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Reactions of Arynes Promoted by Silver Ion

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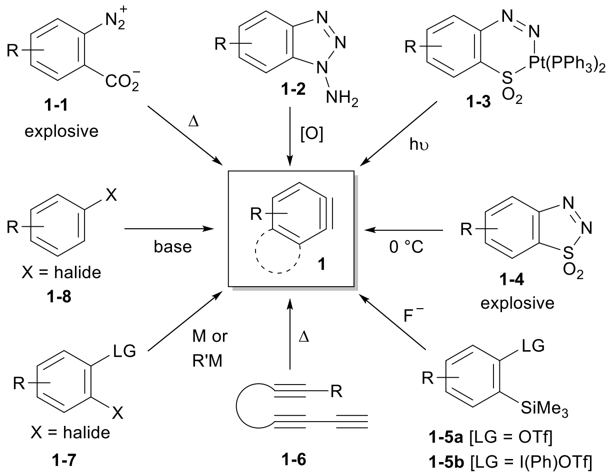
Arynes are unique aromatic species that display versatile reactivity in a variety of tranformations. It has been demonstrated that the reaction profiles of arynes can be altered by transition metal additives, and one of the earliest examples of the metal additive effect was observed with silver ion (Ag^+). Especially, in the presence of Ag^+, benzyne showed distinctive reactivity and selectivity toward π-nucleophiles compared to the corresponding reaction in its abscence. Although more experimental data needs to be accumulated to accurately define the Ag^+ additive effect, based on its role displayed in various transformations, we can infer that Ag^+ interacts with arynes to form a reactive intermediate, which behaves like a silver-bound aryl cation or 1,2-carbene-silver carbenoid. In this tutorial review, various aryne-mediated reactions involving Ag^+ or other organosilver species are discussed, which show a bird's-eye view on the Ag^+ effect in aryne chemistry such that further explorations of unique reactivity of arynes under the influence Ag^+ will be inspired.

1. Introduction

The discovery of aryne (**1**) has led the development of a host of new synthetic methods to construct functionalized arenes through the formation of new carbon-carbon and carbon-heteroatom bonds.[1-4] Incorporation of transition metals as a promoter or catalyst for the reactions of arynes further broadens their reactivity and synthetic applications. Even though many early and late metal aryne complexes have been synthesized and characterized, their synthetic utility in organic chemistry has not been explored extensively.[5,6] Only a small set of late transition metal-aryne complexes display appropriate reactivity for their application in developing new aryne chemistry. Historically, one of the earliest applications of transition metal in benzyne chemistry was reported in 1967 by Friedman using silver ion (Ag^+),[7] whereas palladium-catalyzed reactions of arynes have started to emerge only in late 1990s from the groups of Pérez[8,9] and Yamamoto.[10] Since the initial discovery of the Ag^+ additive effect, there have been many subsequent reports describing the role of Ag^+ and reaction mechanisms involving Ag^+.[7,11-14]

One hypothesis regarding the role of Ag^+ is based on the association of aryne with Ag^+ to form a reactive intermediate of a greater electrophilicity than a free aryne.[7,14] Due to the higher electrophilicity of silver-aryne complexes, they are capable of interacting with both nonbonding and bonding electrons of the reacting counterparts. Thus, it is considered that the increased reactivity of Ag^+-complexed aryne broadens the spectrum of reacting counterparts, and at the same time reduces the possibility of side reaction of arynes.[7,15] After more than thirty years of dormancy of aryne chemistry involving Ag^+ as a catalyst or as a part of reagents, recent discovery of several new aryne-based transformations promoted by Ag^+ species have catalyzed the resurgence of research in this area, including fluorination,[16] trifluoromethylation,[16] and C–H insertion.[17] Compared to the abundant applications of classical aryne-based transformations in natural product synthesis,[18-22] the synthetic utility of the corresponding Ag^+-promoted aryne reactivity is yet to be demonstrated.

The conditions required for generation of arynes pose a great barrier to the discovery and success of new reactions. Many of the known procedures (Scheme 1) need thermal activation (**1-1**,[23,24] **1-6**[25-29]), oxidant (**1-2**),[30] photon (**1-3**),[31] spontaneous decomposition (**1-4**),[32] fluoride (**1-5a**,**b**),[33,34] reductant (**1-7**),[35] or strong base (**1-8**)[36,37]. Furthermore,



Scheme 1 Various routes for the generation of arynes

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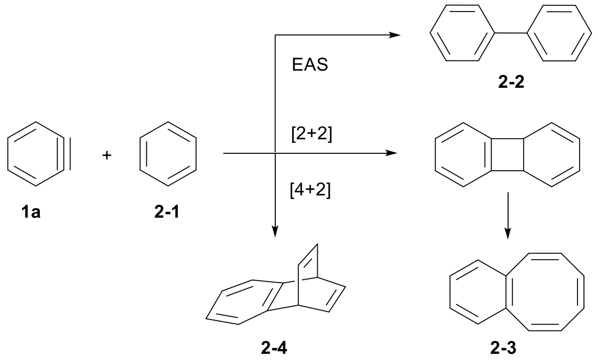
certain precursors such as **1-1** and **1-4** are extremely heat- and shock-sensitive, thus a serious safety precaution must be taken to avoid explosion for their isolation and handling. A simple and mild protocol developed by Kobayashi,[33] wherein treating 1-trimethylsilyl-2-aryl triflates (**1-5a**) with a fluoride source to efficiently generate the corresponding arynes, constitutes the basis for the explosion of recent aryne chemistry.[2–4,18–21] One common nature of most of these methods is the coexistence of by-products with aryne species in the reaction medium. These by-products are not mere spectators in aryne-mediated reactions, which is a significant and sometimes limiting factor for certain reactions. Regarding this limitation, the formation of aryne via hexadehydro Diels-Alder reaction from multiyne precursor eliminates the problem of forming non-innocent by-product, although needs relatively high temperature albeit depending on the substrate structures. This new aryne-forming protocol in combination with the use of Ag$^+$ to modulate their reactivity further broadens the scope of aryne-based transformations.[29]

2. Early Observations of the Ag$^+$ Effect on the π-Nucleophile Addition with Benzyne

One of the earliest examples of the reaction between benzyne and benzene was reported by Miller and Stiles in 1963, where three major products biphenyl (**2-2**), benzocycloocatetraene (**2-3**), and benzobarrelene (**2-4**) were obtained.[38] The involvement of benzyne in this reaction was further confirmed by the isolation of both *m*- and *p*-nitrobiphenyl upon decomposition of 5-nitrobenzenediazonium-2-carboxylate in benzene. The formation of these compounds was proposed as the consequence of an electrophilic aromatic substitution (EAS), a [2+2] addition followed by its valence bond tautomerism, and a [4+2] addition reaction, respectively (Scheme 2).

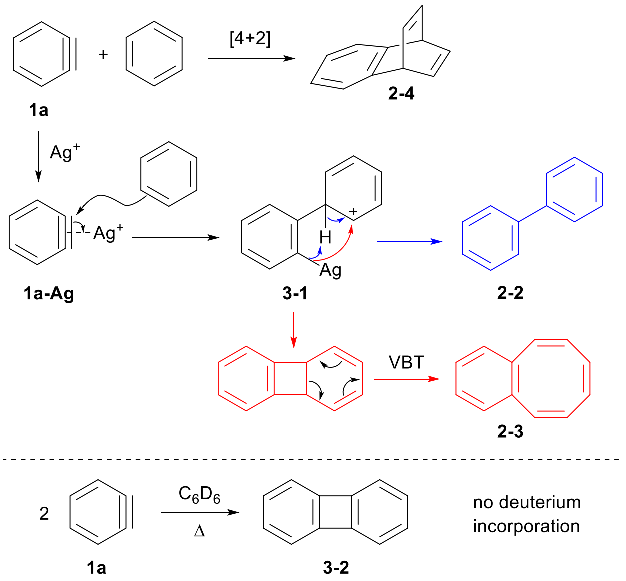
The first demonstration for the effect of Ag$^+$ in aryne-based transformations was made by Friedman in 1967, when the above reaction was carried out in the presence of a silver additive.[7] Noticeable changes in product distribution were observed depending on the amount of AgClO$_4$; upon increasing the amount of AgClO$_4$, the relative yield of **2-2** and **2-3** compared to **2-4** had increased (Table 1). The role of the Ag$^+$ was proposed to explain the observed changes in product distribution (Scheme 3). While the excess amount benzene may react with benzyne before its association with a Ag$^+$ to generate [4+2] adduct **2-4**, the silver complex of benzyne **1a-Ag** would form. Once formed, the increased electrophilicity[7,14] of **1a-Ag** may promote an electrophilic aromatic substitution of benzene molecule to form the Wheland intermediate **3-1**. The partitioning between a proton transfer or C–C bond formation from **3-1** would lead to the observed products **2-2** and **2-3**, respectively. In addition, the formation of a minor product biphenylene **3-2** is the result of a direct [2+2] dimerization of benzyne, which was confirmed by carrying out the reaction in benzene-d_6, where no deuterium incorporation was observed.



Scheme 2 Modes of reaction between benzyne and benzene

Entry	[AgClO$_4$] (mol%)	Product Distribution (%)			
		2-2	2-3	2-4	3-2
1	unknown	37	50	12.5	0
2	unknown	49	44	7.4	0
3	0	1.1	0.4	88	11
4	1.27×10^{-7}	13	7.9	67	12
5	1.27×10^{-3}	29	17	46	8.4
6	1.27×10^{-2}	52	31	17	0.7
7	1.27×10^{-1}	58	35	6.8	0
8	1.27	61	35	3.7	0

Table 1 Effect of Ag$^+$ the product distribution in reactions of benzyne with benzene



Scheme 3 Ag$^+$-catalyzed reaction of benzyne with benzene proposed by Friedman

3. Further Studies on the Role of Ag$^+$ in the Reaction of π-Nucleophiles with Benzyne

3.1. Reactions of benzyne with substituted benzenes

To further explore the role of Ag$^+$ in the reactions of benzyne with π-nucleophiles, substituted benzene molecules were employed as the reacting counterpart (Scheme 4).[14] When benzyne was generated from thermal decompositions of benzenediazonium-2-carboxylate (45 °C) in the presence of a catalytic amount of silver perchlorate ($AgClO_4$) and electron-rich arenes such as anisole and toluene, electrophilic aromatic substitution products with high *ortho* selectivity over *para* were mainly produced. The product distribution was dependent on the amount of silver perchlorate used in the reaction. For example, the reaction of anisole with higher amount of $AgClO_4$ produced greater amount of *o*-methoxybiphenyl over *m*- and *p*-isomers, yet, the sum of *o*-substituted biphenyl and benzocyclooctatetraene products remained constant. This suggested that these two products were derived from a common intermediate, consistent with the Friedman's hypothesis.

On the contrary, the reactions of benzyne with benzene derivatives containing an electron-withdrawing substituent, such as chloro or ester, generated benzocyclooctatetraene derivative as a major product via [2+2] addition followed by valence bond tautomerism along with decent amounts of EAS and Diels-Alder products. The reaction of highly electron-deficient arene **4-1** found to be independent of the presence of Ag^+, and only Diels-Alder product **4-2** was obtained.

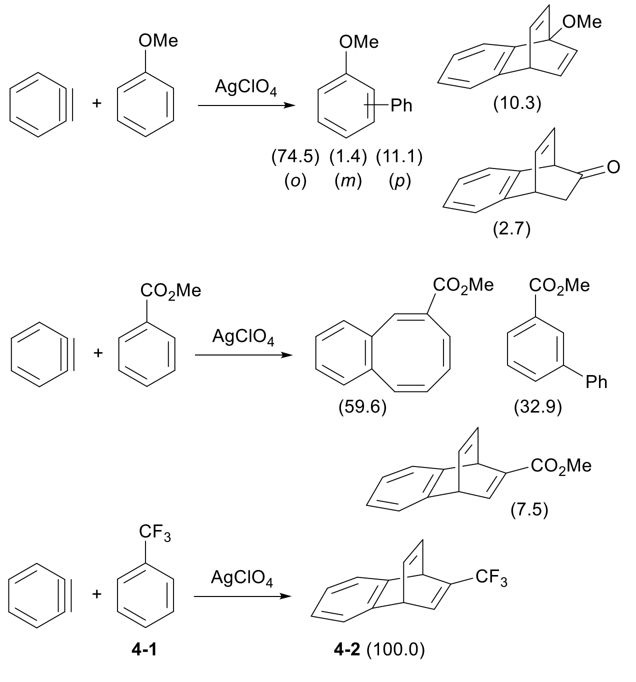
For the reaction of benzyne with *o*-substituted benzene derivatives in the presence of Ag^+, a near linear relationship with higher partial rate factor (F_o) for the electron-rich arenes was observed, where the reaction constant, ρ, was calculated to be –2.0. This implies the involvement of a putative Ag^+-benzyne complex and its higher electrophilicity compared to a normal benzyne (ρ = –1.79).

3.2. Reactions of arynes with polyenes: factors affecting the product distribution

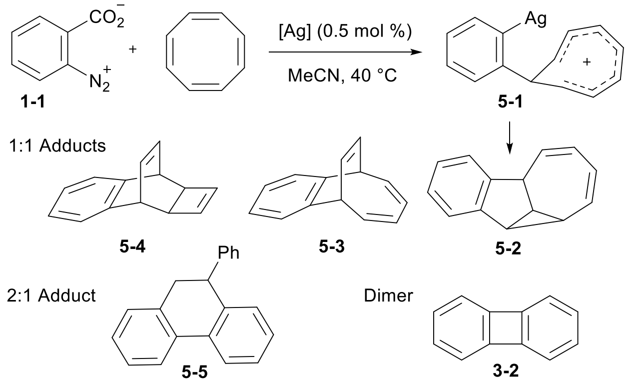
Benzyne may undergo three different types of reactions with conjugated polyenes; a concerted [4+2] cycloaddition, a step-wise [2+2] addition, and an Alder-ene reaction via either a concerted or a step-wise mechanism. The outcome of the reaction is dependent on the structure of polyenes and the presence or absence of Ag^+. In 1973, Vedejs and Shepherd reported the effect of Ag^+ in the reaction of benzyne with cyclooctatetraene (Scheme 5 and Table 2).[15] Following the hypothesis of Friedman, a mechanistic rationale was proposed involving the initial reaction between Ag^+-benzyne complex and cyclooctatetraene to form homotropylium ion **5-1**, followed by its conversion to benzisobullvalene **5-2**. The other products **5-3** ([4+2] addition product) and **5-4** ([2+2+2] addition product) became the minor products, although, they were generated in a significant amount in the absence Ag^+. It was also found that the counter ion of Ag^+ did not affect the product distribution.

An alternative mechanistic rationale for the formation of **5-2** in the reaction was provided by Warner (Scheme 6).[11] A new aspect of this proposal involves the second Ag^+ interacting with homotropylium ion **5-1** to generate intermediate **6-1**, where Ag^+ was assumed to be oxidized to Ag^{2+}. Although the effect of Ag^{2+} on the charge distribution on **6-1** is unknown, the favorable formation of **6-2** with Ag^+ interacting on the conjugated diene is assumed to be more favorable than that of **6-3** with Ag^+ coordinated to its skipped diene. Once formed, the final deargentation from **6-2** would lead to observed product **5-3**.

Paquette, however, argued against Warner's proposal of the formation of Ag^{2+} because of the high potential for the oxidation of Ag^+ ($E°$=+1.98V) and provided another mechanism for this reaction.[12] To bolster this proposal, he also offered a similar justification for the reaction between Ag^+-coordinated benzyne **1a-Ag** and benzene (Scheme 7). In this new mechanism, the association of benzene and cyclooctatetraene on Ag^+-benzyne



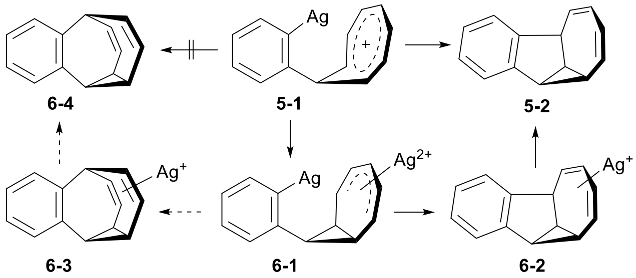
Scheme 4 Reactions of benzyne with substituted benzenes derivatives in the presence of $AgClO_4$ (relative % yield)



Scheme 5 Products from the reaction of benzyne with cyclooctatetraene in presence of a silver catalyst

Entry	Catalyst (0.5 mol %)	Product Distribution (%)				
		5-2	**5-3**	**5-4**	**5-5**	**3-2**
1	None	12	31	28	14	14
2	$AgBF_4$	80	8	6	1	trace
3	AgOAc	82	10	4	1	1
4	Unknown	62	10	8	12	8

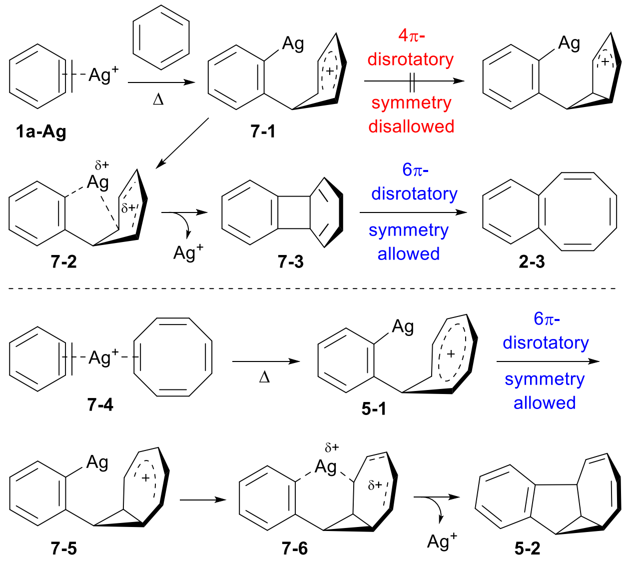
Table 2 Effect of silver catalysts on the reaction of benzyne with cyclooctatetraene



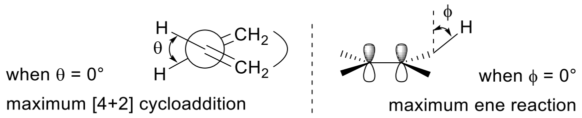
Scheme 6 A rationale for the reaction of benzyne with cyclooctatetraene in the presence of Ag^{+}

produces intermediate **7-1** and **5-1**, respectively. These intermediates may take one of the two major pathways: (1) electrocyclization of the conjugated cation, or (2) direct coordination of aryl-Ag^{+} moiety with the conjugated cation. The geometrically allowed disrotatory 4π-electrocyclization of cyclopentadienyl cation in **7-1** is symmetry-disallowed. Thus, the aryl-Ag^{+} moiety would coordinate at either C2 or C6, a higher positive charge density populated carbon than C4, to generate **7-2**. With concurrent deargentation from **7-2** and C–C bond formation would yield **7-3**, which then rearranges to final product **2-3**. On the contrary, the homotropylium ion in **5-1** formed from **7-4**, would not strongly interact with the aryl-Ag^{+} moiety due to the unfavourable geometry. Hence, geometry- and symmetry- allowed disrotatory 6π-electrocyclization would take place to generate **7-5**, which ultimately leads via **7-6** to **5-2**.

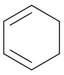
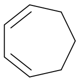
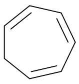
While studying the reactions of benzyne with cyclic polyenes, Crews found that the dihedral angle of adjacent π-systems (θ) and that between the *p*-orbital of a double bond and the C–H bond at the adjacent sp^3 carbon (ϕ) affect reaction pathways (Scheme 8).[39] It was proposed that, in a concerted reaction, a diene with θ = 0° should be the best substrate for a [4+2] addition, whereas a diene with ϕ = 0° would display a maximum propensity for an Alder-ene reaction. On the other hand, a step-wise [2+2] cycloaddition pathway was supposed to be independent of these dihedral angles. Any deviation from these angles would lead to a mixture of products. The reactions of cyclic alkenes with different dihedral angles were in accordance with this proposal. However, the product distribution was also significantly affected by the amount of Ag^{+} in the reaction (Scheme 9).[13] The reaction of 1,3-cyclohexadiene (θ = 17°, ϕ = ~5°) with benzyne generated from benzenediazonium-2-carboxylate (**1-1**) provided mainly the Diels-Alder product in 79% and 81% relative yield in the presence of 0.8 and 7.7 mol % AgBF$_4$ compared to 48% yield without Ag^{+}. However, the actual isolated yield was lower for the reaction with Ag^{+}. Interestingly, the same reaction using 1,2,3-benzothiadiazole-1,1-dioxide (**1-4**) as a benzyne precursor improved the isolated yield up to 35% with 97% relative yield of the Diels-Alder product in presence of 3.2 mol % AgBF$_4$. The reaction with 1,3-cycloheptadiene (θ = 20–25°, ϕ = ~37°), producing 70% of the [4+2] product in absence of Ag^{+}, afforded 89% of the product with 6.2 mol % AgBF$_4$. The reaction of 1,3,5-cycloheptatriene (θ = 40°, ϕ = 33°), which produced Alder-ene product and [2+2] cycloadduct in almost equal amount without Ag^{+}, afforded only the corresponding [4+2] cycloadduct in the presence of 6.2 mol % of AgBF$_4$. Although Paquette's mechanism may justify these results, Crews proposed an alternative explanation for the role of Ag^{+} based on the distance between the carbons of the positively charged cyclic polyene and the aryl-Ag^{+} moiety (Scheme 10).[13] For example, in the intermediate of the reaction of benzyne with cycloheptadiene or cycloheptatriene, the C2–C'4 distance is shorter than C2–C'2 distance, and thus a bond formation between C2 and C'4 is preferred to yield [4+2] cycloadduct, which corroborates the



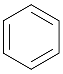
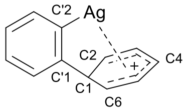
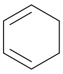
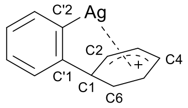
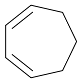
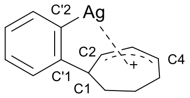
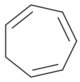
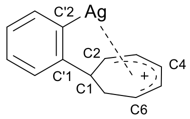
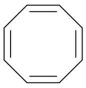
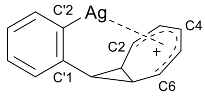
Scheme 7 Paquette's mechanism of Ag^{+}-catalyzed reaction of benzyne with cyclic polyenes



Scheme 8 Dihedral angles to effect reaction pathways

Olefin	Benzyne Precursor	AgBF$_4$ (mol %)	Product Distribution [4+2]	[2+2]	Ene	Net Yield (%)
	**1-1**	0.0	48	13	39	36
	1-1	0.8	79	6	15	6
	1-1	7.7	81	6	13	2
	1-4	0.0	51	14	35	28
	1-4	3.2	97	3	0	35
	**1-1**	0.0	70	2	2	Not reported
	1-1	6.2	89	1	1	Not reported
	**1-1**	0.0	0	55	45	46
	1-1	6.2	100	0	0	20

Scheme 9 Effect of AgBF$_4$ on the reaction of benzyne with cyclic polyenes

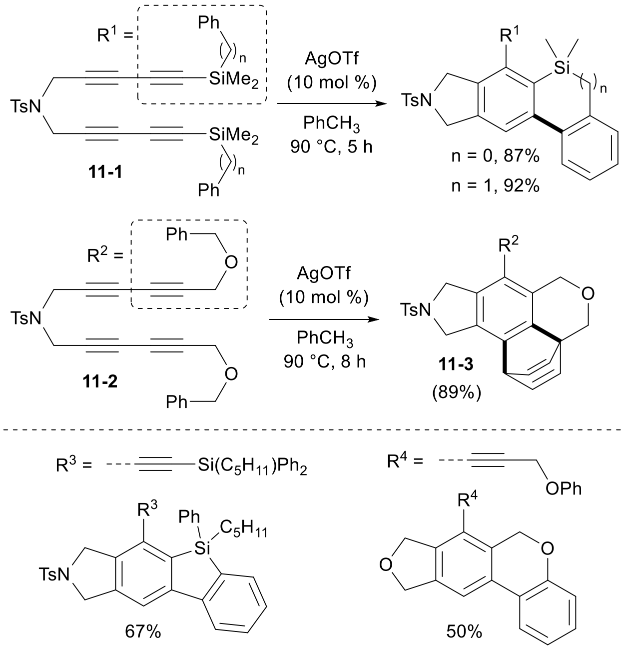
Olefin	Intermediate	Distance (Å)	
		C2–C'2	C2–C'4
		3.0	4.1
		2.65	3.2
		2.7	1.9
		2.75	2.2
		2.5	2.6

Scheme 10 Distances between reactive carbon centers (These values were obtained by using Drieding models of each intermediate to predict the corresponding major product.)

experimental observation. On the other hand, for the reaction of benzyne with benzene, the intermediate has shorter C2–C'2 distance favoring the formation of [2+2] adduct, thus readily isomerizes to benzocyclooctatetraene. The reaction of benzyne with 1,3-cyclohexadiene, however, deviates from the prediction, producing a [4+2] cycloadduct favorably, despite a longer C2–C'4 distance than C2–C'2. Crews suggested that the reaction would choose a pathway of lower energy barrier if the difference in the distances is small (< 0.5 Å). Thus, a six-member transition state is preferred over that of a four- membered one, which generates a [4+2] cycloadduct as the major product. This mechanistic rationale seems to be valid only for the reactions of cyclic polyenes. Reactions of benzyne with acyclic polyenes were found to be independent of Ag^+.

3.3. Intra- and intermolecular hydroarylation reactions of arynes

Recently, a Ag^+-catalyzed intra- and intermolecular hydroarylation of arynes generated from triyne or tetrayne precursors via hexadehydro Diels-Alder (HDDA) reaction has been developed by Lee and co-workers.[40] When 1,3,8,10-tetraynes tethered with arenes were heated at 90 °C in toluene in the presence of AgOTf (10 mol %), the corresponding tethered biaryl products were isolated in high yields (Scheme 11). This reaction is dependent on the tether length: while a one- or a two-atom tethered substrates **11-1** afforded hydroarylated products, a three-atom linker containing system **11-2** provides only Diels-Alder product **11-3** under otherwise identical reaction conditions.



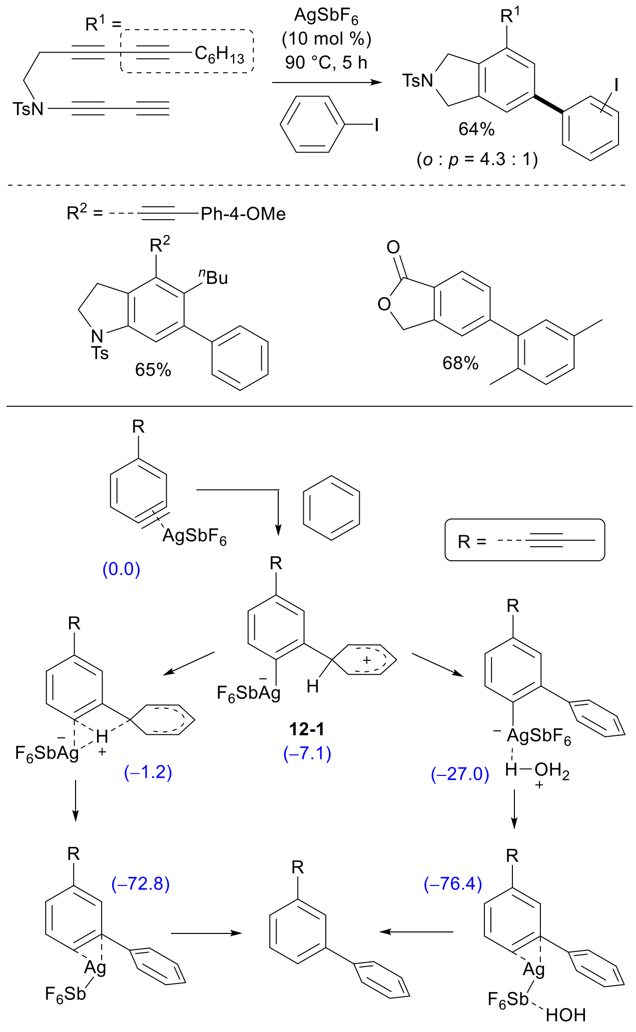
Scheme 11 Intramolecular hydroarylation of arynes in presence of silver catalyst

On the other hand, the corresponding intermolecular hydroarylation using arene as a solvent was less efficient with AgOTf catalyst, especially when a C(sp^3)–H was present at the γ-position, which provides a significant amount of the intramolecular C(sp^3)–H insertion product along with the desired hydroarylated product. It was found that $AgSbF_6$ (10 mol %) was found to be a highly efficient catalyst for the intermolecular hydroarylation (Scheme 12). Unsymmetrical tetraynes or triynes afforded a high level of regioselectivity for the intermolecular hydroarylation reaction.

The regioselectivity in the reaction of symmetrical 1,3,8,10-tetraynes depends mostly on the size of the substituents on the aryne. Unfortunately, many substituted arenes and indoles were not suitable for hydroarylation under the conditions. A competition reaction by a putative Ag^+-aryne intermediate with benzene and benzene-d_6 showed no deuterium kinetic isotope effect, and the isolated crossover products suggest a stepwise mechanism involving electrophilic aromatic substitution. DFT calculation for the mechanism of this hydroarylarion using a simplified model system clearly indicates the formation of an expected Wheland-type intermediate **12-1**, which leads to the observed hydroarylated product through a water-assisted proton transfer process (Scheme 12).

3.4. Intramolecular ene reactions of arynes with tethered alkenes and alkynes

The Alder-ene reactivity of arynes generated via HDDA reactions of *bis*-1,3-diynes was explored under the influence of Ag^+ (Scheme 13).[41] When a *bis*-1,3-diyne containing a tethered ene donor was heated in toluene or acetonitrile at 90 °C for 6 hours the expected intramolecular Alder-ene product was obtained in excellent yield regardless of the presence of AgOTf (10 mol %) or its absence. Although NMR monitoring of the reaction indicates a faster onset of the reaction with the

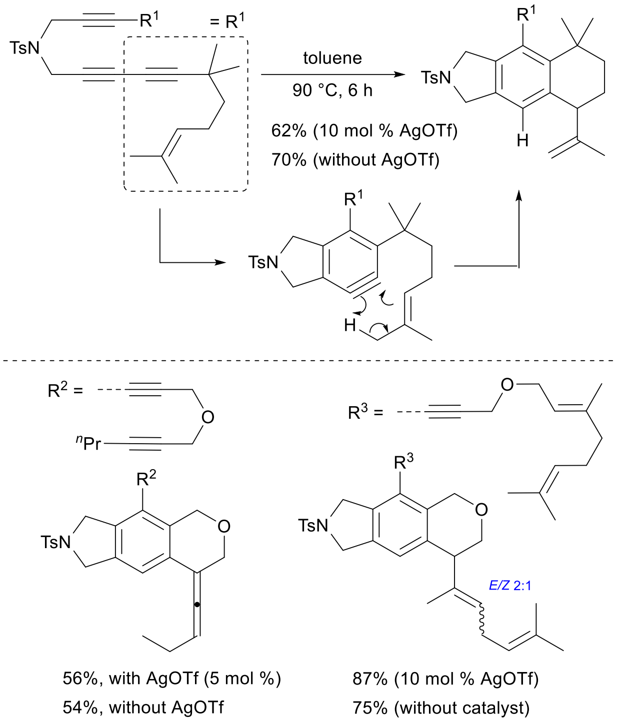


Scheme 12 Intermolecular hydroarylation of arynes catalysed by Ag^+ and plausible mechanisms

catalyst, the overall reaction time for the complete conversion was roughly the same as that without the catalyst. This led to a conclusion that the catalyst does not have a significant impact on the intramolecular Alder-ene reactions.

4. Silver-Promoted Addition of Nucleophiles with Benzynes and Arynes

4.1. Addition of fluoride, trifluoromethylide and trifluoromethyl thiolate



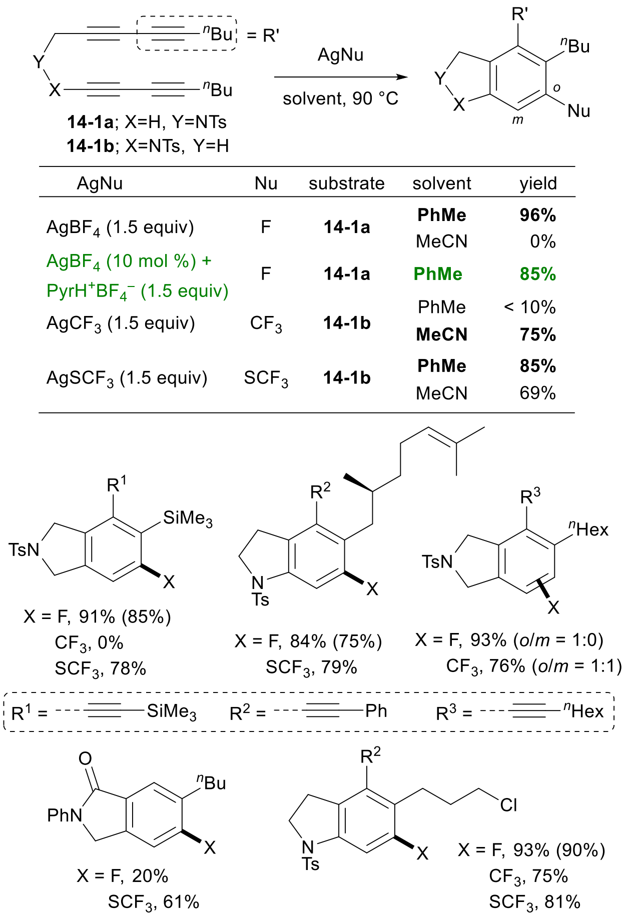
Scheme 13 Intramolecular Alder-ene reaction of aryne

Recently, the unique reactivity of putative Ag^+-aryne complex has been exploited for the synthesis of fluorine-rich molecules. Relying on aryne formation via HDDA reaction in the presence of Ag^+, Lee and co-workers generated fluoro-, trifluoromethyl-, and trifluoromethylthio- substituted indolines and isoindolines.[16] It was assumed that nucleophiles added to Ag^+-activated aryne species to generate nucleophile-added Ag^+-aryne intermediate, which after protodeargentation gives the final products. Selection of a proper solvent is critical for the reactions (Scheme 14). While the reaction with a stoichiometric amount of $AgBF_4$ in toluene yielded fluoroarenes efficiently, the same reaction in acetonitrile failed in affording even a trace amount of the product. In contrast, acetonitrile was found to be the solvent of choice for trifluoromethylation with in situ generated $AgCF_3$ as a nucleophile. Trifluoromethylthiolation proceeds more efficiently in toluene than in acetonitrile with $AgSCF_3$. A catalytic protocol for the hydrofluorination was also achieved by using $AgBF_4$ (10 mol %) as a catalyst along with pyridinium tetrafluoroborate as a source of hydrogenfluoride. The regioselectivity of these reactions is generally high, but it is affected by the steric and electronic nature of the nucleophile as well as the substituents on the aryne.[42]

4.2. Bis-functionalization of arynes: 1,2-bis-halofluorination, iodotrifluoromethylation, and halohydroxylation

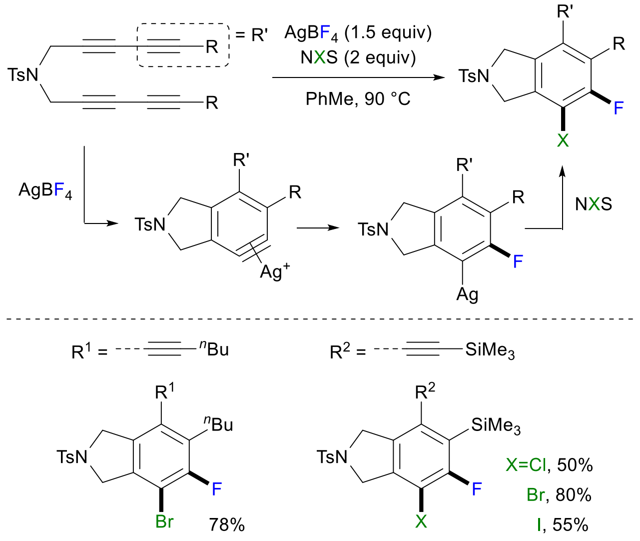
The hydrofluorination of Ag^+-activated arynes was further extended to halofluorination by trapping the putative organosilver-arene intermediate with *N*-halosuccinimide to generate α-chloro, bromo-, and iodofluoroarenes (Scheme 15).[16] Recently, the Hu group has discovered a silver-free method for *o*-iodofluorination of arynes where diphenyliodonium triflate has been used as a catalyst.[43]

Another silver-mediated bis-functionalization was reported by Hu and co-workers, where iodo-trifluoromethylation was instituted on arynes generated from 2-(trimethylsilyl)aryl trifluoromethanesulfonate (Scheme 16).[44] Even though $AgCF_3$ was identified as the best nucleophile for this reaction, most of the electrophilic counterparts including benzaldehyde, *N*-halosuccinimides, allyl halides, and 1-halophenylacetylene,



AgNu	Nu	substrate	solvent	yield
$AgBF_4$ (1.5 equiv)	F	**14-1a**	**PhMe** MeCN	**96%** 0%
$AgBF_4$ (10 mol %) + $PyrH^+BF_4^-$ (1.5 equiv)	F	**14-1a**	**PhMe**	**85%**
$AgCF_3$ (1.5 equiv)	CF_3	**14-1b**	PhMe **MeCN**	< 10% **75%**
$AgSCF_3$ (1.5 equiv)	SCF_3	**14-1b**	**PhMe** MeCN	**85%** 69%

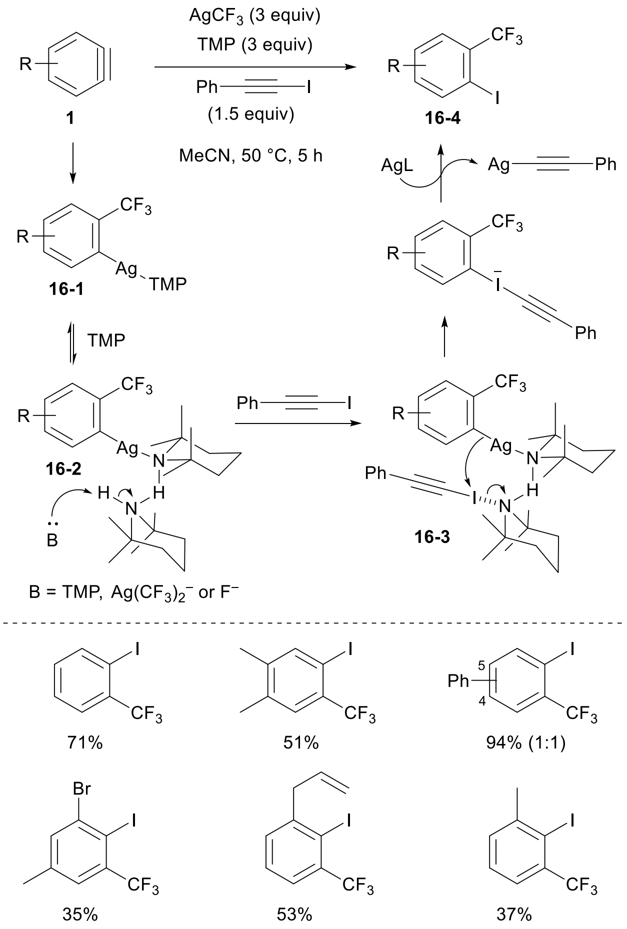
Scheme 14 Fluorination, trifluoromethylation and trifluoromethyltiolation of arynes



Scheme 15 *o*-Halofluorination of arynes

afforded either protonated products or only traces of *bis*-functionalized products. On the other hand, when 1-iodophenylacetylene was employed as an electrophile, an iodotrifluoromethylated product was obtained in 31% yield along with 43% of a prototrifluoromethylated compound. Efforts to minimize the undesired protonation event subsequent to the trifluoromethylation led to the discovery that the use of 2,2,6,6-tetramethylpiperidine (TMP) as an additive efficiently suppressed the protonation, ultimately enhancing the yield of the 1,2-iodotrifluoromethylation up to 82%. 3-Substituted arynes led to the formation of the desired products in diminished yield yet as a single isomer. On the other hand, the reactions of 4-substituted arynes afforded higher yields but no regioselectivity. The authors suggested that TMP activates $AgCF_3$ by forming a complex, $AgCF_3{\cdot}TMP$ (identified by ^{19}F NMR), which remains in equilibrium with a highly nucleophilic species $Ag(CF_3)_2^-$.[45] At the same time TMP increases the electrophilicity of 1-iodophenylacetylene by forming a strong halogen-bonding to the nitrogen moiety of TMP (identified by ^{13}C NMR).[46] Thus, in terms of the overall mechanism, this reaction commences with forming *o*-trifluoromethyl TMP-Ag-arene **16-1** from in situ generated aryne and $AgCF_3{\cdot}TMP$. Upon association of another TMP via H-bonding to form **16-2** followed by deprotonation would promote the halogen bonding of 1-iodophenyl acetylene. The proximity of the TMP-Ag-arene to 1-iodophenyl acetylene in **16-3** would promote the iododeargentation with the concurrent elimination of silver phenylacetylide eventually leads to the formation of *o*-iodotrifluoromethylation product **16-5** and silver acetylide as a by-product.

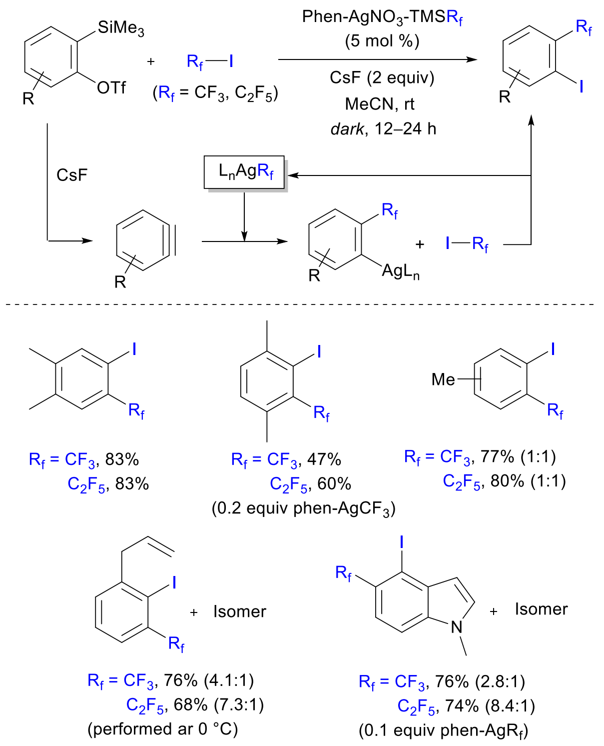
The 1,2-iodotrifluoromethylation relying on stoichiometric $AgCF_3$ and iodoalkyne as a source cationic iodine atom has been



Scheme 16 α-Iodotrifluoromethylation of benzyne

further developed into a catalytic version by employing $AgNO_3$ as a catalyst and perfluoroalkyl iodide (R_f-I) (Scheme 17).[47] In the optimized conditions, acetonitrile solution of benzyne, generated in situ from 2-(trimethylsilyl)phenyl trifluoromethane sulfonate and cesium fluoride, was treated with R_f-I in presence of AgR_f (5 mol %) prepared in situ by 1:1 reaction of $AgNO_3$ and $TMSR_f$ and 1,10-phenanthroline at room temperature in the dark for 12–14 hours. This protocol afforded *o*-iodoperfluoroalkylated products in good to excellent yield, however, only trifluoromethyl and pentafluoroethyl iodide could be successfully used because of the low stability of other AgR_f species. Additionally, the reaction conditions needed to be modified to get better yield of the products. Regioselectivity for 3-substituted aryne is moderate to excellent, whereas no selectivity was observed in case of 4-substituted arynes.

Hydration of arynes for the synthesis of phenols is difficult to achieve most likely because of the immiscibility of water with the common organic solvents. Recently, Lee and co-workers reported a facile indirect hydration of arynes generated via HDDA reaction by using silver trifluoroacetate (AgO_2CCF_3) as a surrogate of hydroxyl group (Scheme 18).[48,49] This protocol relies on the easy hydrolysis of the incorporated trifluoroacetate on silica gel, thus produces phenol derivatives as the isolated product in excellent yield. Although chemically effective, the regioselectiivty in this reaction is only marginal except form the trapping of the silyl-substituted arynes. While symmetrical *bis*-1,3-diynes with alkyl or phenyl substituents provided the corresponding phenolic products with opposite regioselectivity, silyl substituted substrates provides single isomers in high yields. The trapping of organosilver-arene intermediates derived from the addition of AgO_2CCF_3 with *N*-bromo or *N*-iodosuccinimide afforded the corresponding α-halotrifluoroacetate derivatives with good to excellent regioselectivity along with a varied amount of the expected α-halophenols. This suggests that the α-halogen significantly slows down the hydrolysis of the trifluoroacetate. Although the use of other nucleophiles with silver counter cation led to the *bis*-functionalization of the aryne, all attempts to incorporate chlorine atom using *N*-chlorosuccinimide led to only protonation of the organosilver-arene intermediate, generating the corresponding hydration product of aryne.

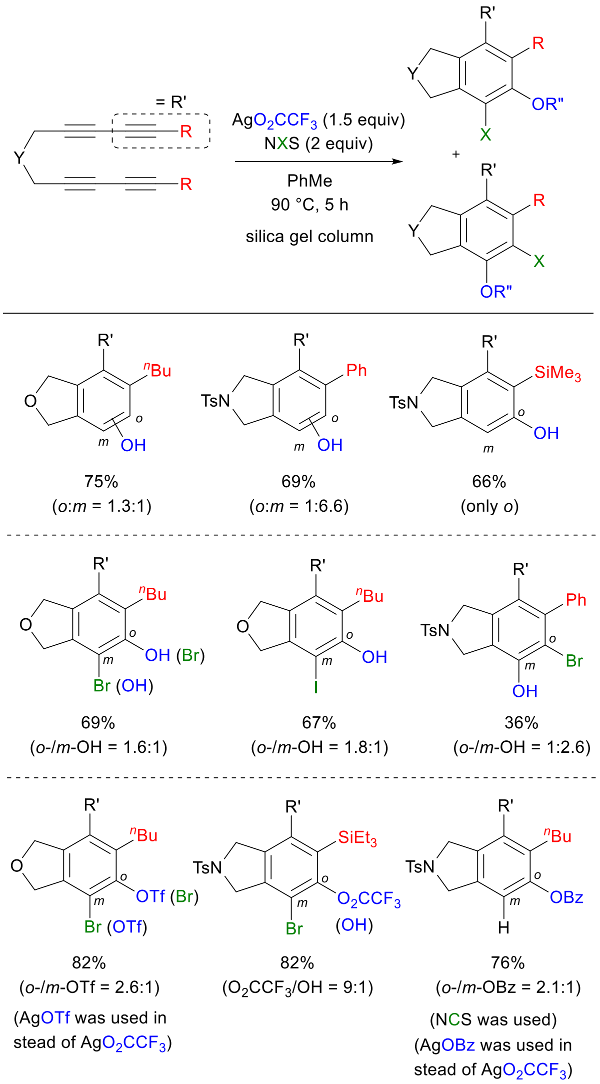


Scheme 17 α-Iodoperfluoroalkylation of arynes under Ag-catalyzed conditions

5. Silver-Catalyzed C–H Insertion by Arynes

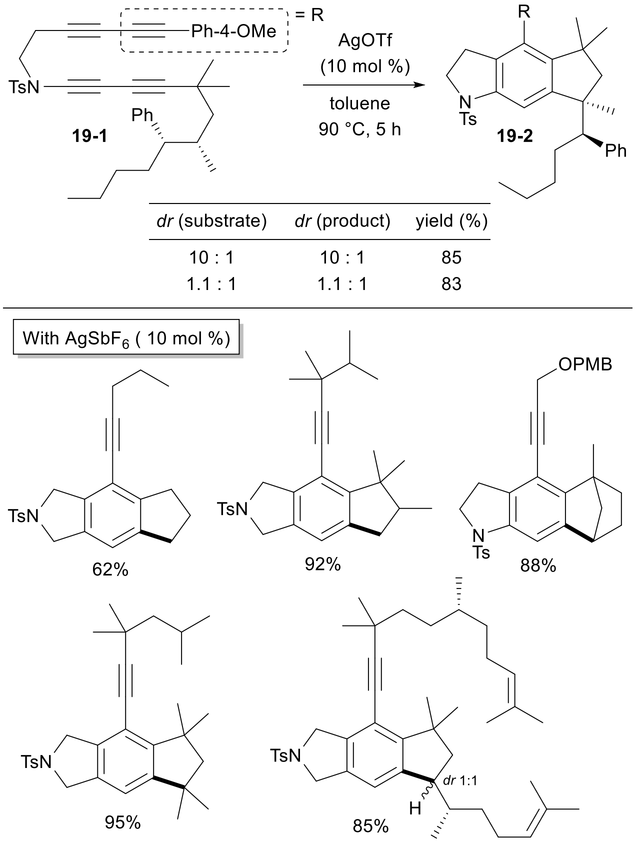
5.1. Intramolecular C–H insertion with tethered alkyl groups

The C–H functionalization is one of the most widely explored classes of organic transformations in recent years. In this regard, an effective intramolecular C(sp^3)–H insertion by arynes in



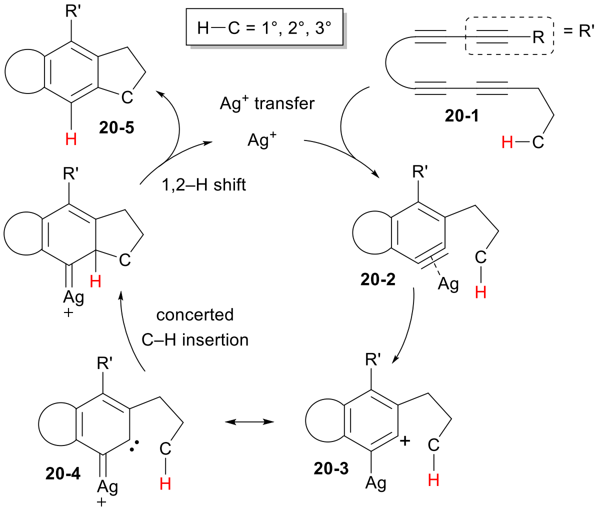
Scheme 18 Synthesis of phenol and halophenol derivatives from aryne precursors

presence of Ag$^+$ catalyst was reported by Lee and co-workers.[17] Although many early and late transition metal complexes are suitable as a catalyst for this C–H insertion, AgOTf was found to be the catalyst of choice. Under a typical conditions with 10 mol % of AgOTf in toluene at 90 °C, in situ generated arynes from 1,3,8,10-tetraynes via HDDA reaction provided 1°, 2°, and 3° C(sp^3)–H bond insertion product of fused and bridged 5-memberd carbocycles (Scheme 19). Clearly *gem*-dialkyl substituents in the alkyl tether is an important factor to improve the efficacy of the C–H insertion. As expected, a 2° C–H bond shows higher preference for the insertion than a 1° C–H bond if both are present in the substrate. A substrate dideuterated at the position of insertion afforded the corresponding deuterated product with 98% deuterium incorporation on the newly formed arene moiety, suggesting a concerted mechanism of the reaction. It was found that the corresponding monodeuterated substrate showed negligible deuterium kinetic isotope effect, implying that the C–H insertion step is not a rate-determining step. The C–H insertion induced by a putative Ag$^+$-aryne complex is proved to be stereospecific in nature. Based on the observed characteristics of the reaction, a plausible mechanism of this reaction is formulated as shown in Scheme 20. Once tetrayne **20-1** undergoes a thermal HDDA reaction in the presence of Ag$^+$ to generate Ag$^+$-aryne complex **20-2**, it will reveal its reactivity either via cationic intermediate **20-3** or its resonance-related 1,2-carbene-carbenoid **20-4** for the C–H insertion. After the C–H insertion, the Ag-carbenoid would undergo a [1,2]-H shift to complete the catalytic cycle, providing final product **20-5**.



dr (substrate)	*dr* (product)	yield (%)
10 : 1	10 : 1	85
1.1 : 1	1.1 : 1	83

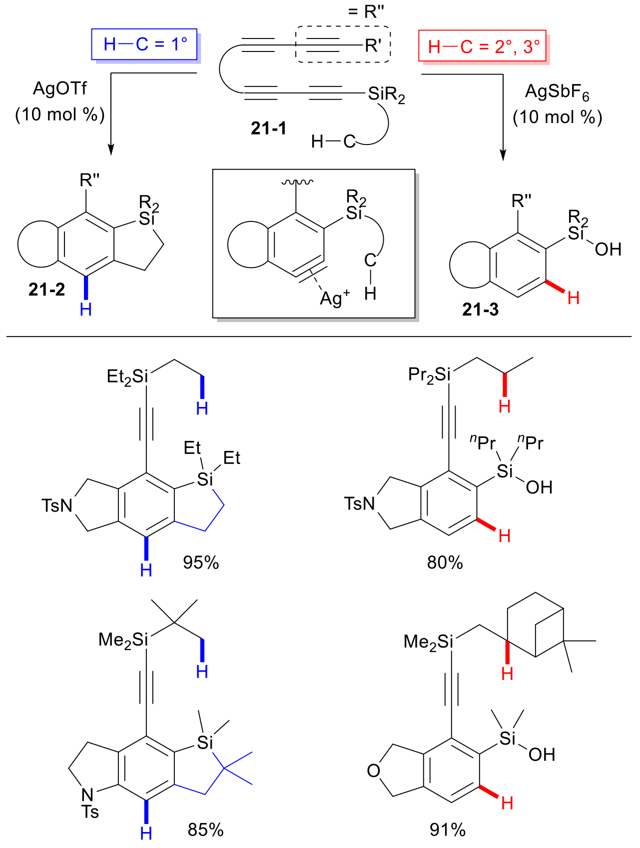
Scheme 19 Intramolecular C–H insertion of aryne



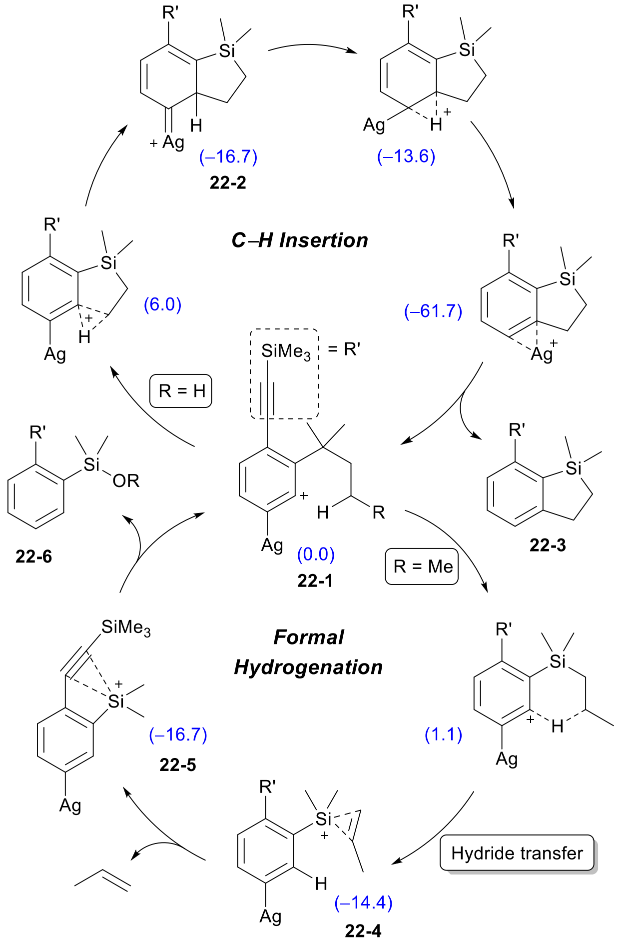
Scheme 20 A plausible mechanism for the Ag$^+$-catalyzed C–H insertion of arynes

5.2. Intramolecular insertion of C–H bond with β-silyl groups

In the exploration of Ag$^+$-aryne-based activation of C–H bonds, it was recognized that two distinctive mechanisms are simultaneously operating; a C–H insertion pathway and a formal hydrogenation of arynes.[50] When the C–H activation occurs from the 1° β-carbon of a silyl group only C–H insertion occurs, whereas the C–H activation involves the 2° and 3° β-carbon of a silyl group, formal hydrogenation prevails (Scheme 21). This bifurcated reaction profiles of substrate **21-1** leading to two different products **21-2** and **21-3** clearly indicate that the Ag$^+$-aryne species can behave either the cationic form **20-3** or its carbene form **20-4**; the former favors a hydride from 2° and 3° C–H bond with AgSbF$_6$ (10 mol %), whereas the latter favors C–H insertion with 1° C–H bonds with AgOTf (10 mol %). This reactivity difference based on the subtle electronic and steric differences is general except for one case where dimethylcyclohexylsilyl group undergoes 2° C–H bond insertion rather than a hydride transfer. In this formal hydrogenation of arynes, one of the hydrogens is transferred as a hydride from the tethered silyl group, while the other hydrogen incorporated as a proton, most likely from adventitious water. Deuterium labelling studies corroborates this conclusion. To gain further insight into this novel mechanistic change, DFT- based theoretical studies were carried out (Scheme 22). The calculations, albeit with simplified model systems, clearly indicate that for the activation of a 1° C–H bond in Ag-complexed intermediate **22-1**, a concerted C–H insertion is a preferred pathway (activation barrier = 3.1 kcal mol^{-1}) to form silver carbenoid **22-2**. A subsequent 1,2-H shift followed by deargentation leads to final product **22-3**. On the other hand, calculations with **22-1** containing a 2° C–H bond choose a pathway with almost no barrier (1.1 kcal mol^{-1}) to generate propene-coordinated silyl cation **22-4** formed via a hydride transfer. After propylene dissociation to form **22-5** with alkyne-stabilized silicon cation followed by water addition would generate formal hydrogenation product **22-6**.



Scheme 21 C–H insertion versus hydride transfer by Ag^+-aryne complex with β-silyl C–H bonds



Scheme 22 Mechanisms for the C–H insertion and a hydride transfer leading to formal hydrogenation of arynes

6. Conclusion

Since the initial discovery, various methods have been developed for the preparation of benzyne and structurally more complex arynes. Among these, elimination with 1,2- silyltriflate promoted by fluoride seemed to be one of the most general and efficient methods, which is the basis for the burgeoning of broad application of arynes in organic synthesis. Another important discovery in aryne chemistry is the silver ion (Ag^+) effect in modulating the reactivity of aryne species and the selectivity in multiple product formation. The efforts to understand the origin of the role of Ag^+ in the addition of π-nucleophile to arynes provided a framework whereby a variety of Ag^+-activated aryne-based transformations have emerged. Recent fruitful advances of aryne chemistry rely on the formation of structurally elaborated arynes from 1,3,8,10-tetraynes via the hexadehydro Diels–Ader reaction and their concurrent activation by a Ag+ catalyst. Several representatives of these include hydrofluorination, trifluoromethylation, C–H insertion, hydroarylation, and hydration of arynes. The newly discovered Ag^+-promoted aryne functionalizations have significant potential to be applied to the synthesis of natural products and pharmaceuticals. Especially, the efficient synthesis of structurally elaborated fluoride- and trifluromethyl-containing arene compounds is of particular interest in the field of medicinal chemistry. Another area of future development of aryne chemistry may involve chiral environments, such as chiral Ag^+-aryne-mediated asymmetric C–H insertion. Based on the emergence of unconventional reactivity of Ag^+-activated arynes coupled with the development of more effective methods for their formation, a variety of unconventional reactions of arynes will continue to unfold.

Acknowledgements

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Notes and references

1 H. Pellissier and M. Santelli, *Tetrahedron*, 2003, **59**, 701.
2 A. Bhunia, S. R. Yetra and A. T. Biju, *Chem. Soc. Rev.*, 2012, **41**, 3140.
3 A. V. Dubrovskiy, N. A. Markina and R. C. Larock, *Org. Biomol. Chem.*, 2013, **11**, 191.
4 C. Wu and F. Shi, *Asian J. Org. Chem.*, 2013, **2**, 116.

5 S. L. Buchwald and R. B. Nielsen, *Chem*. *Rev*., 1988, **88**, 1047.
6 J. F. Hartwig, R. A. Andemen and R. G. Bergman, *J. Am*. *Chem*. *Soc*., 1989, **111**, 2717 and the references therein.
7 L. Friedman, *J. Am*. *Chem*. *Soc*., 1967, **89**, 3071.
8 D. Peña, S. Escudero, D. Pérez, E. Guitián and L. Castedo, *Angew*. *Chem*. *Int*. *Ed*., 1998, **37**, 2659.
9 D. Peña, D. Pérez, E. Guitián and L. Castedo, *J. Am*. *Chem*. *Soc*., 1999, **121***,* 5827.
10 K. V. Radhakrishnan, E. Yoshikawa and Y. Yamamoto, *Tetrahedron Lett*., 1999, **40**, 7533.
11 P. Warner, *Tetrahedron Lett*., 1971, **12**, 723.
12 L. A. Paquette, *J. Chem*. *Soc*. *D*, 1971, 1076.
13 P. Crews and J. Beard, *J. Org*. *Chem*., 1973, **38**, 529.
14 I. Tabushi, H. Yamada, Z. Yoshida and R. Oda, *Bull*. *Chem*. *Soc*. *Jpn*., 1977, **50**, 291.
15 E. Vedejs and R. A. Shepherd, *Tetrahedron Lett*., 1970, **11**, 1863.
16 K.-P. Wang, S. Y. Yun, P. Mamidipalli and D. Lee, *Chem. Sci.*, 2013, **4**, 3205.
17 S. Y. Yun, K.-P. Wang, N.-K. Lee, P. Mamidipalli and D. Lee, *J. Am*. *Chem*. *Soc*., 2013, **135**, 4668.
18 R. Sanz, *Org*. *Prep*. *Proced*. *Int*., 2008, **40**, 215.
19 C. M. Gampe and E. M. Carreira, *Angew*. *Chem*. *Int*. *Ed*., 2012, **51**, 3766.
20 P. M. Tadross and B. M. Stoltz, *Chem*. *Rev*., 2012, **112**, 3550.
21 S. D. Vaidya and N. P. Argade, *Org*. *Lett*., 2013, **15**, 4006.
22 A. E. Goetz, A. L. Silberstein, M. A. Corsello and N. K. Garg, *J. Am*. *Chem*. *Soc*., 2014, **136**, 3036.
23 M. Stiles, R. G. Miller and U. Burckhardt, *J. Am*. *Chem*. *Soc*., 1963, **85**, 1792.
24 F. M. Logullo, A. H. Seitz and L. Friedman, *Org*. *Synth*., 1968, **48**, 12 and the references therein.
25 K. Miyawaki, R. Suzuki, T. Kawano and I. Ueda, *Tetrahedron Lett*., 1997, **38**, 3943.
26 A. Z. Bradley and R. P. Johnson, *J. Am*. *Chem*. *Soc*., 1997, **119**, 9917.
27 T. R. Hoye, B. Baire, D. Niu, P. H. Willoughby and B. P. Woods, *Nature*, 2012, **490**, 208.
28 B. Baire, D. Niu, P. H. Willoughby, B. P. Woods and T. R. Hoye, *Nat*. *Protoc*., 2013, **8**, 501.
29 C. Holden and M. F. Greaney, *Angew*. *Chem*. *Int*. *Ed*., 2014, **53**, 5746; *Angew*. *Chem*., 2014, **126**, 5854.
30 C. D. Campbell and C. W. Rees, *J. Chem*. *Soc*. *C*, 1969, 742.
31 T. L. Gilchrist, F. J. Graveling and C. W. Rees, *J. Chem*. *Soc*. *C*, 1971, 977 and the references therein.
32 G. Wittig and R. W. Hoffmann, *Org*. *Synth*., 1967, **47**, 4.
33 Y. Himeshima, T. Sonoda and H. Kobayashi, *Chem*. *Lett*., 1983, 1211.
34 T. Kitamura and M. Yamane, *J. Chem*. *Soc*., *Chem*. *Commun*., 1995, 983.
35 G. Wittig and L. Pohmer, *Angew*. *Chem*., 1955, **67**, 348.
36 T. Matsumoto, T. Hosoya, M. Katsuki and K. Suzuki, *Tetrahedron Lett*., 1991, **32**, 6735.
37 A. M. Dyke, A. J. Hester and G. C. Lloyd-Jones, *Synthesis*, 2006, 4093.
38 R. G. Miller and M. Stiles, *J. Am*. *Chem*. *Soc*., 1963, **85**, 1798.
39 P. Crews and J. Bear, *J. Org*. *Chem*., 1973, **38**, 522.
40 N.-K. Lee, S. Y. Yun, P. Mamidipalli, R. Salzman, D. Lee, T. Zhou and Y. Xia, *J. Am*. *Chem*. *Soc*., 2014, **136**, 4363.
41 R. Karmakar, P. Mamidipalli, S. Y. Yun and D. Lee, *Org*. *Lett*., 2013, **15**, 1938.
42 J. M. Medina, J. L. Mackey, N. K. Garg and K. N. Houk, *J. Am*. *Chem*. *Soc*., 2014, **136**, 15798.
43 Y. Zeng, G. Li and J. Hu, *Angew*. *Chem*. *Int*. *Ed*., 2015, **54**, 10773.
44 Y. Zeng, L. Zhang, Y. Zhao, C. Ni, J. Zhao and J. Hu, *J. Am*. *Chem*. *Soc*., 2013, **135**, 2955.
45 R. R. Burch and J. C. Calabrese, *J. Am*. *Chem*. *Soc*., 1986, **108**, 5359.
46 P. D. Rege, O. L. Malkina and N. S. Goroff, *J. Am*. *Chem*. *Soc*., 2002, **124**, 370.
47 Y. Zeng and J. Hu, *Chem*. *Eur*. *J*., 2014, **20**, 6866.
48 R. Karmakar, S. Y. Yun, K.-P. Wang, and D. Lee, *Org*. *Lett*., 2014, **16**, 6.
49 R. Karmakar, S. Ghorai, Y. Xia and D. Lee, *Molecules*, 2015, **20**, 15862.
50 P. Mamidipalli, S. Y. Yun, K.-P. Wang, T. Zhou, Y. Xia and D. Lee, *Chem*. *Sci*., 2014, **5**, 2362.