthiolation–iodination of arynes with (trifluoromethylthio)silver and 1-iodo-2-phenylacetylene (Scheme 43).[71] The in situ generated aryne undergoes insertion in the Ag–S bond to provide an o-SCF$_3$-substituted arylsilver intermediate, which is further trapped by 1-iodo-2-phenylacetylene to afford 1-iodo-2-(trifluoromethylthio)arenes in good yields. These products are important precursors for Yagupolskii–Umemoto-type electrophilic trifluoromethylation reagents.
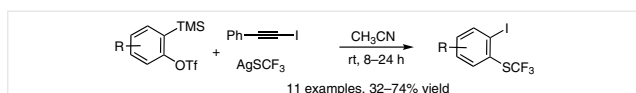

Scheme 43 Ag-mediated trifluoromethylthiolation–iodination of arynes

Multicomponent reactions of arynes thus provide an efficient and elegant access to novel disubstituted arenes, which otherwise would require multistep transformations.

6 Miscellaneous Reactions of Arynes

Arynes have also been used in the synthesis of large-ring-size structures and biphenyls. The use of arynes in polymerization reaction has also been reported.

The *ortho*-palladated derivatives of α,α-dimethylphenethylamine (phentermine) **68** (R = Me, X = H) and homoveratrylamine **68** (R = H, X = OMe) were reacted with benzyne to give eight-membered palladacycles **69**. This is the first report of the isolation of an aryne-inserted palladacycle. The palladacycle on reaction with CO in methanol produced unnatural amino acids **71** (Scheme 44).[72]
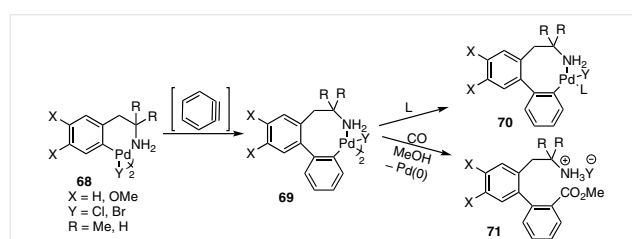

Scheme 44 Synthesis of unnatural amino acids

The 10- and 11-membered palladacycles were also synthesized by reacting the *ortho*-palladated derivative of homoveratrylamine **68a** with insertion of two molecules of benzyne. The palladacycle **72** reacted with CO or RNC to afford products **75** and **76**, respectively (Scheme 45).[73]
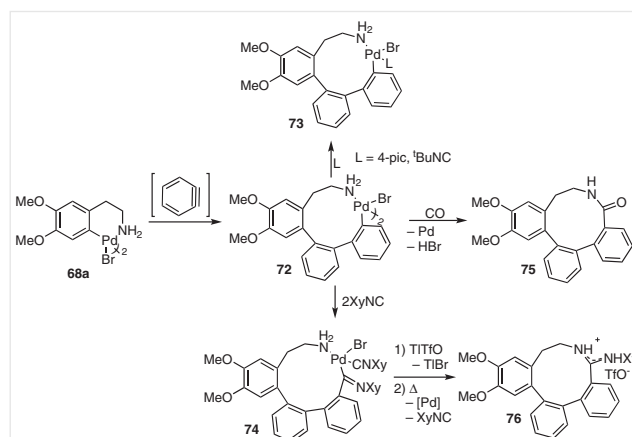

Scheme 45 Synthesis of 10- and 11-membered palladacycles

Knochel and co-workers utilized 2-iodophenyl arenesulfonate precursors **77** for the generation of arynes using *i*PrMgCl.[19] Studer and co-workers used this aryne precursor for the synthesis of 2,2′-disubstituted biphenyls **78**. Li$_2$CuCl$_4$ was a suitable catalyst for the homocoupling under an oxygen atmosphere. Moderate yields of 2,2′-disubstituted biphenyls **78** were obtained (Scheme 46).[74]

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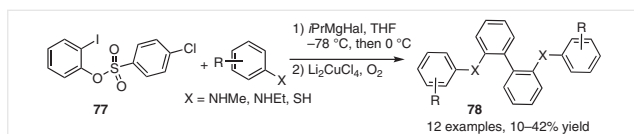
Scheme 46 2,2′-Disubstituted biphenyls from arynes and anilines or benzenethiols

Arynes have been extensively used in organic chemistry, but there are very rare reports in polymer chemistry. Uchiyama and co-workers performed the polymerization of an aryne for the synthesis of a poly(o-arylene) that consisted of aromatic rings connected through the *ortho*-position (Scheme 47).[75] The initiator for polymerization was a copper 'ate' complex, which was prepared from CuCN and n-BuLi. The obtained polymer has potential in new areas for nanocarbon and materials science.
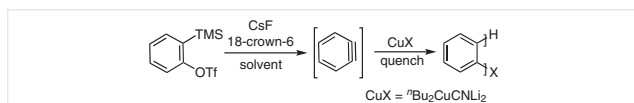

Scheme 47 Synthesis of a poly(o-arylene)

7 Total Synthesis of Natural Products Using Arynes

Arynes have been used to generate key synthetic intermediates for the synthesis of different bioactive natural products. Various complex natural products have been synthesized by employing arynes in metal-catalyzed MCR, σ-bond insertion, [4+2] and [2+2] cycloaddition reactions.[5,6]

Argade and Patel reported a concise synthesis of justicidin B, retrojusticidin B, and the formal synthesis of analogous natural products (Scheme 48) by using their well-established Pd-catalyzed [2+2+2] cocyclization of arynes and unsymmetrical conjugated dienes in the presence of an N-heterocyclic carbene ligand (Scheme 26).[57]

Jeganmohan and Pimparkar extended their methodology (Scheme 15) for the synthesis of bioactive natural products phenaglydon, 6(5H)-phenanthridin-5(6H)-one, and N-methylcrinasiadine in moderate to good yields (Scheme 49).[44]
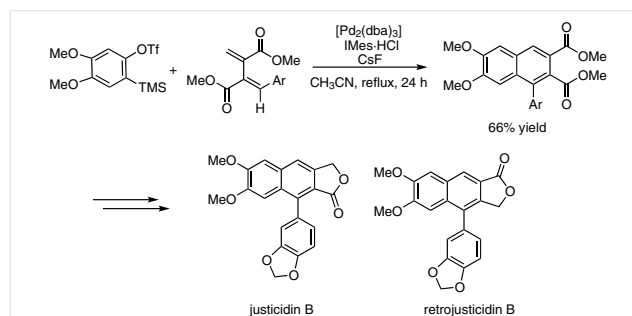
**Scheme 48** Synthesis of justicidin B and retrojusticidin B
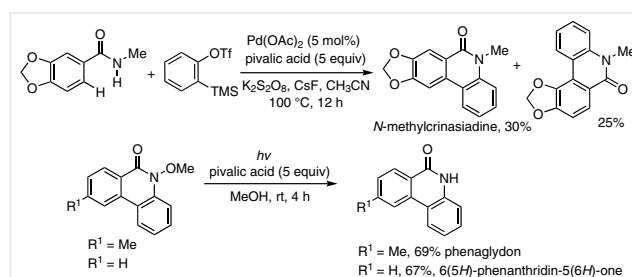
**Scheme 49** Synthesis of phenaglydon, 6(5H)-phenanthridin-5(6H)-one, and N-methylcrinasiadine

Jiang and co-workers extended their well-established methodology (Scheme 40) to the synthesis of the phenanthridinone alkaloids; N-methylcrinasiadine, N-isopentylcrinasiadine, and N-benzylcrinasiadine in excellent yield. The protocol was also applied to the synthesis of the acridone alkaloid 10-methyl-2,3-(methylenedioxy)acridin-9(10H)-one in moderate yield (Scheme 50).[68]

Yao and co-workers extended their protocol (Scheme 17) to the formal synthesis of the phenanthrene-based natural product (±)-tylophorine. A good yield was observed for the key step of the synthetic route wherein the Pd-catalyzed annulation furnished the desired phenanthrene core of the natural product (Scheme 51).[46]

In continuation of their research interest, Jiang and co-workers developed a methodology for the synthesis of phenanthridinones (Scheme 41). The same methodology was applied as a key step in the total synthesis of natural products N-methylcrinasiadine, N-isopentylcrinasiadine, and N-benzylcrinasiadine (Scheme 52).[69]
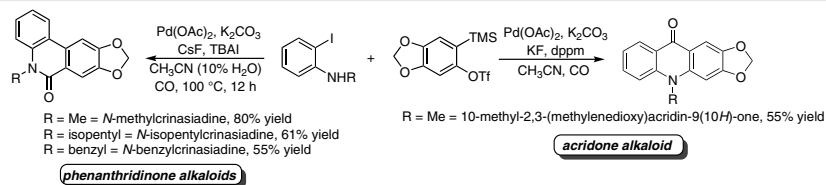
Scheme 50 Synthesis of N-methylcrinasiadine, N-isopentylcrinasiadine, and N-benzylcrinasiadine
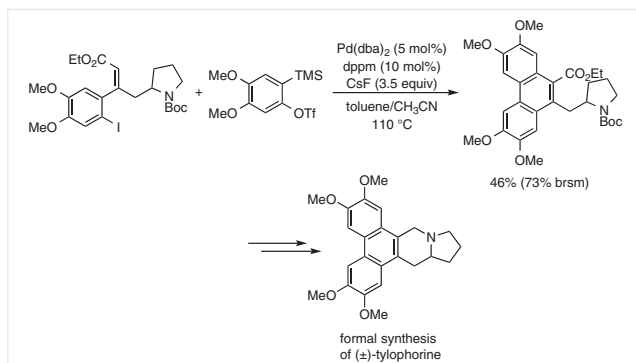
Scheme 51 Formal synthesis of the phenanthrene-based natural product (±)-tylophorine
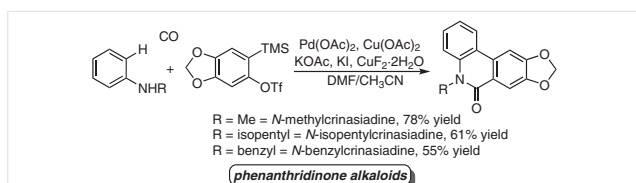

Scheme 52 Synthesis of *N*-methylcrinasiadine, *N*-isopentylcrinasiadine, and *N*-benzylcrinasiadine

Gogoi and co-workers applied their methodology (Scheme 18) to the total synthesis of the biologically active natural product flemichapparin C. The developed protocol was performed using 4-hydroxy-7-methoxycoumarin and 4,5-(methylenedioxy)benzyne to afford the desired natural product (Scheme 53).[47]
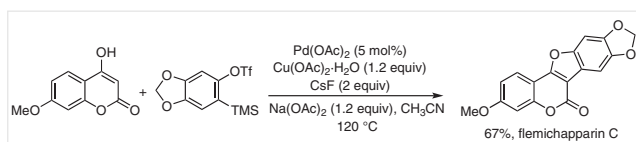
Scheme 53 Synthesis of flemichapparin C

Zhang and co-workers utilized their Cu-catalyzed methodology (Scheme 19) for the synthesis of phenaglydon and crinasiadine natural products. The removal of the directing group in the presence of BBr_3 and $PhI(TFA)_2$ afforded the respective natural products (Scheme 54).[48]
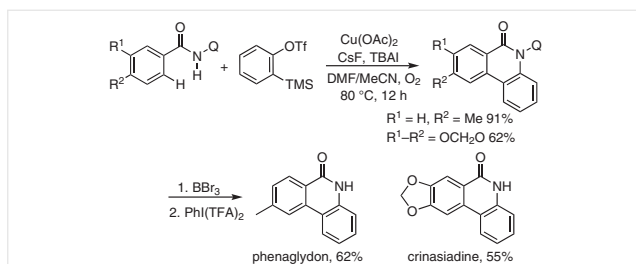
Scheme 54 Cu-catalyzed synthesis of phenaglydon and crinasiadine; Q = 8-quinolinyl

Diversity oriented natural product synthesis is a rapidly developing area of research.[5,6] In this context, aryne chemistry paves a new pathway to achieve this goal through various types of transition-metal-catalyzed reactions.

8   Conclusion

This review highlights the scope and importance of the transition-metal-catalyzed aryne reactions in synthetic organic chemistry. The highly reactive aryne species in combination with a transition metal made it possible to construct biaryl motifs, fused polycyclic aromatic compounds, different novel carbocycles, various heterocycles, and complex natural products. From a laboratory curiosity to a highly explored reactive intermediates; arynes have travelled a long path. To cross the barrier from basic to applied research, a completely 'off the shelf' practical method of aryne generation is essential. The current rate at which this area of research is growing, we have no doubt that aryne chemistry might occupy an important position in combination with transition metals as a key step in the synthesis of drugs and advanced materials.

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