# Aryne-Based Multi-Component Coupling Reactions

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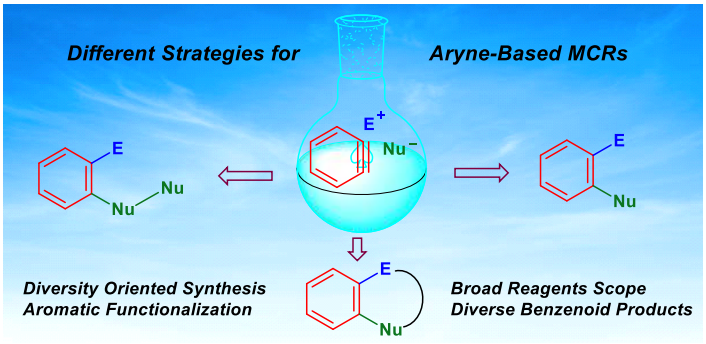


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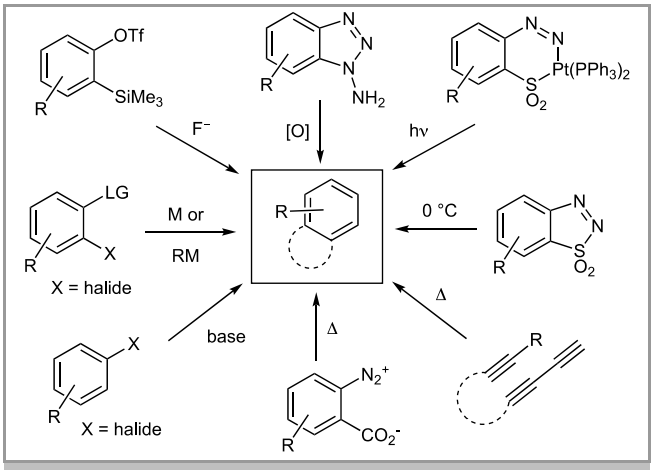
**Abstract** Multicomponent reactions (MCRs) constitutes a powerful synthetic tool to generate a large number of small molecules with high atom-economy, which thus can efficiently expand the chemical space with molecular diversity and complexity. Aryne-based MCRs are versatile to construct functionalized arenes and benzo-fused heterocycles due to the electrophilic nature of arynes couple with a broad range of nucleophiles that can favorably react with arynes. Thus, a variety of aryne-based MCRs have been developed, the representative of which are summarized in this account.



**Key words** Aryne, multicomponent reaction, Diels-Alder reaction, silver, heterocycles

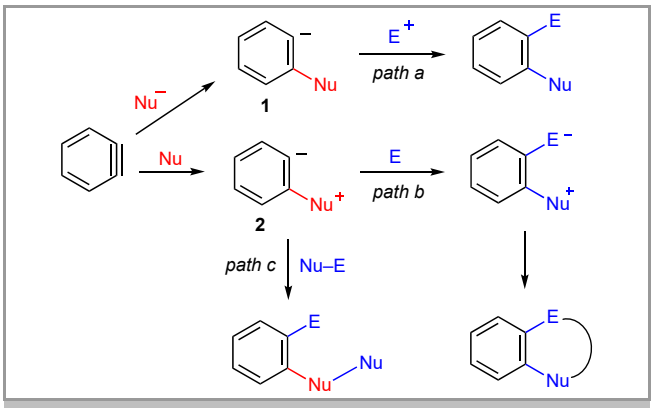
## 1. Introduction

Aryne, a highly electrophilic transient intermediate, has been widely used in the synthesis of functionalized aromatic compounds through the formation of carbon–carbon and carbon–heteroatom bonds.[1–4] In 1902, Stoemer and Kahlert first postulated the existence of an aryne species (known as 2,3-didehydrobenzofuran) to justify the formation of 2-ethoxybenzofuran from 3-bromobenzofuran under basic conditions in ethanol solvent.[5] After few decades, Robert,[6] Husigen,[7] and Wittig[8] independently investigated the aryne reactivity and its existence. Due to high reactivity, arynes are generated in situ from suitable aromatic or non-aromatic precursors. Typical methods to generate arynes include fluoride-promoted 1,2-elimination of aryl silyl triflates,[9] metalation or base-mediated 1,2-elimination of aryl halides,[10] thermal decomposition of arenediazonium-2-carboxylate,[11] hexadehydro Diels-Alder reaction of multiynes,[12] and thermal,[13] photochemical[14] and oxidative[15] elimination of nitrogen from various precursors (Scheme 1).

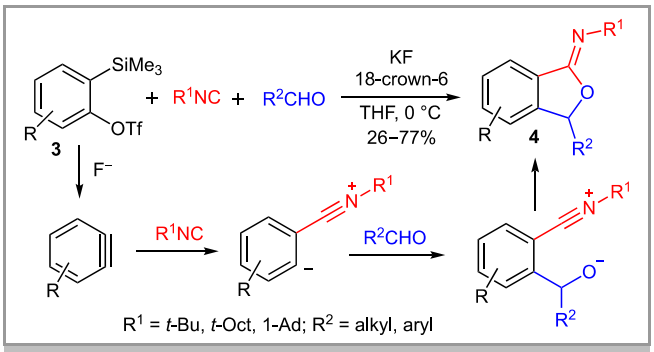



**Scheme 1.** Different strategies for aryne formation

Multicomponent coupling reaction (MCR) is a powerful synthetic tool to merge three or more organic compounds in a single-step operation to generate relatively complex molecular structures with high atom-economy.[16–19] This strategy has become increasingly popular in the synthesis of a large number of small molecules. Aryne-based multicomponent reactions have been developed to generate diverse aromatic compounds.[20] Due to their salient electrophilicity, arynes readily react with anionic or neutral nucleophiles to generate aryl anions **1** or zwitterions **2** (Scheme 2). In turn, depending on the electronic and structural features of the reaction components, these intermediates could participate in different modes of subsequent transformations. For example, once generated, aryl anion **1** could be trapped by a cationic electrophile to generate 1,2-disubstituted arenes (path a). On the other hand, trapping of zwitterion **2** with a neutral electrophile leads to benzo-annulated cyclic compounds (path b), or nucleophile-electrophile (Nu-E) insertion products (path C).




**Scheme 2.** Different modes of coupling reactions with arynes




**Scheme 3.** Three-component coupling reaction of arynes, isocyanides, and aldehydes

## 2. Aryne-based Multicomponent Reactions

Aryne-based MCRs are exploited to increase the molecular diversity and complexity on aromatic systems. Different MCR strategies have been developed, among which 'single reactant strategy (SRR)', 'modular reaction sequences (MRS)', and 'conditions-based divergence (CBD)' are most effective.[18]

### 2.1. Trapping with Isocyanide

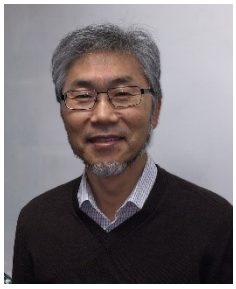
MCRs of arynes with isocyanides have been employed for the synthesis of functionalized benzo-fused heterocycles.[21,22] In 2004, Yoshida and coworkers reported that arynes derived from 2-(trimethylsilyl)phenyl triflates **3** in the presence of KF and 18-crown-6, readily react with isocyanides and aldehydes to generate iminodihydroisobenzofurans **4** in moderate to good yield (scheme 3).[23] This reaction is believed to involve an initial nucleophilic addition of isocyanide to the aryne intermediate and trapping of aldehyde by the aryl anion followed by an intramolecular cyclization, leading to the observed product **4**. Subsequently, they found that ketones and benzoquinones also could be employed to generate iminodihydroisobenzofuran derivatives **6** or **7** (Scheme 4).[24]

These MCRs were further expanded by Yoshida,[25] Stoltz,[26] and Nishihara,[27,28] via trapping intermediate **5** with other carbonyl compounds (ester and cyanoformate) and *N*-tosylaldimines (Scheme 4). These are representatives of SRR of MCR, where replacing one component (e.g. aldehyde) with a structurally related one (e.g. ester) increases the structural space of the framework relying on the same mode of reactivity.

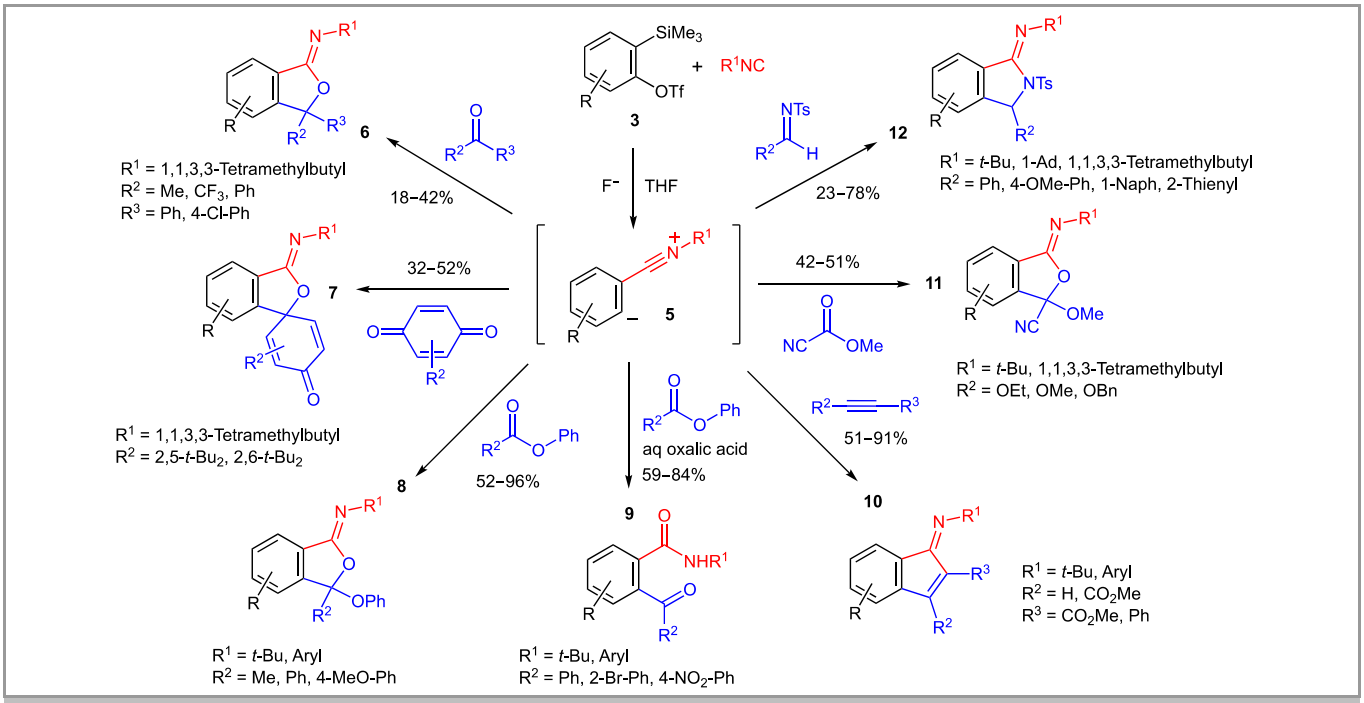
In 2011, Stoltz reported that the zwitterionic aryne-isocyanide adduct **5** could be effectively trapped by phenyl esters to generate phenoxy iminoisobenzofurans **8**, which could be hydrolyzed in-situ by using aqueous oxalic acid to generate *o*-ketobenzamides **9**. When aryne-isocyanide adduct **5** was intercepted by electron-deficient alkynes (e.g. methyl propiolate), iminoindenones **10** were isolated. Nishihara employed cyanoformate as the third component in this reaction, which was activated by [Pd(PhCN)$_2$(dppf)(BF$_4$)] (10 mol %) to afford cyano-substituted iminoisobenzofuran **11**. By replacing cyanoformate with imine, Yoshida and coworkers developed another MCR to form iminoisoindolines **12**.

## Biographical Sketches

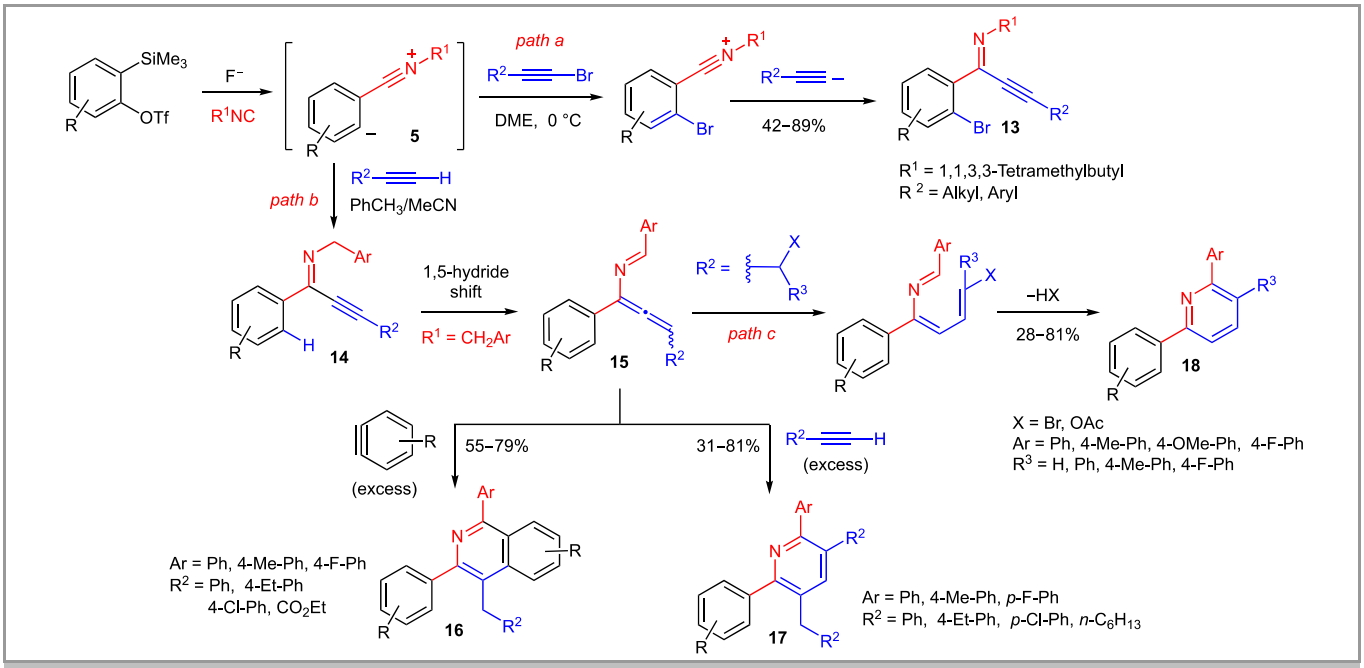
**Sourav Ghorai**, born in 1992 in India, received a BSc in chemistry from University of Calcutta in 2009. Later, he joined Indian Institute of Technology, Kanpur for MSc degree in chemistry. After moving to the University of Illinois at Chicago in 2014, he started his graduate studies in the lab of Professor Daesung Lee. Where his current research focus is the Development of new synthetic methods for aromatic functionalization via aryne intermediate and to explore click reaction with terminal 1,3-diynes.



**Daesung Lee**, born in 1962 in Korea, completed his doctorate under the direction of Professor Paul Wender at Stanford University in 1998. After two years of postdoctoral training with Professor Stuart Schreiber at Harvard, he joined the chemistry Department at the University of Wisconsin-Madison in 2000. Later in 2007, he moved to University of Illinois at Chicago as an assistant professor in Chemistry Department. His current research interests include the development of new synthetic methods and synthesis of biologically active natural compounds.




**Scheme 4.** Three-component coupling reaction of arynes, isonitriles, and carbonyls or carbonyl equivalents




**Scheme 5.** Three-component coupling reaction of arynes, isocyanides, and alkynes

Depending on the structure of alkynes and reaction conditions, arynes react with isocyanides and alkynes to take different manifolds of reactions. In 2011, Yoshida reported the synthesis of alkynyliminoaryl bromides from arynes, isocyanides, and alkynyl bromides (Scheme 5, path a).[29] It was postulated the initially formed zwitterionic aryne–isocyanide adduct reacts with alkynyl bromide to form the arene-Br bond and the corresponding acetylide, which then reacts with the nitrilium moiety to afford the final product **13**. Similarly, pyrimidines and isoquinolines could be generated from arynes, benzyl isocyanides, and terminal alkynes (path b).[30] In this reaction, the aryne-isocyanide adduct **5** reacts with an alkyne to form imine **14**, which undergoes a 1,5-hydride shift to generate imino allene **15**. Subsequent [4+2] cycloaddition of **15** with another aryne species or terminal alkyne provides isoquinoline derivatives **16** or pyrimidines **17**, respectively. On the other hand, *N*-allenyl imine intermediate **15** derived from 3-bromopropyne did not participate in a cycloaddition but engaged in a 1,3-hydride shift (path c) to generate azatriene,[31] which ultimately delivered disubstituted pyrimidines **19** via electrocyclization followed by extrusion of HBr. By employing

alkynes containing a propargyl acetoxy substituent, trisubstituted pyrimidines were obtained.

### 2.2. Trapping with Imines

MCRs of arynes with imines led to the synthesis of various benzo-fused heterocycles. In 2006, Yoshida showed that the zwitterionic aryne-imine adduct **19** could be trapped with carbon dioxide (1 atm) to generate **20**, which upon cyclization provided benzoxazinones **21** (Scheme 6).[32]

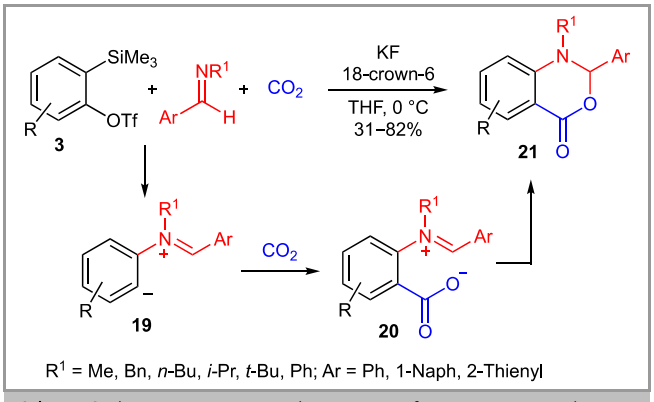
Aryne-based zwitterionic species are versatile intermediates for developing new transformations. Similar to imines, azaarenes can serve as a source of an imine moiety to generate zwitterionic intermediate **22** (Scheme 7). In the presence of suitable protic pro-nucleophiles, **22** can undergo proton transfer followed by nucleophilic trapping to generate dearomatized nitrogen-containing heterocycles **23**. Chein-Hong Cheng and coworkers reported that the reaction of arynes with pyridines, quinolines, and isoquinolines together with aliphatic nitriles provided *N*-arylated 2-acetonitrile substituted 1,2-dihydro-2-pyridine (**23a**), 1,2-dihydro-2-quinoline (**23b**) and 1,2-dihydro-1-isoquinoline (**23c**).[33] By employing other pro-nucleophiles, such as ketones, terminal alkynes,[34] dialkylphosphites,[35] chloroform,[36] and carbon tetrachloride,[37] structurally diverse nitrogenous compounds **24a–24e** were obtained (Scheme 8).

In 2013, Hu reported the synthesis of benzo-fused 1,3-oxazine derivatives by intercepting aryne-azaarene adduct **22** with aldehydes and ketones (Scheme 9). The reaction is proposed to proceed in a stepwise manner; first, addition of zwitterion **22** into the carbonyl group to generate 1,4-dipole **25**, which subsequently cyclizes to deliver oxazine derivatives **26**.[38] Biju and coworkers further expanded this MCR by employing isatin as a C=O source, which delivered spirooxazino isoquinoline derivatives **27a**. On the other hand, when pyridine was used instead of isoquinoline indolin-2-one derivatives **27b** containing 3,3-penoxypyridyl substituents were obtained as opposed to the expected oxazine derivatives, which was proposed to be the consequence of forming a pyridinium ylide intermediate via a proton transfer by the aryl anion from 2-position of the pyridinium moiety.[39]

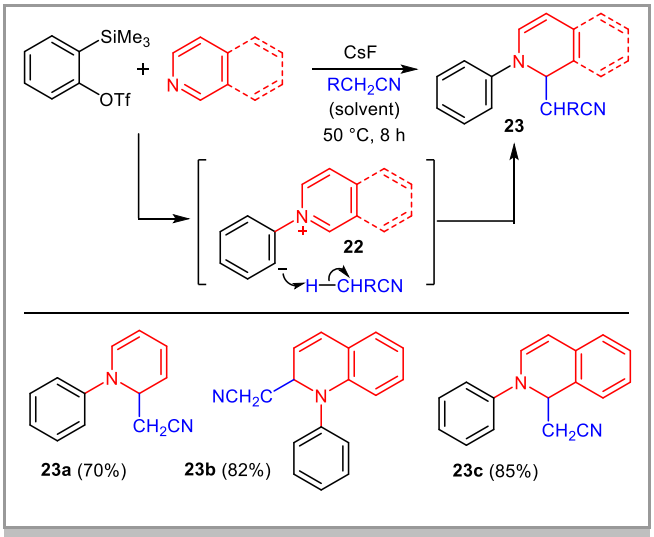
Pyridine can play an alternative role in aryne-mediate MCRs other than forming aryne-pyridine adduct. Zhang[40] and Huang[41] reported that by employing pyridine together with reactive alkyl halide such as a-bromo ketones and esters, azomethine ylides **28** could be formed first, which then participate in a [3+2] cycloaddition with arynes to generate pyrido[2,1-a]isoindoles **29** (Scheme 10). Under the reaction conditions, the initially formed product **29** was readily oxidized by atmospheric oxygen to afford isoindoles **30**.

### 2.3. Trapping with Amines

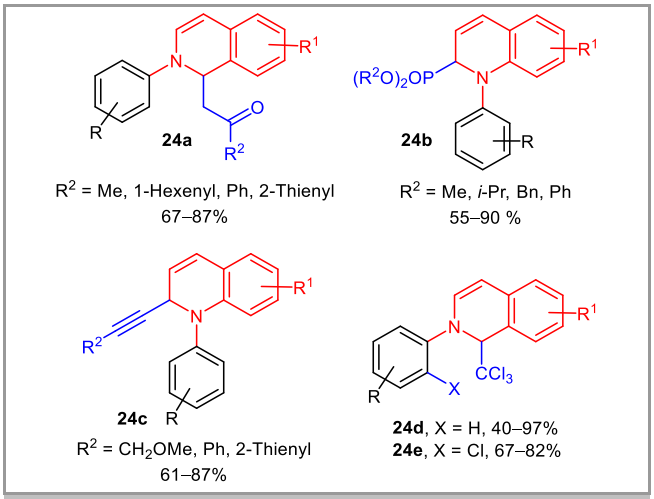
MCRs of arynes initiated by forming aryne-amine adducts were exploited in the double functionalization of arynes (Scheme 11). Secondary amines readily react with arynes to generate zwitterion **31**, which further reacts with π-bond electrophiles followed by a proton transfer to generate final product **32**. Yoshida reported that zwitterion **31** could be effectively trapped by aldehydes[42] and sulfonyl imines[43] to generate 2-aminobenzhydrols **32a** and **32b**. To maximize efficiency of the three-component coupled products and minimize the amine-triggered undesired reactions, aminosilanes were used as a precursor of amines, which maintain a low concentration of amines throughout the reaction. Carbon dioxide was an effective electrophile for this



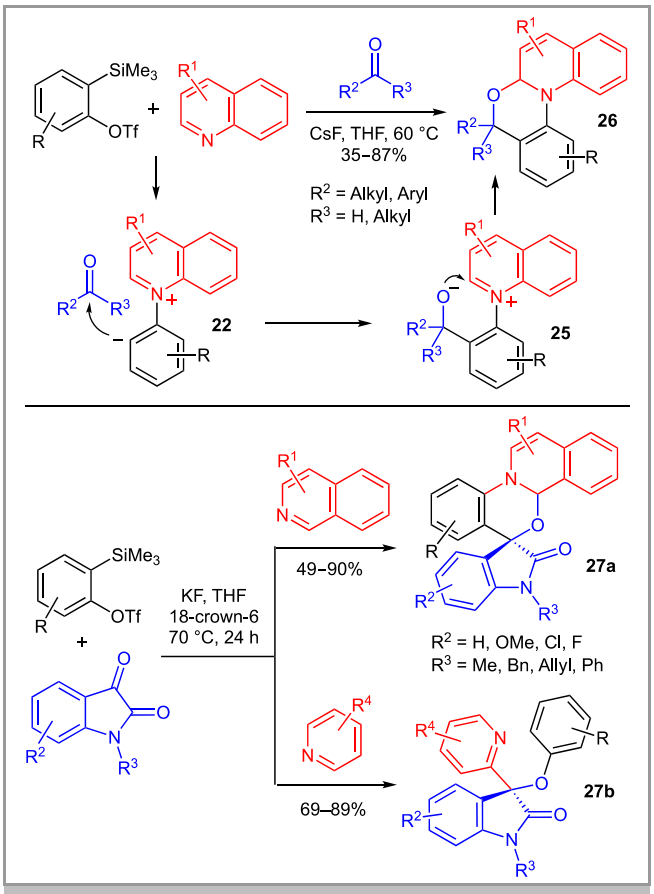

**Scheme 6.** Three-component coupling reaction of arynes, imines, and $CO_2$



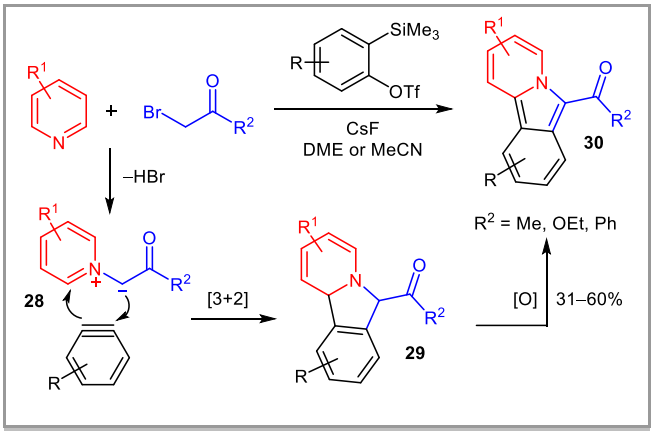

**Scheme 7.** Three-component coupling reaction of arynes, azaarenes, and nitriles



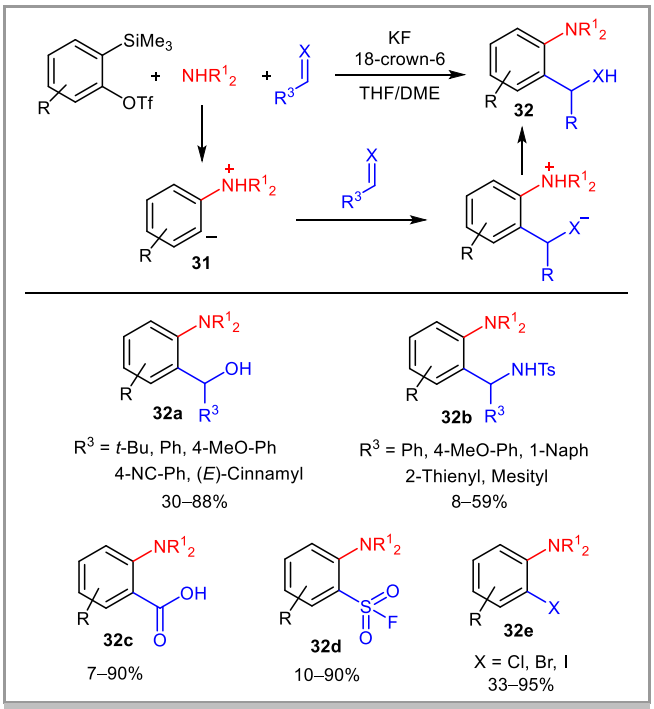

**Scheme 8.** Three-component coupling products from different nucleophiles.




**Scheme 9.** Three-component coupling reaction of arynes, azaarenes, and carbonyl moieties for the synthesis of 1,3-oxizine derivatives




**Scheme 10.** Three-component coupling reaction of arynes, pyridines, and α-bromo carbonyl compounds




**Scheme 11.** Three-component coupling reaction of arynes, secondary amines, and different electrophiles

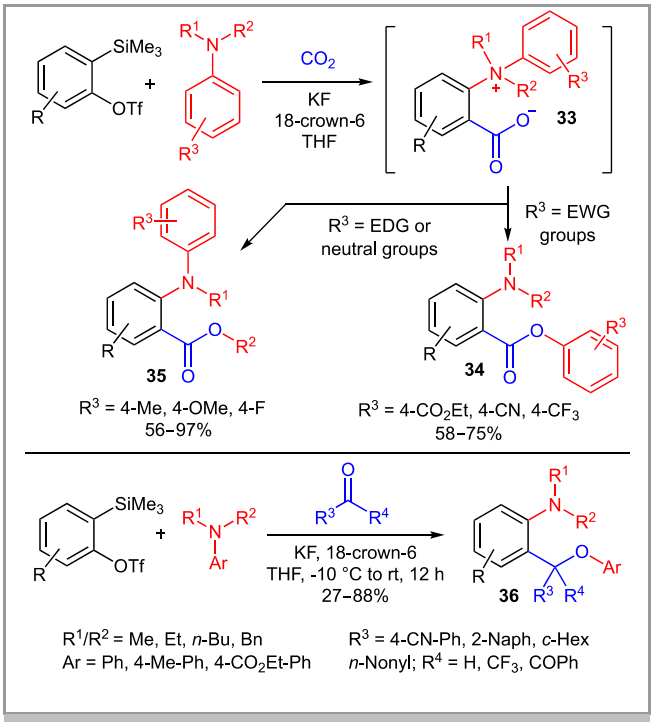
reaction, which provided anthranilic acid derivatives **32c**.[44] In 2018, Kim reported that zwitterion **31** could be trapped with sulfuryl fluoride to generate structurally diverse 2-amino arenesulfonyl fluoride **32d**.[45] Later in 2019, Tian showed that in the presence of organic halides ($CCl_4$, NCS, $CBr_4$, NBS, NIS), can trap zwitterionic intermediate **31** to provide the corresponding 2-chloro, 2-bromo, 2-iodo aniline derivatives **32e**.[46]

Biju and coworkers reported that MCRs of arynes with tertiary aromatic amines and carbon dioxide formed zwitterionic intermediate 33, which could undergo either *N*→*O* alkyl or aryl group migration to generate anthranilic acid derivatives (Scheme 12).[47] The preferential migration of one of the groups depends on the electronic nature of the aromatic amines. With amines bearing an electron-deficient aromatic group, 2-aminoaryl benzoates **34** were selectively generated. Employing an electron-rich or neutral aromatic group, an alkyl group migration occurred to deliver **35**. On the contrary, replacing carbon dioxide with aldehydes provided only **36** via a selective aryl group migration.[48]

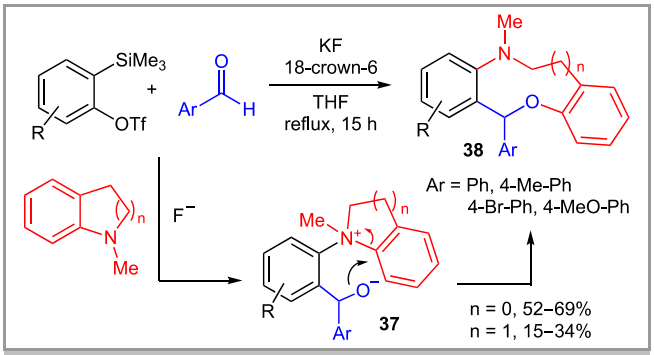
Okuma reported that 9- and 10-membered *N*,*O*-containing heterocycles could be synthesized from the reaction between arynes and *N*-phenylmorpholines and *N*-methylindolines, respectively (Scheme 13).[49] Zwitterion **37** derived from of arynes, benzannulated tertiary amines, and aromatic aldehydes readily underwent intramolecular nucleophilic aromatic substitution to generate ring-expanded *N*,*O*-heterocycles **38**.

MCRs of arynes with cyclic amines (aziridines and azetidines) and pronucleophiles have been developed (Scheme 14). In 2013, Larionov reported the synthesis of γ-aminobutyronitriles and δ-aminovaleronitriles **40a** from aziridines and azetidines.[50] This reaction is proposed to proceed through the formation of zwitterionic intermediate **39**, which, after proton transfer, undergoes ring opening to generate **40a**. In this reaction, arynes play an activator of cyclic amines and a strong base. Sha and Biju independently showed that zwitterionic intermediate **39** could be intercepted by fluoride,[51] trifluoroacetic acid,[52] carboxylic acids, and phenols[53] to generate α-fluoro-β-amino acids **40b**, *N*-aryl β-amino alcohols **40c** and their derivatives **40d**/**40e**.

MCRs involving arynes and aziridines were further exploited in the synthesis of trisubstituted *N*-aryl α-amino epoxides (Scheme 15).[54] Biju showed that adduct **41** formed from electron-deficient aziridines readily undergoes intramolecular




**Scheme 12.** Three-component coupling reaction of arynes, tertiary amines, and carbonyl moieties

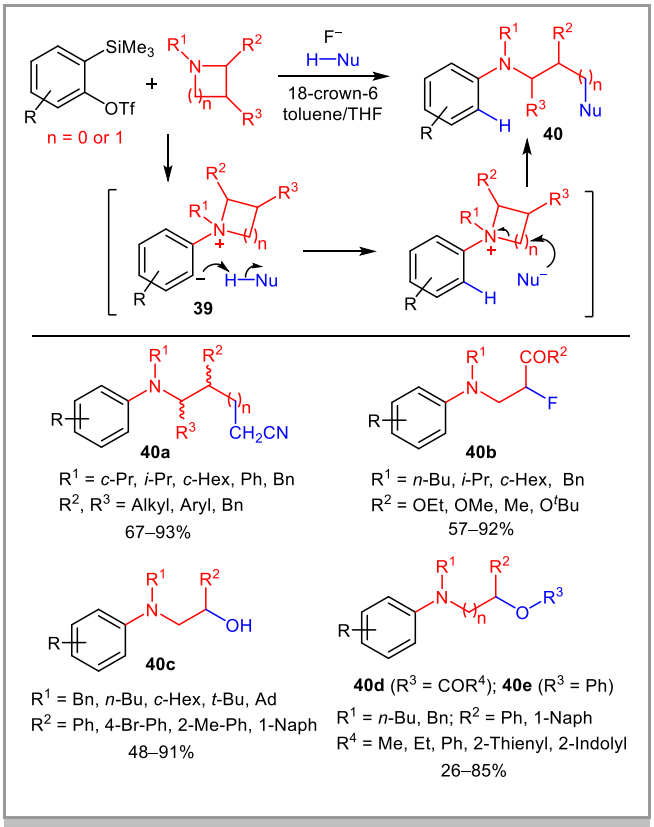



**Scheme 13.** Formation of 9- and 10-membered dibenzo[1,5]oxaza heterocycles from arynes, tertiary amines and aldehydes.

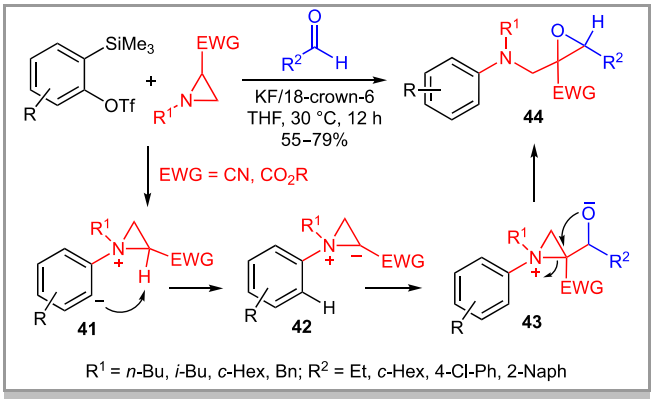
proton transfer to generate ylide **42**. Subsequent addition of aldehyde generates zwitterionic alkoxide **43**, which through intramolecular nucleophilic substitution furnishes epoxide **44**. Cyano and ester substituents were chosen as an electron-deficient group to generate and stabilize ylides.

### 2.4. Insertion into π-Bonds

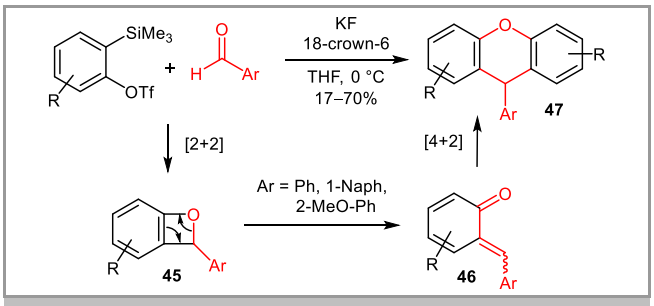
Insertion reactions of arynes into π-bonds (C=O, $S^+$–$O^-$, P=O,[55] C=C, C=N[56]) have been developed for the synthesis of functionalized arenes. Insertions into C=O and $S^+$–$O^-$ are representative for these examples. In 2004, Yoshida reported the synthesis of xanthene derivatives via MCR of arynes and aldehydes (Scheme 17).[57] This reaction is justified by a formal [2+2] cycloaddition between aryne and aldehyde to generate benzoxetene **45**, which due to ring strain opens up into its valence isomer *o*-quinone methide **46** followed by [4+2] cycloaddition with another arynes to generate the observed xanthene s **47**. *o*-Quinone methide **48** derived from aryne and formamide efficiently participated in a [4+2] cycloaddition




**Scheme 14.** Three-component coupling reaction of aryne, cyclic amines, and pro-nucleophiles




**Scheme 15.** Synthesis of N-aryl α-amino epoxides via a three-component assembly of arynes, aziridines, and aldehydes




**Scheme 16.** Three-component coupling reaction of arynes and aldehydes

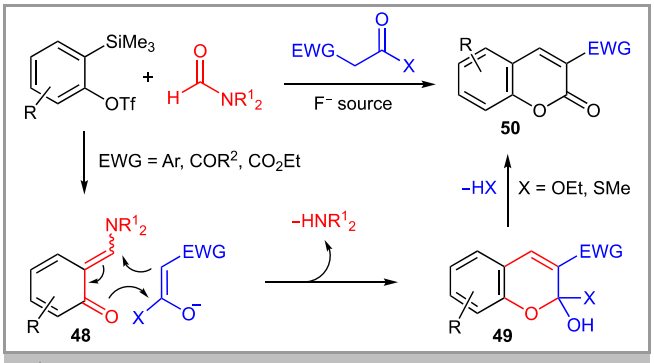
with active methylene species to generate 2*H*-chromene **49** or coumarin derivatives **50** (Scheme 18). Miyabe,[58] Yoshida,[59] Li,[60] and Gogoi[61] independently explored this transformation by

using different active methylene species including acetyl acetones, β-keto esters, ester enolates, ketenimine anions, *N*,*S*-ketene acetals, methyl-2-(bromomethyl)acrylates.

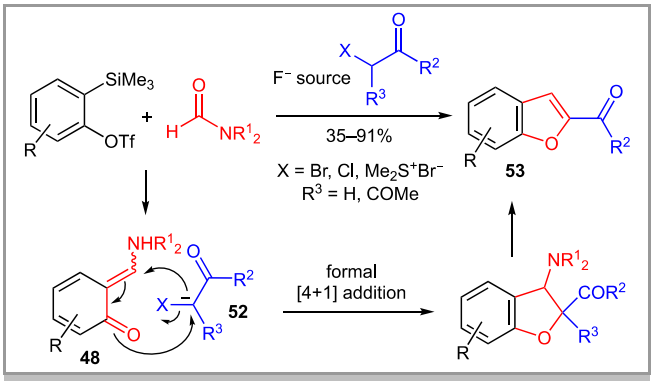
Depending on the electronic nature of the active methylene **52**, formal [4+1] cycloaddition with *o*-quinoid **48** becomes more favorable to generate 2-acyl and 2-aroyl benzofuran derivatives **53** (Scheme 18). Miyabe,[62] Gogoi,[63] and Chandrasekhar[64] expanded the scope of this transformation by employing various active methylene **52** including chloroacetyles, 2-bromoacetophenones, and sulfonium bromide salts, respectively.

In the presence of suitable electrophiles *o*-quinone methide could be transformed into corresponding 2-alkoxy substituted benzaldehydes (Scheme 19). Jinag reported the synthesis of *o*-formyl diaryl ethers using diaryliodonium salts as an electrophile.[65] Gogoi effectively trapped *o*-quinone methides with sulfonyl chlorides[66] and allyl halides,[61] and in the presence of $H_2O$, salicylaldehyde derivatives were generated.[67]

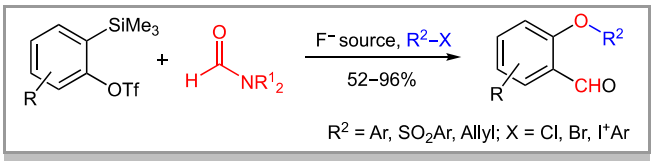
Similar to carbonyl (C=O), insertion of aryne into $S^+–O^-$ of sulfoxides proceeds via a formal [2+2] cycloadduct **54** (Scheme 20). Depending on the structure of sulfoxides and reaction conditions, various thioethers or sulfonium salts have been synthesized. In 2014. Xia developed MCR of arynes with dimethyl sulfoxide and α-bromo carbonyl compounds to generate methyl thioethers **55**.[68] Wang[69] and Gogoi[70] further




**Scheme 17.** Synthesis of 2H-chromenes or coumarins from arynes




**Scheme 18.** Synthesis of benzofurans via aryne intermediate



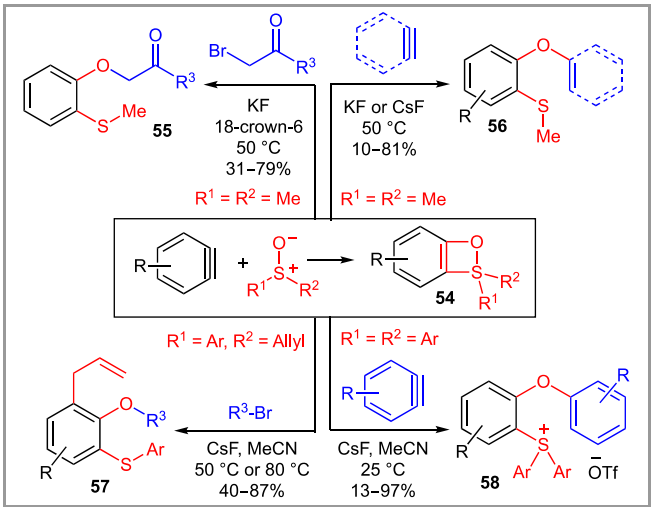

**Scheme 19.** Synthesis of salicylaldehyde derivatives via *o*-quinone methide

expanded the transformation by employing arynes or activated alkynes as the third component to generate thioether derivatives **56**. Using aryl allyl sulfoxide, Li accomplished the 1,2,3-trifunctionalization of arynes via a Claisen rearrangement to generate **57**.[71] In 2017, Peng reported the synthesis of *o*-aryloxy triarylsulfonium salts **58** from the reaction of arynes and diaryl sulfoxides.[72]

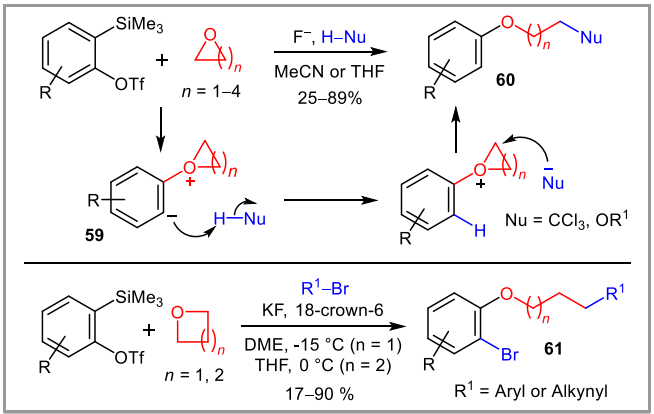
### 2.5. Trapping with Ethers and Thioethers

Cyclic ethers can act as an arynophile in aryne-based MCRs. Okuma reported that nucleophilic addition of cyclic ethers (oxirane[73], oxetane, THF,[74] and THP[75]) to aryne generates oxonium species **59**, which deprotonates pro-nucleophiles followed by subsequent ring opening leads to trichloroalkyl phenyl ethers **60** (Scheme 21). Biju reported that the reaction of arynes with alcohols in THF solvent preferentially generates three component assembly product **60** over the alcohol insertion product.[76] Yoshida reported that **59** readily reacts with aryl or alkynyl bromides followed by ring opening to generate *o*-bromoaryl ether **61**.[29]

Cyclic thioethers react with arynes in a similar manner as cyclic ethers (Scheme 22). Nakayama reported that in situ generated sulfonium species readily reacts with chloride ion to generate ring-opened products **62**.[77] Recently, Jiajing and Kun




**Scheme 20.** Three-component coupling reactions with arynes and sulfoxides



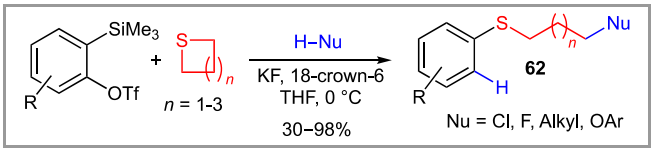

**Scheme 21.** Cyclic ether based multicomponent reactions

further expanded the scope of this transformation by employing fluoride[78] and other nucleophiles (C, O, S, N centered nucleophiles)[79] to capture the sulfonium species.

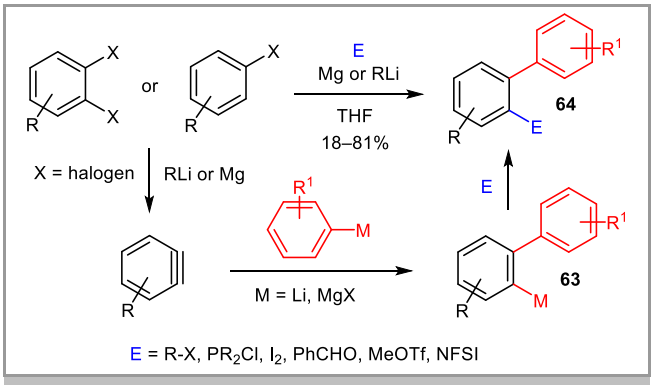
### 2.6. Trapping with Carbanions

Carbometalation of arynes is a powerful tool to synthesize *ortho*-functionalized biaryls (Scheme 23). In the presence of magnesium turnings or organolithium reagents, *ortho*-dihaloarenes or haloarenes smoothly transformed into arynes. Carbometallation of the in situ generated aryne with aryl lithium or aryl magnesium bromide to generate **63** followed by quenching with an electrophile provide *ortho*-functionalized biaryl compound **64**. Buchwald trapped the biaryl metallic intermediate **63** with chlorodialkylphosphine to generate functionalized biphenyl-based phosphine ligands.[80] Schlosser,[81] Leroux,[82] Comoy[83] independently reported that 2-biaryllithium intermediate **63** (M = Li) could abstract bromide and iodide from the aryl halides to generate 2-halobiaryls. Yoshida generated a broad array of biaryls with different electrophiles relying on this approach.[84] Pawlas reported the synthesis of phenanthridines **65** by trapping 2-fluoro-2'-lithiobiaryls **63-a** with nitriles (Scheme 24).[85] Further, Suzuki developed an alkynyllithium-catalyzed protocol to synthesize iodoaryls **66** from 2-iodoaryl triflate (Scheme 25).[86] In this transformation, lithium acts as an initiator for aryne formation and transporter of iodide.

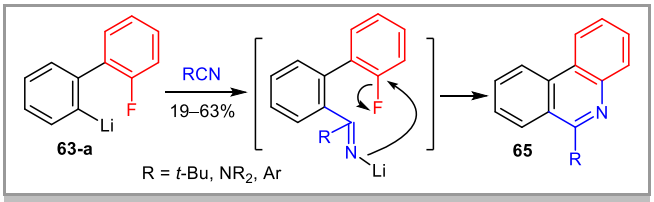
Carbocupration of arynes has been developed in the preparation of homobenzylic of alkenes (Scheme 26).[87] Snowden's three component MCR or arynes with lithium di[3-(prop-1-enyltrimethylsilyl)]cuprate **67** and electrophiles delivered functionalized homobenzylic vinylsilanes **68** with high *E*-diastereoselectivity. Barrett and coworkers exploited aryne carbometallation strategy for natural products (Scheme 28).[69] The core structure of clavilactone B (**69**) was constructed via the three-component coupling of aryne with allyl magnesium bromide and appropriately functionalized aldehyde. The aryne cabometallation strategy was further



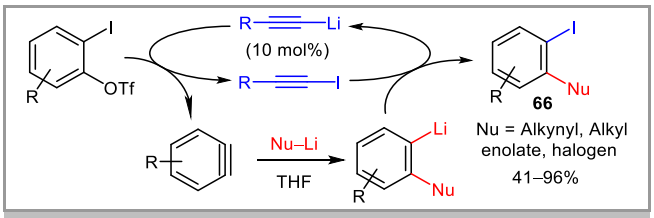

**Scheme 22.** There-component coupling reactions with cyclic thioethers



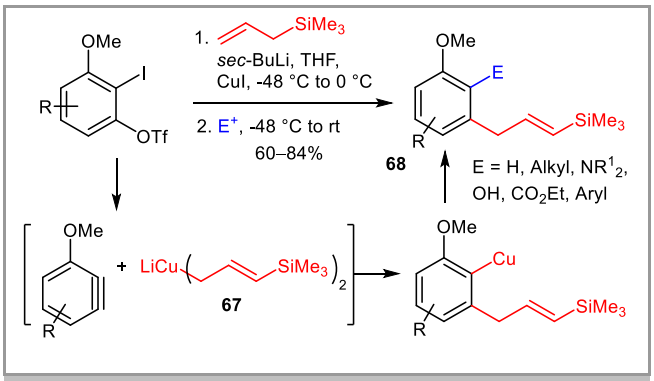

**Scheme 23.** Synthesis of biaryls via aryne intermediate



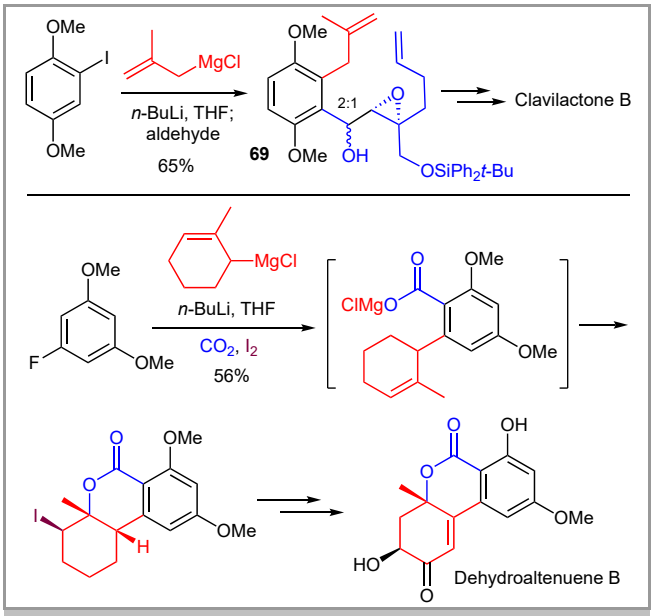

**Scheme 24.** Synthesis of phenanthridines




**Scheme 25.** Synthesis of iodoaryls via aryne intermediates




**Scheme 26.** Carbocupration of arynes




**Scheme 27.** Aryne MCR strategies for the synthesis of clavilactone B and dehydroaltenuene B

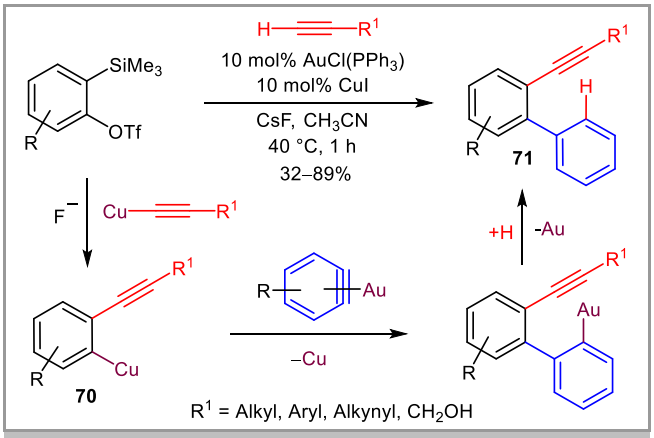
expanded to a four-component MCR of benzyne with 2-methyl-2-cyclohexenylmagnesium chloride, carbon dioxide and iodine to generate an advanced intermediate for a total synthesis of dehydroaltenuene B.[88]

### 2.7. Transition Metal-catalyzed Approaches

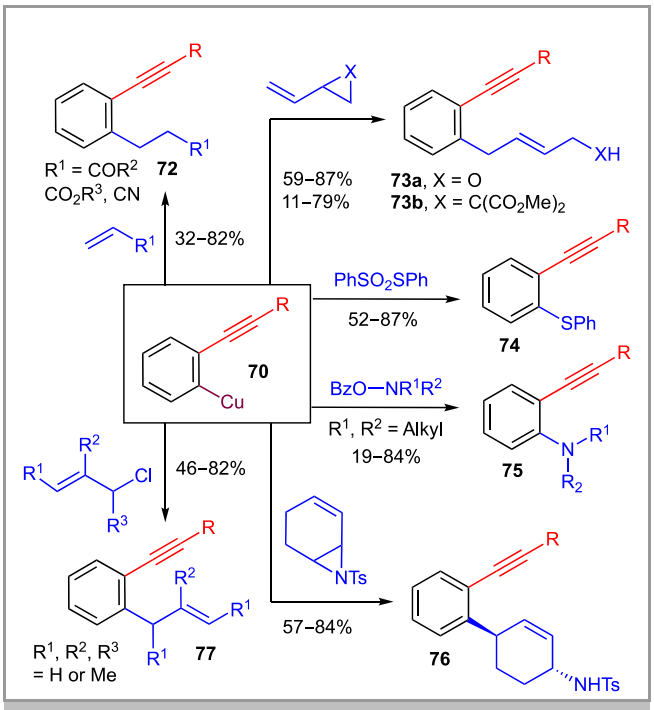
Transition metal-catalyzed MCRs add a new dimension in 1,2-bisfuctionalization of arynes.[89] In 2008, Zhang reported a tandem assembly of arynes and terminal alkyne in the presence of CuI and AuCl(PPh$_3$) catalysts (Scheme 28).[90] The reaction begins with the formation of copper acetylide from alkyne and copper catalyst. In turn, carbometallation of aryne with copper acetylide generates aryl copper species **70**. Subsequent reaction with another molecule of Au-activated aryne followed by protonation provides alkynylated biphenyls **71**. Yoshida and coworkers improved the transformation by using CuCl as catalyst.[91] Transient aryl-copper intermediate could be trapped by different electrophiles other than aryne itself, which generates various 1,2-disubstituted arene derivatives **72**–**77** (Scheme 29). Cheng successfully trapped the aryl-copper intermediate with activated alkenes[92] and allylic epoxides[93] to generate **72** and **73a**. Replacing the epoxide with vinyl cyclopropane dicarboxylate provided **73b**.[94] Pd(dba)$_2$ was used as co-catalyst to facilitate the ring-opening of epoxide or cyclopropane. Xu,[95] Xiao,[96] and Pineschi[97] independently reported MCR of arynes with benzenesulfonothioates, *O*-benzoylhydroxylamines and alkenyl aziridines, respectively. Trapping of aryl-copper species **70** with allylic chloride provided **77**.[98]

Intermolecular carbopalladation of aryne is another efficient method to generate benzo-fused carbocycles and 1,2-functionalized arenes via MCRs. Yamamoto reported the aryne insertion into $\pi$-allylpalladium complex **78** (Scheme 30).[99] It was found that sequential insertion of two arynes generated phenanthrene derivatives **80**. The putative carbopalladation product **79** could further react with alkyltributylstannane to form 1-alkyl-2-allyl arenes (Scheme 31). Cheng explored the reaction with alkynyl,[100] aryl,[101] and allenylstannanes,[102] which successfully installed valuable functional groups in aromatic systems.

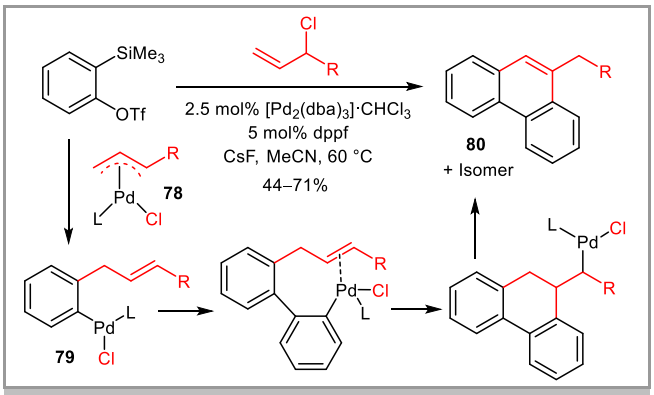
Aryl halides and a palladium catalyst are smoothly couple with aryne to generate biaryl palladium species, which, due to lack of β-hydrogen can react with other $\pi$-systems (Scheme 32). Highly substituted triphenylene derivatives **82** could be generated from **81** via an annulation with another aryne.[103] Heck reaction of **81** generated functionalized biaryl products **83**.[104]



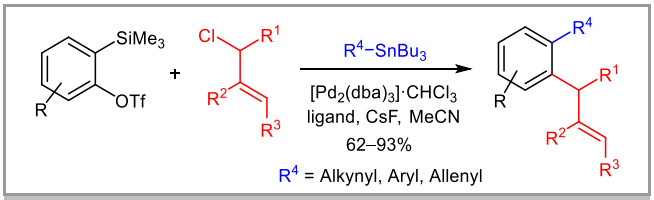

**Scheme 28.** MCR of arynes and terminal alkynes




**Scheme 29.** Trapping of aryl copper intermediate with different electrophiles

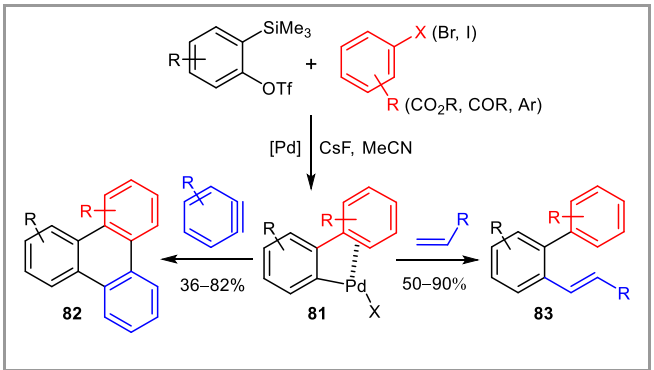



**Scheme 30.** Carbopalladation of arynes with allyl chlorides

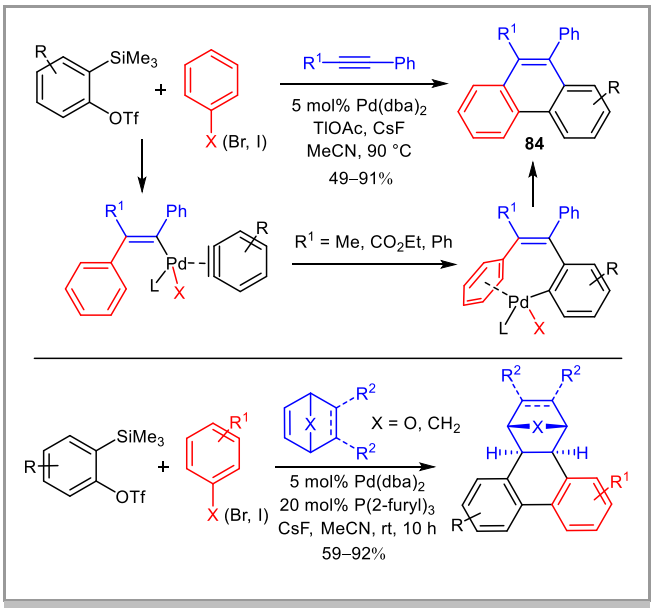



**Scheme 31.** Three-component coupling reaction of arynes, allyl chlorides, and stannanes

Larock reported a carbocyclization of arynes with aryl halide and alkynes, which led to the formation of substituted phenanthrenes **84** (Scheme 33).[105] The reaction proceeds through a regio- and chemoselective carbopalladation of aryl halide with internal alkyne followed by carbopalladation of the vinyl palladium species with arynes and cyclization. It was shown that the alkyne could be replaced with strained alkenes containing norbornene or norbonadiene framework to generate 9,10-dihydrophenanthrene derivatives.[106]




**Scheme 32.** Pd catalyzed reaction between aryne and aryl halides

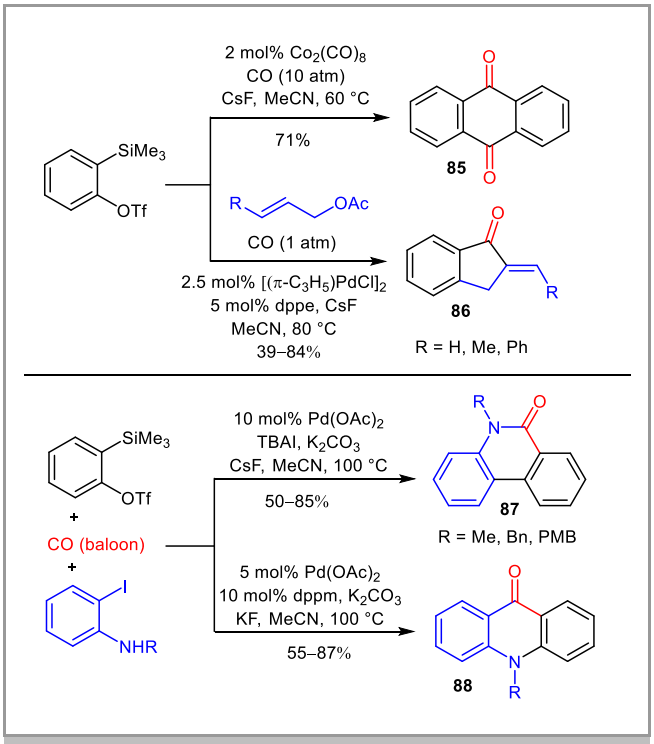



**Scheme 33.** Three-component coupling reaction of arynes, aryl halides, and alkynes

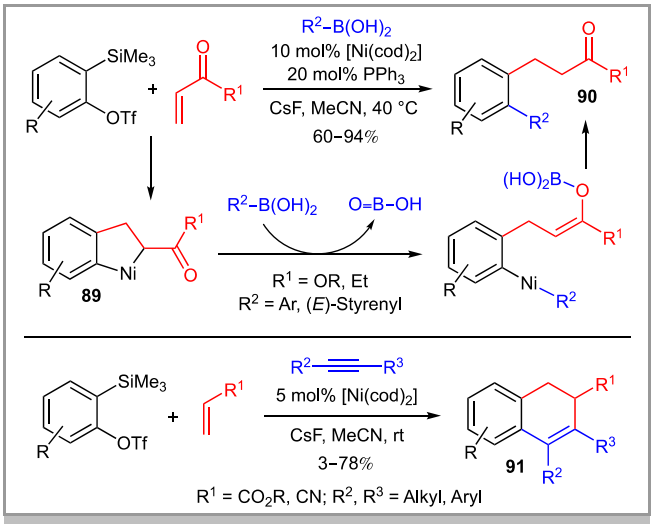
Transition metal-catalyzed carbonylation of arynes is an effective way to generate cyclic ketone frameworks (Scheme 34). Chatani reported a $Co_2(CO)_8$ catalyzed annulation of arynes and carbon monoxide to generate anthraquinone **85**.[107] It was also found that in the presence of $[(\pi\text{-}C_3H_5)PdCl]_2$ catalyst aryne, carbon monoxide, and allyl acetate could be annulated to provide 2-methyleneindanone derivatives **86**. Liang and Li explored the ligand effect on the selectivity of carbonylation between aryne and allylcarbonate.[108] Jiang reported a $Pd(OAc)_2$-catalyzed three component assembly of arynes, CO, and 2-iodoanilines to generate phenanthridinone **87** and acridone derivatives **88**.[109] Relying on this MCR strategy, phenanthridinone and acridone alkaloids were successfully synthesized.[110]

Nickel-catalyzed three component MCRs of arynes with alkenes were first reported by Cheng in 2007 (Scheme 35).[111] It was found that, in the presence of $Ni^0$ catalyst, eneones are coupled with aryne to generate nickelacycle **89**. Subsequent transmetalation with boronic acid followed by reductive elimination and protonation leads to the formation of **90**. Xie reported that the putative nickelacycle **89** could be annulated with an alkyne to generate 1,2-dihydronaphthlenes **91**.[112]

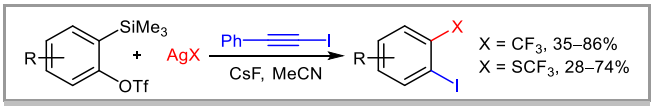
Hu showed that silver halide promotes the reaction of aryne with alkynyl iodide to generate 1,2-bishalogenated arenes




**Scheme 34.** Different carbonylation methods of arynes




**Scheme 35.** Ni-catalyzed three-component coupling reactions of arynes




**Scheme 36.** Silver mediated trifluoromethylation–iodination and trifluoromethylthiolation-iodination of arynes

(Scheme 36). Relying on this protocol, a novel trifluoromethylation–iodination of arynes was developed using triflormethyl silver ($AgCF_3$) as the $CF_3$ source and phenylethynyl iodide as the iodide supplier.[113] By using trifluoromethylthiosilver ($AgSCF_3$) trifluoromethylthiolation reaction could be achieved.[114]

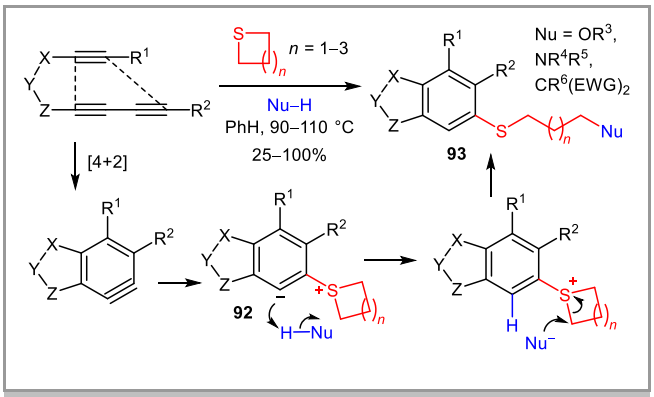
## 3. Hexadehydro Diels-Alder Reaction-based Strategies

Cycloisomerization of 1,3-diynes and diynophiles, so called hexadehydro Diels-Alder (HDDA) reaction,[12] is a versatile source for the formation of arynes. Appropriately tethered triynes and tetraynes can undergo HDDA reaction at temperature ranging from 28 °C to as high as 580 °C depending on the structure of the multiynes. This reaction was independently reported by Ueda[115] and Johnson[116] in 1997, which is subsequently explored by the groups of Hoye, Lee and Hu. Recently, arynes generated from HDDA have been extensively exploited in the synthesis of functionalized aromatic systems.

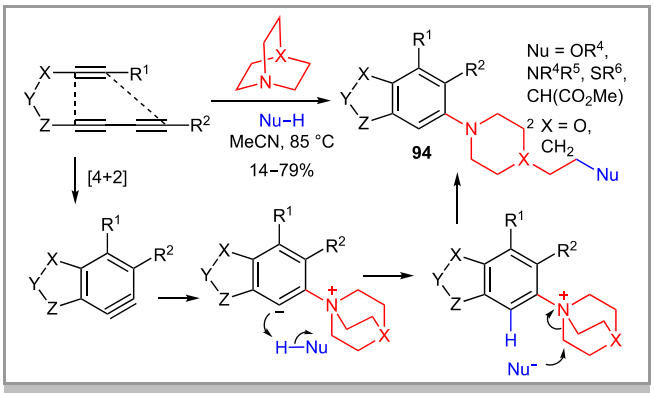
In 2014, Hoye reported the multicomponent reaction of cyclic thioethers and thermally generated arynes (Scheme 37). Initially formed 1,3-zwitterions **92** formed from cyclic thioethers was effectively intercepted by protic nucleophile to generate ring opened product **93**. C-, N-, and O-centered nucleophiles, including heterocycles were explored in this reaction.[117]

When bridged bicyclic tertiary amines were employed instead of cyclic thioether, three component adduct **94** was isolated (Scheme 38).[118] A broad spectrum of amines including *N*-substituted 3–6 membered cyclic amines were also explored along with diverse *O*- and *N*-based pronucleophiles.

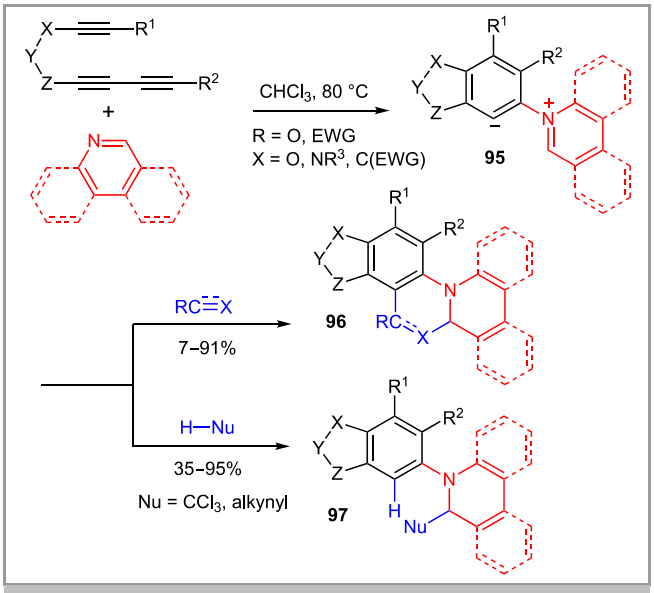
In a similar approach, they developed MCRs of arynes with azaarenes, which led to the formation of structurally diverse polyaromatic molecular frameworks **96** and **97** (Scheme 39).[119] Depending on electronic nature of trapping agent, zwitterion **95** can produce a new 6-membered ring in product **96** or generate **97** through reacting with pronucleophiles.



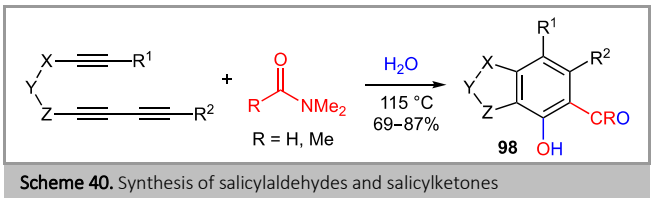

**Scheme 37.** MCR of HDDA derived arynes with cyclic thioethers



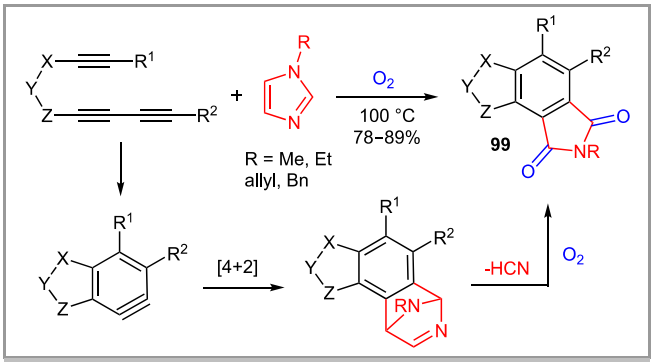

**Scheme 38.** Three-component coupling reaction with bicyclic amines




**Scheme 39.** MCR of HDDA derived aryne and azaarenes




**Scheme 40.** Synthesis of salicylaldehydes and salicylketones




**Scheme 41.** Synthesis of isoindole-1,3-diones from tetraynes and imadazole using molecular oxygen

Hu reported the synthesis of fused multifunctionalized salicylaldehydes and salicylketones from tetraynes and *N*,*N*-dimethylformamide or *N*,*N*-dimethylacetamide as a source of the formyl group (Scheme 40).[120]

The reaction proceeds via a formal [2+2] cycloaddition between aryne and amides, followed by hydrolysis generates the phenol derivatives **98**. Later, it was shown that [4+2] cycloadduct of aryne with imidazole could be oxidized by molecular oxygen after extrusion of HCN into isoindole-1,3-diones **99** (Scheme 41).[121]

Hoye also developed a novel cascade process to build naphthalene framework by trapping benzocyclobutadiene intermediate with an alkyne (Scheme 42).[122] Thermally generated arynes readily underwent [2+2] cycloaddition with an electron-rich alkyne to generate benzocyclobutadiene intermediate **100**, which subsequently reacts with an electron-deficient alkyne to generate alkynyl naphthalene derivatives **102**. The reaction is believed to proceed via the formation of a hemi-Dewar benzene moiety in intermediate **101**. This reaction shows excellent regioselectivity and delivered **102** preferentially over other possible constitutional isomers.

Due to the inherent reactivity of $Cl_2$ with alkynes, $Cl_2$ is not a suitable halogenating agent in HDDA-mediated aryne chemistry. To overcome this problem, Hoye and coworkers employed dilithium tetrachlorocuprate as a mild chlorinating agent of arynes to generate 1,2-arenes (Scheme 43).[123]

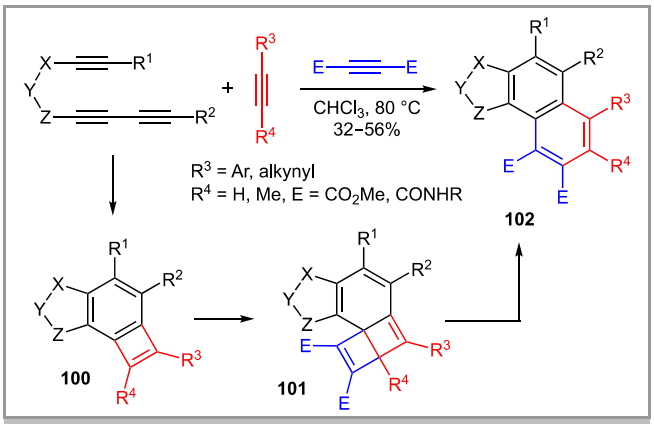
Recently, Lee and coworkers explored novel transformations of arynes generated via a HDDA reaction; which include C–H insertion,[124] nucleophilic trapping,[125] hydroarylation,[126] ene-reaction,[127] hydride transfer reaction[128] and so forth.[129–133] These arynes were also exploited in developping novel MCRs, which are versitile tools for the synthesis of functionalized arenes and benzo-fused heterocycles and carbocycles.

### 3.1. Dihalogenation

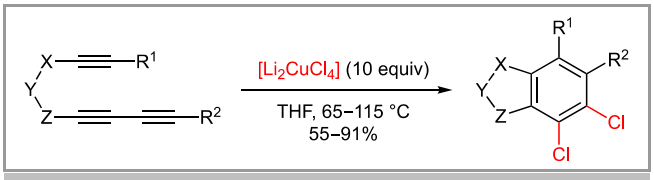
Based on the unique reactivity arynes in the presence of a silver catalyst,[134,135] we surmised that these arynes can be employed for the synthesis of fluorinated arenes under conditions than Balz-Schimann reaction[136] and the Halex process.[137] For example, silver-complexed aryne species **103** can be trapped with fluoride to provide an adduct **104**, which can be protonated to give fluorinated arenes **105** (Scheme 44).[138] It was found that the organosilver species **104** could be trapped with other electrophiles. Thus, by employing a catalytic amount of silver catalyst in the presence of NXS, 1,2-fluorohalogenated products **106** were generated efficiently (Scheme 45).

### 3.2. Halohydroxylation and Haloacylation

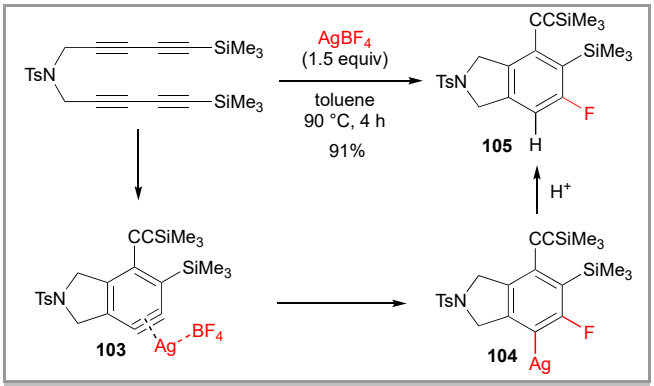
Although arynes can interact with a broad spectrum of nucleophiles direct hydration arynes to generate phenol derivatives is difficult due to immiscibility of water with organic solvent. This problem was by employing silver trifluroacetate ($AgO_2CCF_3$) to generate organosilver adduct **107**, which was readily deacylated during purification on silica gel and provided the corresponding phenol derivative **108** (Scheme 46).[139] The regioselectivity of trifluroacetate addition into arynes was tailored by the substituents present in the



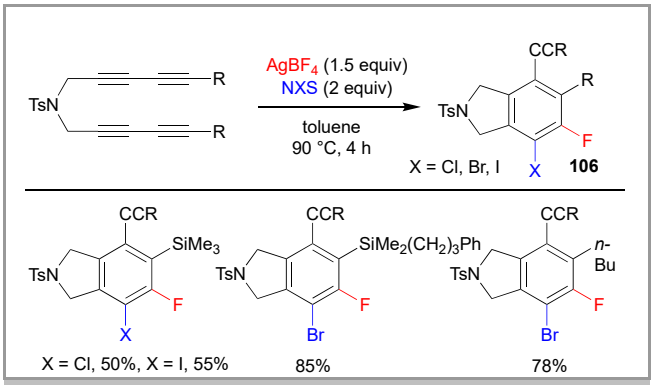

**Scheme 42.** Naphthalenes derivatives via benzocyclobutadiene intermediate



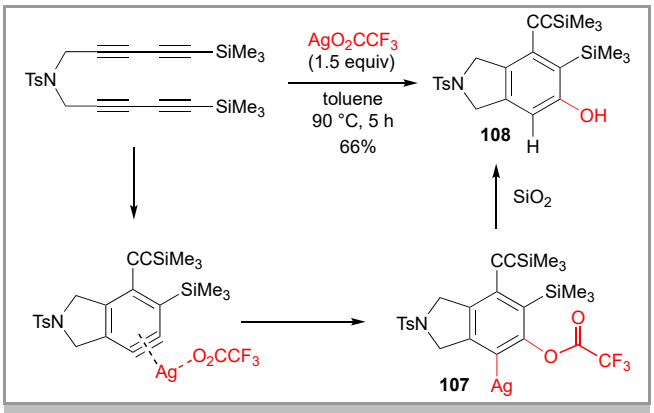

**Scheme 43**. Synthesis of bis-halogenated arenes




**Scheme 44.** Fluorination of arynes with silver tetrafluoroborate



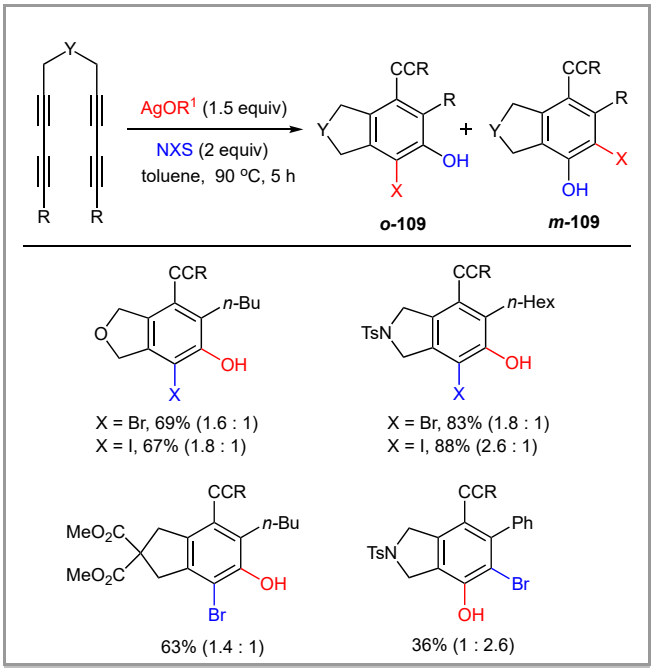

**Scheme 45.** Dihalogenation of arynes




**Scheme 46.** Synthesis of phenols via aryne intermediate

tetraynes, wherein, with trimethyl silyl group, ortho-isomer was formed preferentially.

This aryne hydration method was further extended to the synthesis of α-halophenol derivatives by intercepting organosilver intermediate **107** with suitable electrophilic halogen source (Scheme 47). Thus, with 1.5 equiv $AgO_2CCF_3$, and 2 equiv NXS, the corresponding α-bromo- and α-




**Scheme 47.** Synthesis of halophenol derivatives via aryne intermediate

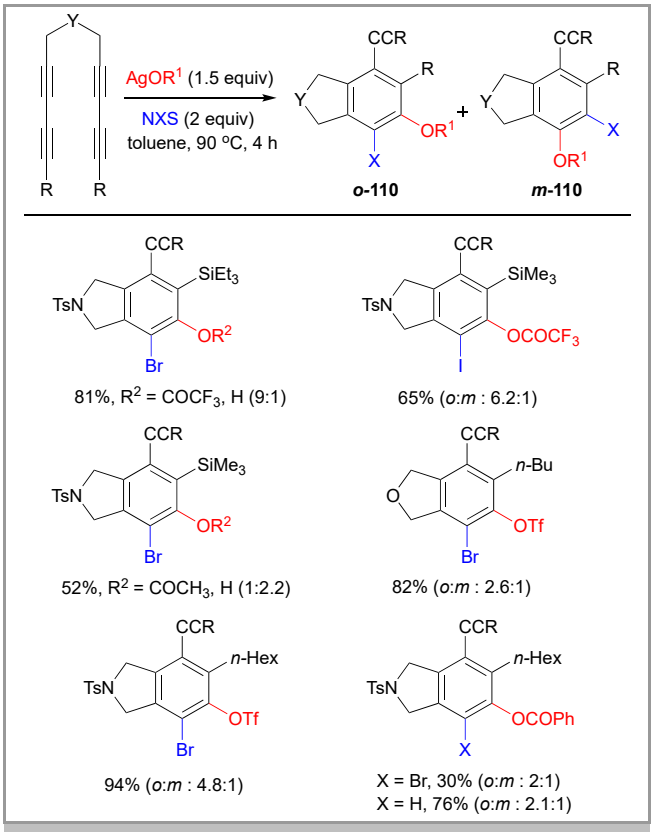
iodophenol derivative **109** were generated. The ratios of ortho- and meta-isomers depend both on the substituent and halogen source.

It was found that the presence of a silyl group and a halogen substituent both ortho to trifluoroacetate significantly slow down the diacylation, thus haloacylated products **110** were obtained as a mixture of isomers (Scheme 48). Other silveracylates can provides the corresponding haloacylated products except for the reaction with silver benzoate and *N*-chlorosuccinimide (NCS), which provided only aryl benzoate without chloride incorporation.

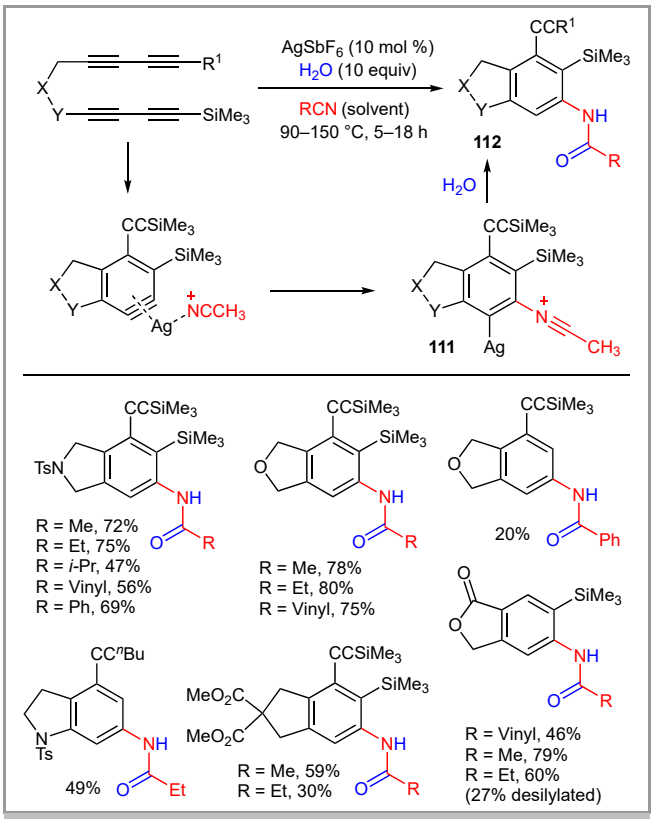
### 3.3. Amides and Imides

Being inspired by previous silver catalyzed transformations of HDDA derived aryne, we further studied its reactivities in the presence of various nitrogen centered nucleophiles. We reasoned that arynes can participate in a Ritter-type transformation[140] if nitrile reacts with aryne to generate nitrilium intermediate **111** and subsequently with water, leading to the formation of amide derivative **112** (Scheme 49).[141] Indeed, in the presence of 10 mol% silver hexafluoroantimonate ($AgSbF_6$), assorted tri- and tetraynes and nitriles provided amide **112**. In this reaction, wet acetonitrile was enough for hydration of intermediate **111** but adding additional water (10 equiv) improved the yield of the products. The regioselectivity in the formation of these products was controlled by the strong electron directing effect of the $SiMe_3$ group.[142]

Based on the efficient trapping of nitrilium intermediate **111** with water, it was envisioned that the nitrilium ion might be trapped with carboxylic acid to generate imide **113** (Scheme 50). One caveat of this planned MCR reaction is the high reactivity of carboxylic acids toward arynes., which may generate aryne-carboxylic acid adduct directly. However, in the




**Scheme 48.** Haloacylation products



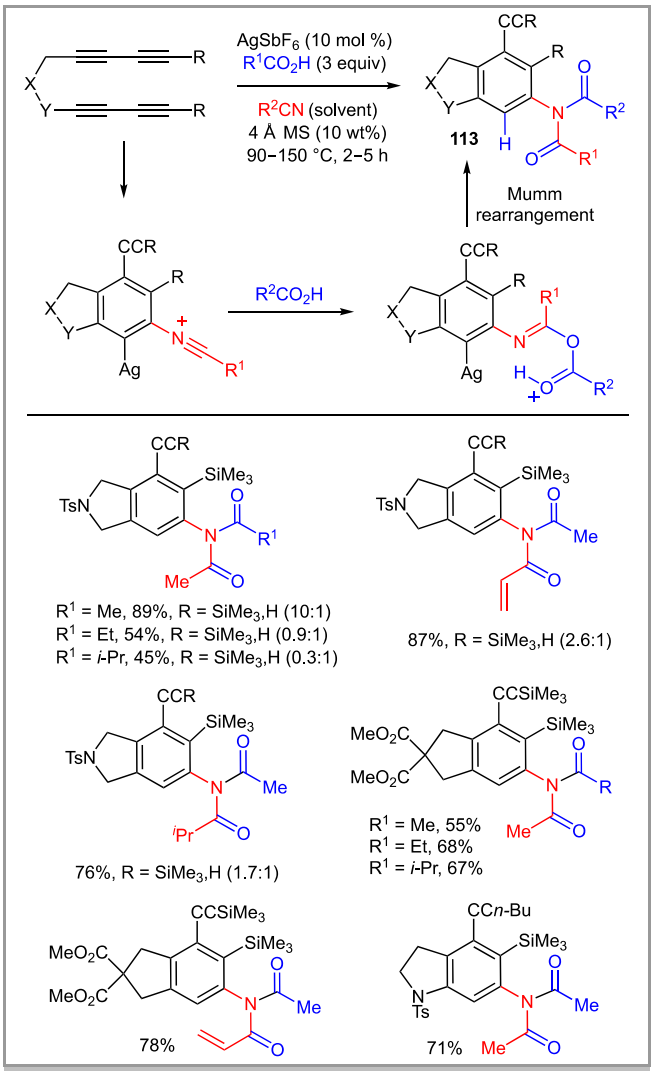

**Scheme 49.** Three-component coupling of arynes with nitrile and water to synthesize arylamides

Presence of silver catalyst and using excess amount of nitrile (as solvent), the right sequence of addition with arynes first with nitrile followed by carboxylic acid to generate three component assembly product **113**. It was found that addition of 4 Å molecular sieves (10 mol %) in the reaction mixture significantly reduces or eliminates the reduce the formation of amide derivatives derived from water trapping. Under standard conditions (10 mol% $AgSbF_6$, 3 equiv of carboxylic acid, 10 mol% 4 Å molecular sieves, and nitrile, 90 °C, 2–5 h), the reaction of assorted nitriles and carboxylic acids provided structurally diverse imides **113**.

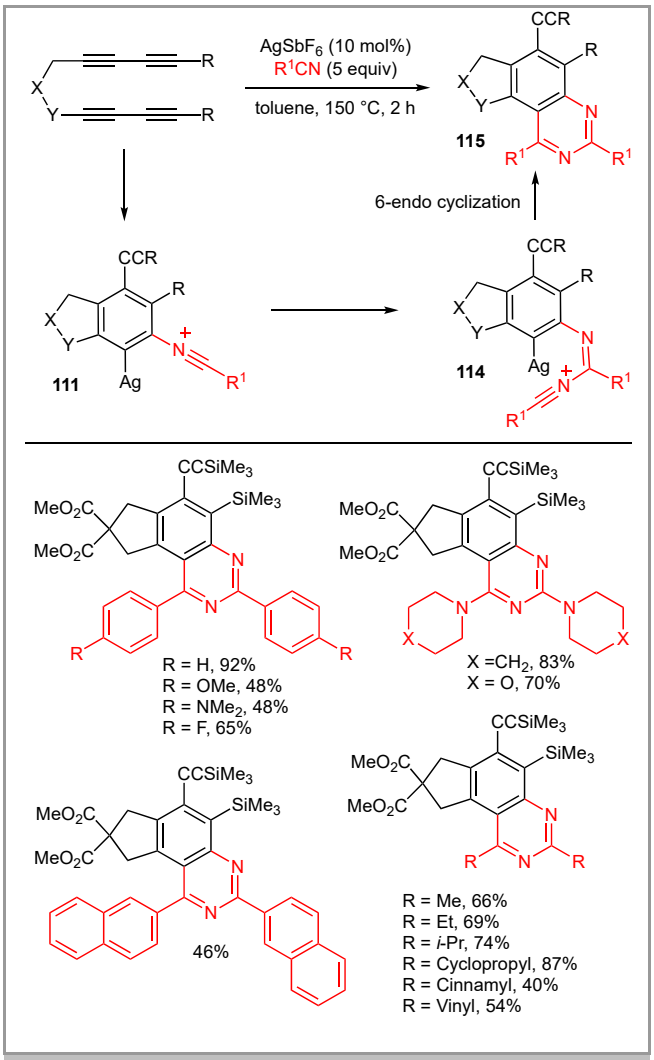
### 3.4. Quinazolines

Quinazoline is a family of nitrogen-based bicyclic aromatic compounds that constitutes the core of many biologically active molecules and phamaceuticals.[143] Although many protocols are available to systhesize quinazoline derivatives, development of new methodology to synthesize structurally diverse quinazolines is highly desireable. We envision that aryne-based MCR would constitute a novel approach to the synthesis of structurally elaborated quinazolines.[144]

In this regard, we envisage that omission of nucleophiles that trap organosilver nitrilium ion **111** in previous amide- and imide-forming MCRs would generate quinazolines via 6-*endo*-*dig* cyclization of intermediate **114** (Scheme 51). Indeed, under



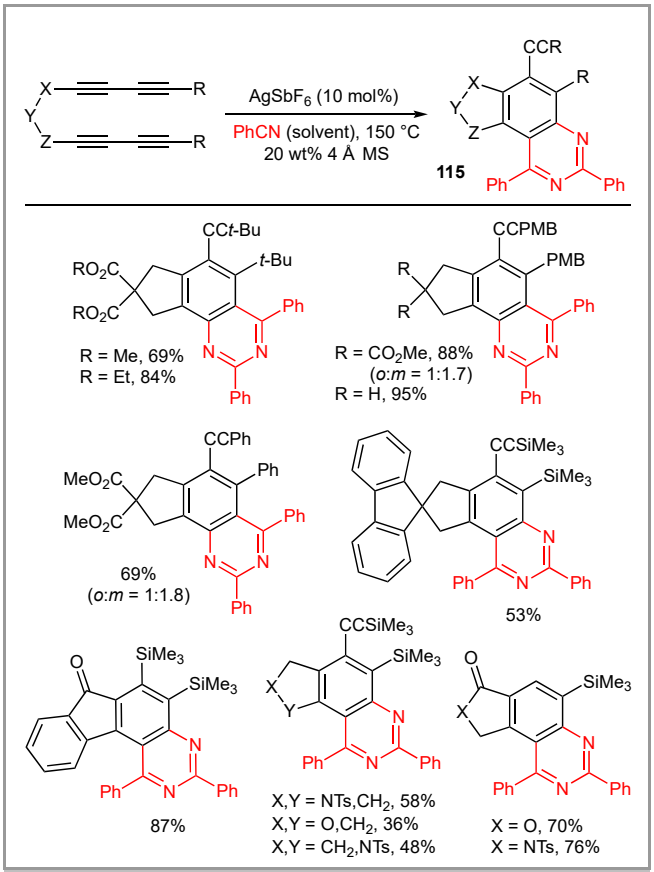

**Scheme 50.** MCRs of arynes with nitriles, and carboxylic acids




**Scheme 51.** Annulation with nitriles to generate quinazoline derivatives

optimized conditions with $AgSbF_6$ (10 mol %, 150 °C, 2 h), a range of structurally diversified quinazolines were obtained. In general, electroneutral or electron-rich aliphatic and aromatic nitriles participated in the reaction to furnish 2,4-disubstituted quinazoline derivatives in moderate to high yields. On the other hand, the reaction with electron-deficient nitriles or nitriles containing a sensitive functional group (e.g. hydroxy, halide, carbonyl, silyl) provided no or low yield of quinazoline products.

Having seen these results in hand, the scope of this MCR was further explored with arynes derived from other tetraynes and triynes (Scheme 55). The fluctuating yields for different substrates is most likely caused by adventitious water, thus molecular sieve (4 Å, 20 wt%) was added to the reaction medium. Under this optimized conditions more consistent and improved yields were obtained. The regioselectivity of the first nitrile addition is controlled by the substituents present on the arynes. Due to unfavorable steric interaction with approaching nitriles, a *t*-Bu group on the arynes directs the first nitrile addition at the meta position. On the other hand, a $SiMe_3$ group directs the addition at the ortho position because of its β-silicon effect. With aryl substituents, a mixture of two regioisomers were obtained with slight meta preference.



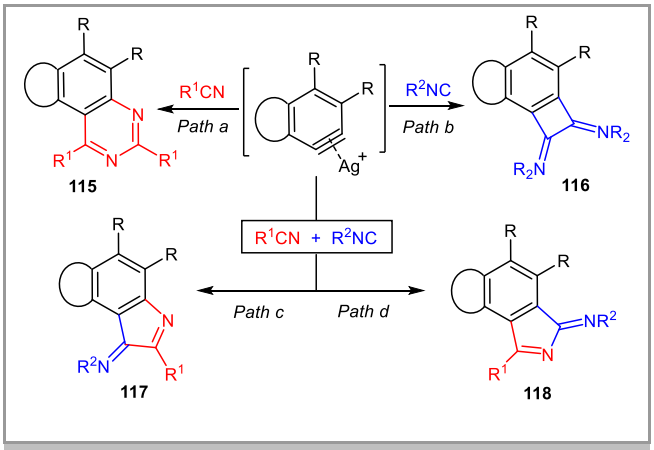

**Scheme 52.** MCRs for the formation of quinazolines

### 3.5. Benzocyclobutene-1,2-diimines and 3*H*-Indole-3-imines

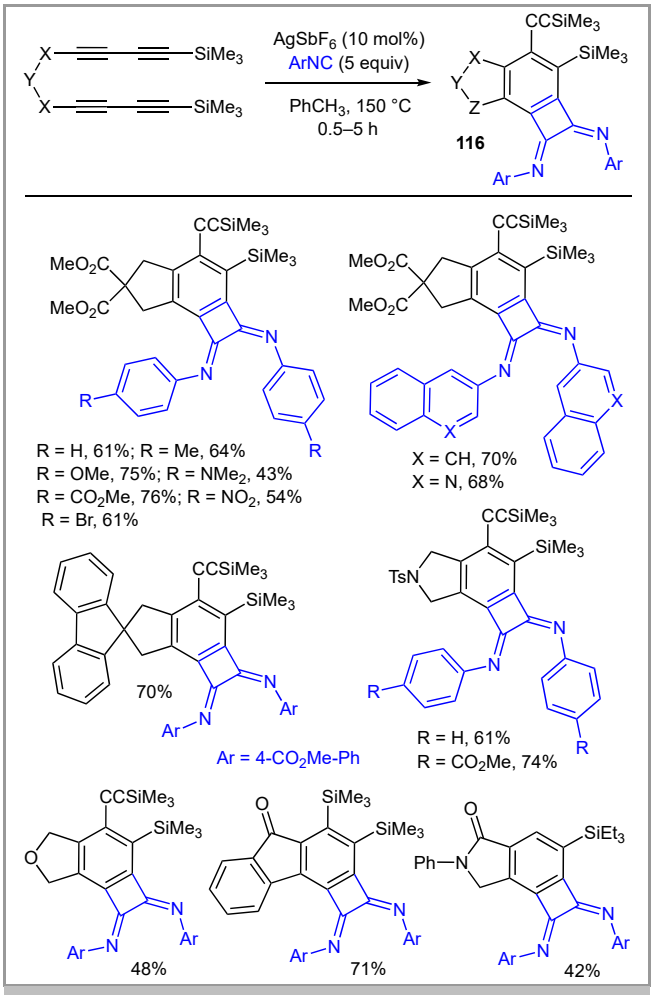
Aryne-based MCRs involving isocyanides have been explored over the last 20 years mainly with benzynes generated from the fluoride-promoted 1,2-elimination of aryl silyl triflates, which is discussed in Section 2.1. Based on the silver-catalyzed MCRs involving nitriles, we envision new NCRs involving isocyanides (Scheme 56).[145] We expect that the higher nucleophilicity of isocyanides compared to nitriles would allow the formation of doubled addition product **116** even more favorably than the formation of **115** from nitriles (Path b). Depending on the stoichiometry and inherent reactivity of isocyanide and nitrile, silver coordinated aryne might take Path c or Path d to generate hetero-MCR products **117** and **118.**

We found that under silver catalyzed condition, MCRs of arynes with isocyanides provided benzocyclobutene-1,2-diimine **116** (Scheme 54). Among many catalysts, silver hexafluoroantimonate ($AgSbF_6$) was proved to be most efficient catalyst for this MCR. No double annulated product (**116**) was observed in the absence of silver catalyst. Assorted arynes and arylisocyanides provided structurally diverse benzocyclobutene-1,2-diimine. In contrast, aliphatic isocyanides did provide the expected product **116**.

The aryne-based MCRs to generate [A+B+C] type hetero-MCR product **117** (Path c) and **118** (Path d) are expected to be complicated due to multiple competing reactions. We envisioned, however, that by controlling the stoichiometry of isocyanide and nitrile, the reaction pathways leading [A+B+C]




**Scheme 53.** Silver-catalyzed MCRs with isocyanides and nitriles

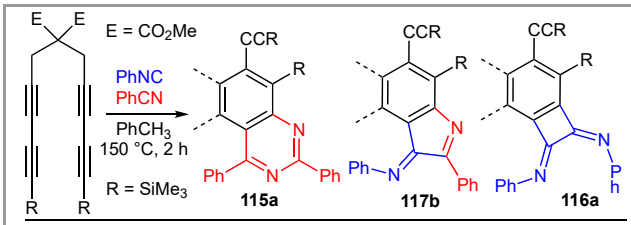



**Scheme 54.** MCRs for the synthesis of benzocyclobutene-1,2-diimine

type MCR products could be kinetically populated. In addition, modulating the reactivity of aryne, nitrile and isocyanide by the silver catalyst will be crucial. Having these issues in mind, we examined the product distribution of the hetero MCR (Scheme 55). In the presence of silver catalyst, with equimolar of isocyanide (PhNC) and nitrile (PhCN), significant amounts of benzocyclobutene-1,2-diimines (**116a**) was generated along with 3*H*-Indole-3-imine (**117b**) derivative. By running the reaction in nitrile as the solvent with 3–5 equivalents of

isocyanide, excellent selectivity for the formation of [A+B+C] was observed. In this reaction, neither quinazoline (**115a**) nor alternative hetero-MCR product (**118a**) was generated.

With the optimized condition in hand, we next explored the reaction with different substrates in the presence of various combination of isocyanides and nitriles (Scheme 56). With sterically hindered or electronically stabilized nitriles such as isobutyronitrile and benzonitrile, the MCRs afforded 3*H*-indol-3-imine **117**. On the other hand, with sterically unhindered nitriles such as, $CH_3CN$, $C_2H_5CN$, the expected 3*H*-indol-3-imine **117** was not obtained, rather it spontaneously hydrated




| entry | PhCN : PhNC (equiv) | **115a + 117b + 116a**(%)[a] | **115a : 117b : 116a**[a] |
|---|---|---|---|
| 1 | 1 : 1 | 30 | 0 : 1 : 0.45 |
| 2 | 2 : 2 | 43 | 0 : 1 : 1.2 |
| 3 | 2 : 1 | 48 | 0 : 1 : 0.8 |
| 4 | 3 : 1 | 52 | 0 : 1 : 0.7 |
| 5 | 5 : 5 | 63 | 0 : 1 : 10 |
| 6[b] | 300 : 3 | 85 | 0.1 : 1 : 0 |
| 7[b] | 300 : 5 | 83 | 0.1 : 1 : 0.1 |

[a]NMR yield with an internal standard ($CH_2Br_2$); [b]$PhCH_3$ was replaced by PhCN

**Scheme 55.** The influence of the stoichiometry of nitrile and isocyanide on the yield and product distribution

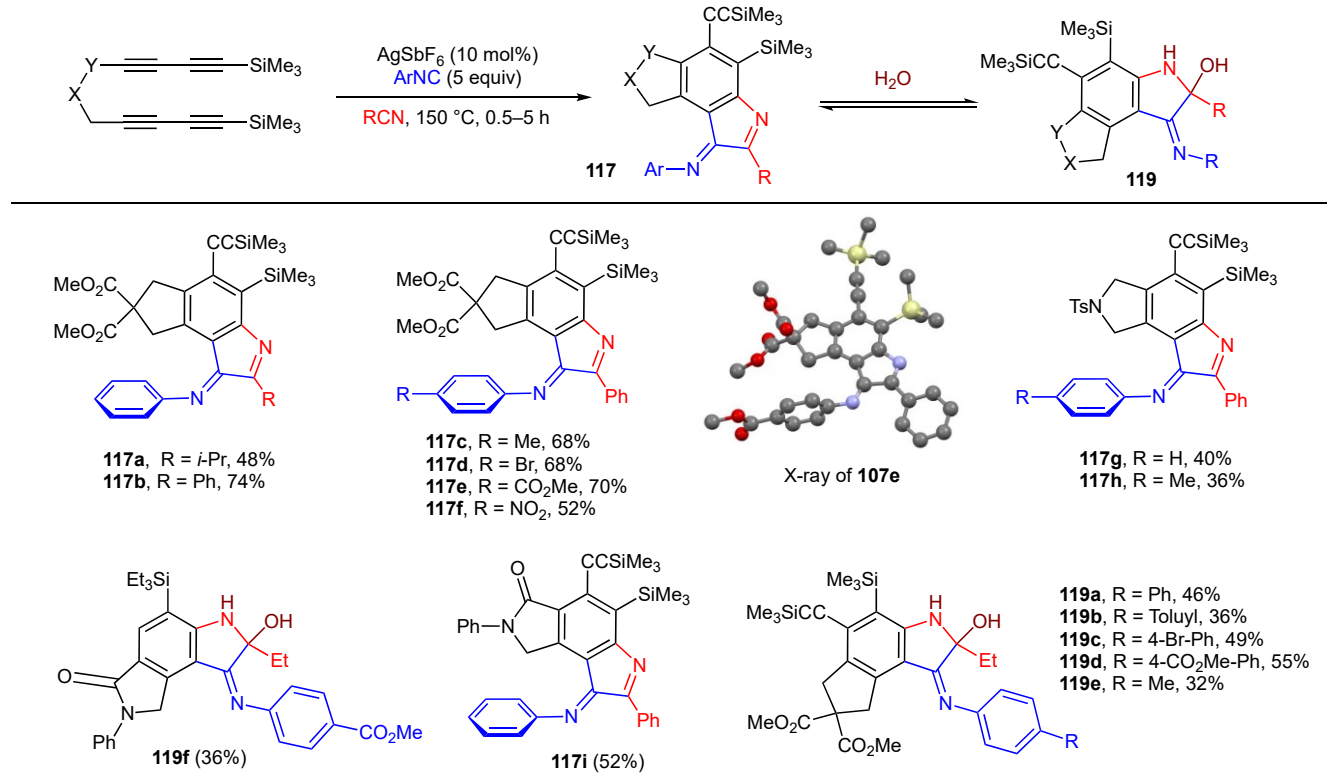
under the reaction conditions to generate 3-iminoindolin-2-ol **119**.

To gain further insight into the mechanism and the path selectivity leading to formation of 3*H*-indol-3-imines, DFT calculations were carried out (Scheme 57). The calculated reaction profiles show that the differentiating factor for Path b and Path c is the lower activation barrier of **IN4** to form nitrile adduct **IN5** via **TS2** (15.1 Kcal/mol) compared to that of **IN2** to form **IN3** via **TS1** (22.8 kcal/mol). Once intermediate **IN5** is generated, it reacts with nitrile or isocyanide in the subsequent step. In Path a, **IN5** reacts with nitrile to generate **IN6**, which proceeds to generate intermediate **IN7** via **TS3**. Subsequent ring closing of **IN7** leads to the formation of quinazolines **115**. On the other hand, in Path c, **IN5** forms isocyanide complex **IN8**, which leads to the next intermediate **IN9** via transition state **TS4**. The reaction profile in Path c, calculated to be the most favorable one, is consistent with the actual reaction occurred to generate 3*H*-indol-3-imines or 3-iminoindolin-2-ols **117**.

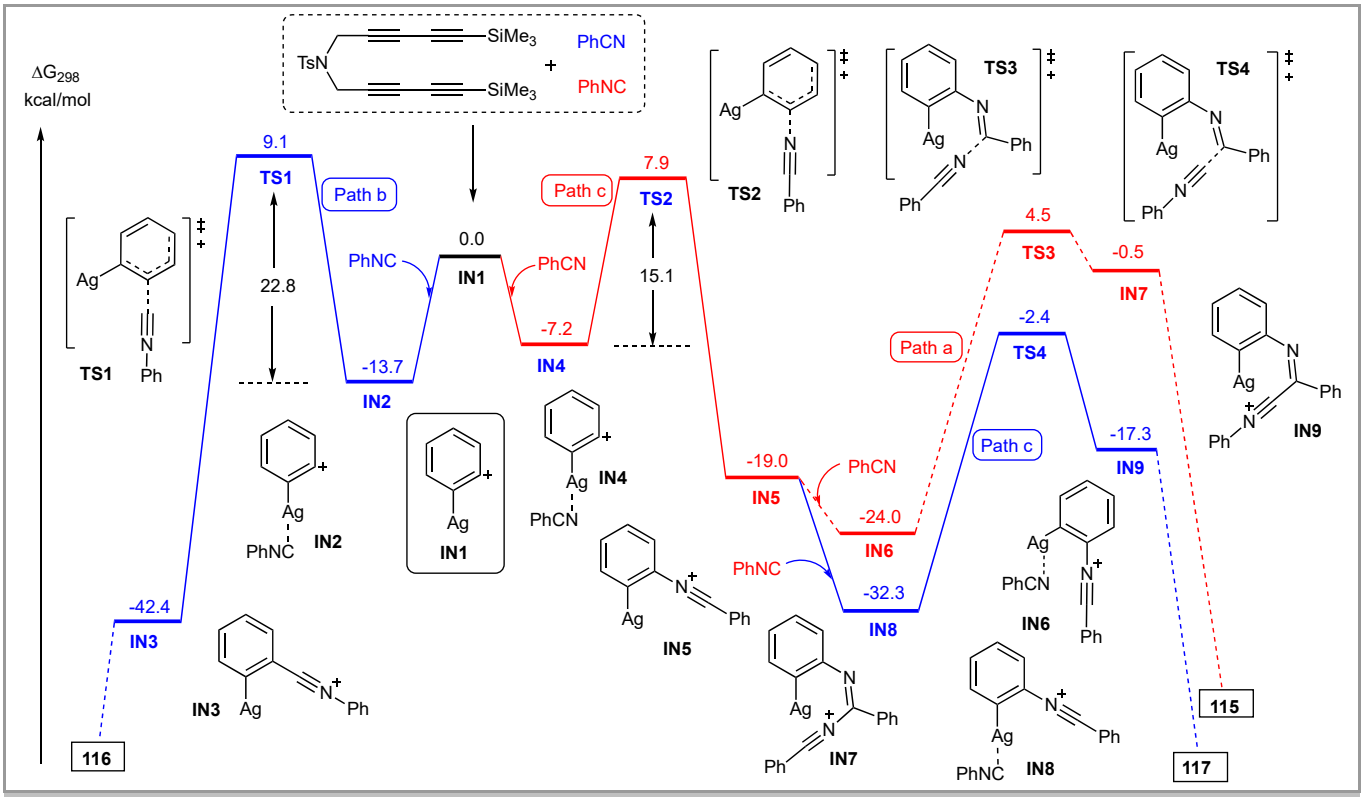
### 3.6. Other MCRs of Arynes and Isocyanides

The favorable reactivity of isocyanide with arynes over other weak nucleophiles including carboxylic acids, alcohols, amines, and water, allows for the development of new aryne-based MCRs that will provide an efficient access to imides, imidates, amidines, and amide functionalities (Scheme 61).[146]

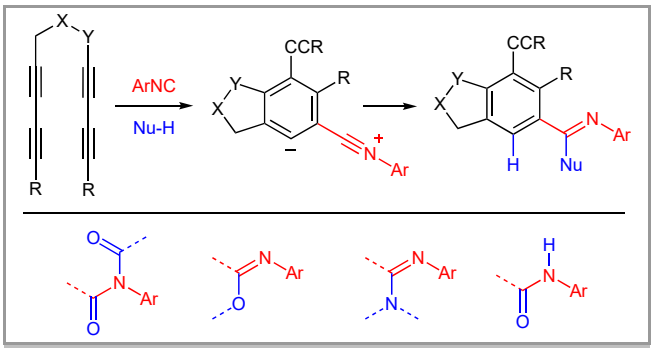
The generality of the three-component reaction of arynes with isocyanides and carboxylic acids have been proved regarding all three components (Scheme 59). A series of




**Scheme 56.** Synthesis of 3- iminoindolin-2-ol and 3*H*-indol-3-imine via aryne intermediates




**Scheme 57.** Calculated potential energy profiles for selective formation of 3*H*-indol-3-imines over other products (all substituents on the phenyl moiety from the HDDA reaction are omitted for clarity)



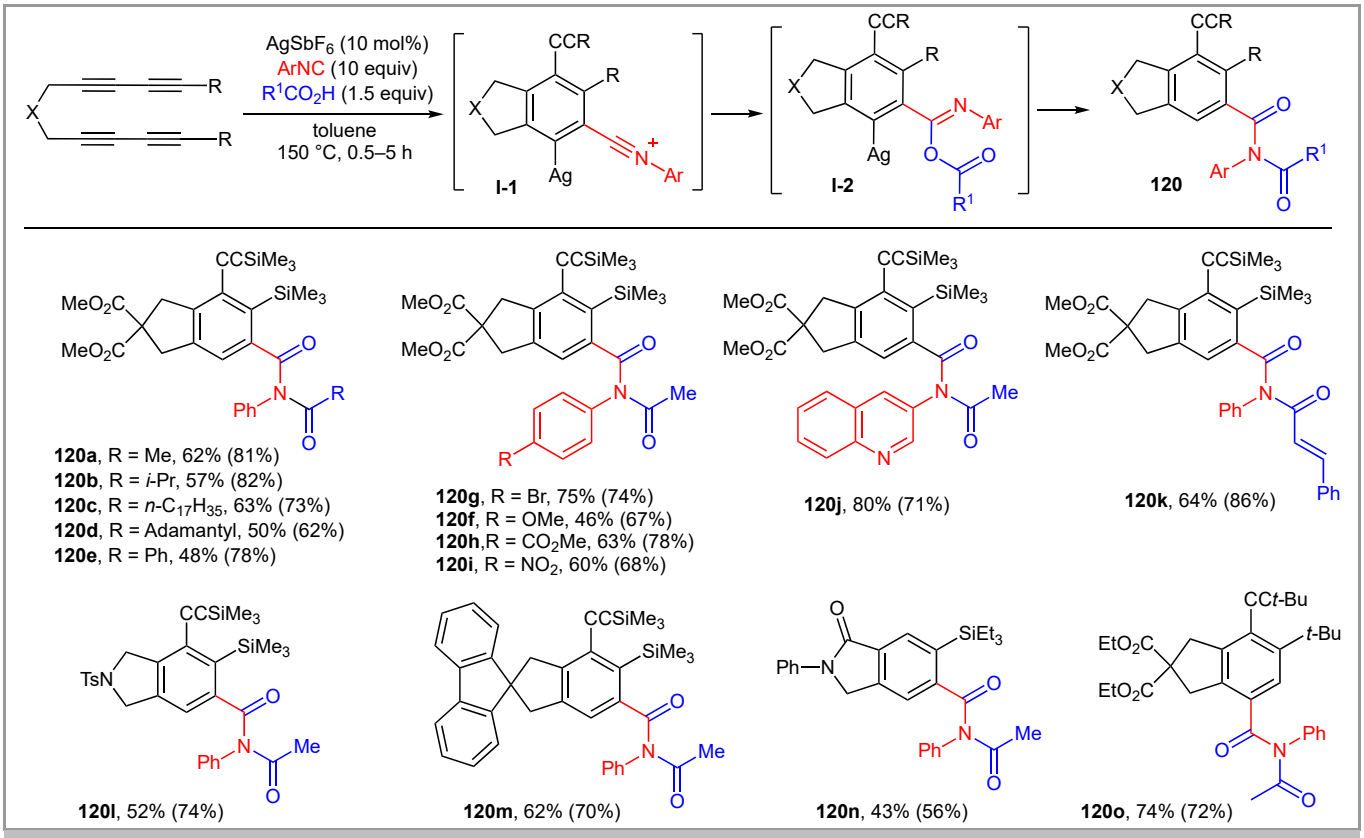

**Scheme 58.** New aryne and isocycanide-based MCRs

aliphatic and aromatic carboxylic acids have been studied with malonate ester-tethered tetrayne in the presence of phenyl isocyanide, which generate **120a–120e** and **120k** in moderate to high yield both in catalyzed and uncatalyzed condition. Aryl isocyanides with variety of functional groups for example, 4-MeO, 4-Br, 4-$CO_2$Me, 4-$NO_2$-substituted phenyl isocyanides were all tolerated. Reactions with 3-isocyanoquinoline was also effective and generated corresponding imide in good yield. The structure of arylimides was further diversified by using different aryne precursors. Reactions with *N*Ts-, fluorenyl- and phenyl amide-tethered tetraynes generated imides **120l–m**. The reaction of *t*-Bu-substituted tetrayne provided imide **120o** with reversed regioselectivity.

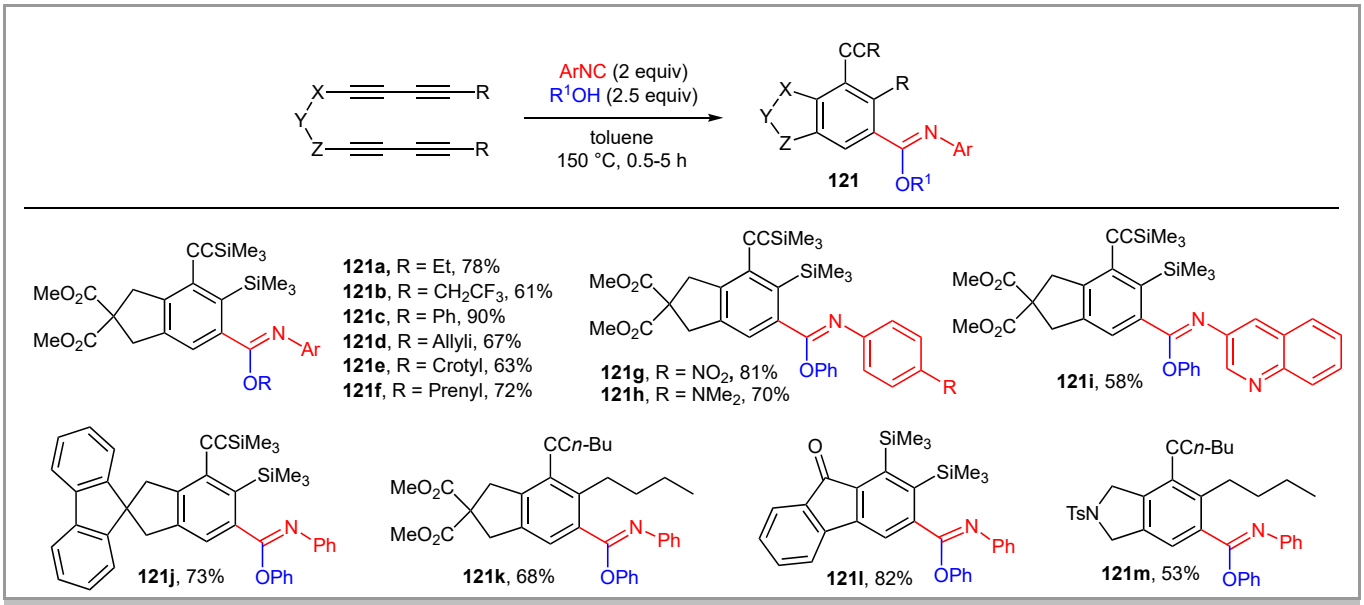
MCR of arynes with isocyanides and alcohols leads to the formation of imidates **121** (Scheme 60). Although this reaction does not need a catalyst it was found that using silver catalyst delivered higher yield of the imidates. This reaction showed a wide scope of alcohols and isocyanides, thus electron-deficient trifluoroethanol, phenol, and allylic alcohols including allyl, crotyl, and prenyl alcohol effectively participated in the reaction to deliver imidate **121b–121f** in good yield. An electron-withdrawing (4-$NO_2$) or electron-donating (4-OMe) group on phenyl isocyanide does not significantly affect the outcome of the reaction. Reaction with 3-isocyanoquinoline, imidate **121i** was isolated in 58%. Try- and tetraynes containing different tethers and substituents delivered imidates **121j–121m** in 53–82% yields.

Replacing alcohols with sulfonamides in the above MCRs generated amidines **122** (Scheme 61). Reactions employing alkyl and aryl amines such as *n*-Bu$NH_2$ and Ph$NH_2$ often led to the formation of direct amine addition product or intractable material. On the other hand, weakly nucleophilic sulfonamides participated in the MCR sequence to deliver amidine products **122a** and **122b** in 58% and 70% yield as a mixture of two tautomers (1:1 ratio). Then a series of alkyl and aryl sulfonamides were tested in the standard reaction condition, which provided imidates **122c–122h** in 36–89% yield.

The aryne-isocyanide adduct could be trapped with water to generate amides in good yield (Scheme 62). In the presence of 2 equivalents phenyl isocyanide and 10 equivalents of water at 150 °C, an aryne intermediate derived from a tetrayne delivered amide **123a** in 88% yield. Reactions with other isocyanides afforded amides **123b–123e** in moderate to good yields.




**Scheme 59.** Synthesis of arylimides via MCRs of arynes with aryl isocyanides and carboxylic acids. (Yields in parentheses are for the reaction without the silver catalyst)

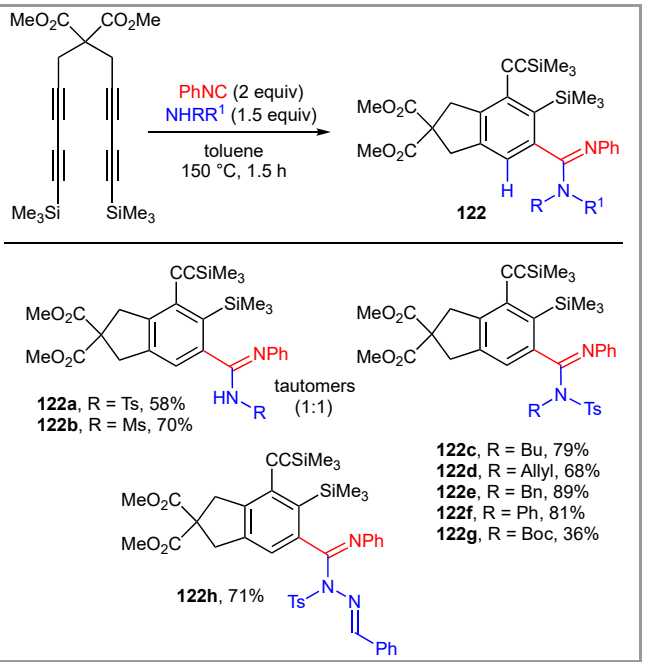



**Scheme 60.** Synthesis of arylimidates via MCRs of arynes with aryl isocyanides and alcohols

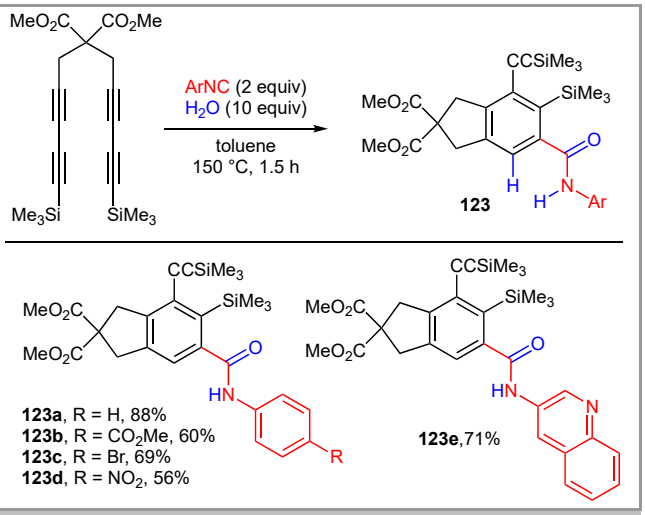
## 4. Conclusion

In the last 20 years, many strategies have been developed in aryne-based MCRs for the synthesis of functionalized arenes fused with carbo- and heterocycles. This account summarizes representative strategies including the recently developed new aryne-forming HDDA approaches. Although *ortho*-silylaryl triflates have been widely used as aryne precursors MCRs, structurally elaborated multiynes could be used as an alternative source of arynes. Due to the inherent differences in chemical environments wherein the arynes are generated from multiynes, these thermally generated arynes added a new

dimension in aryne-based MCRs. Especially, by employing a silver catalyst in these reactions, the scope of aryne-based MRCs were further expanded.




**Scheme 61.** Synthesis of arylamidines via MCR of aryne with aryl isocyanide and sulfonamides




**Scheme 62.** Synthesis of arylamides via MCR of arynes with aryl isocyanide and water

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