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CRITICAL REVIEW

Silver-Catalysed Reactions of Alkynes: Recent Advances

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Silver is a less expensive noble metal. Superior alkynophilicity due to π-coordination with the carbon-carbon triple bond, makes silver salts ideal catalysts for alkyne-based organic reactions. This review highlights the progress in alkyne chemistry *via* silver catalysis primarily over the past five years (*ca.* 2010–2014). The discussion is developed in terms of the bond type formed with the acetylenic carbon (*i.e.*, C–C, C–N, C–O, C–Halo, C–P and C–B). Compared with other coinage metals such as Au and Cu, silver catalysis is frequently observed to be unique. This *critical review* clearly indicates that silver catalysis provides a significant impetus to the rapid evolution of alkyne-based organic reactions, such as alkynylation, hydrofunctionalization, cycloaddition, cycloisomerization, and cascade reactions.

1. Introduction

Alkynes and their derivatives are among the most valuable chemical motifs, because of their abundance and versatile reactivities.[1] These fundamental chemicals can serve as molecular building blocks in designing novel organic reactions and assembling functional materials.[2] In particular, as verified by the recent advances in transition metal-catalysed transformations, they can be used to rapidly access complex molecular architectures.[3] Silver, which possesses the electronic configuration [Kr] $4d^{10}5s^1$ in group 11, the so-called "coinage metals", is inexpensive compared to gold. The outer orbital $5s^1$ electronic configuration of silver allows it, either alone or in combination with other transition metals, to form a series of silver(I) salts with a variety of counter anions. Similar to gold(I) salts that have been shown to be powerful catalysts for alkyne transformations,[4] silver(I) salts also function as σ- and/or π-Lewis acids.[5] Silver exhibits special properties towards alkyne activation due to its d^{10} electronic configuration, favouring interactions with the carbon-carbon π-bond of alkynes, referred to as alkynophilicity; therefore, silver can be considered to be one of the most powerful activators of a carbon-carbon triple bond.[6] As shown in Fig. 1, upon coordination to the carbon-carbon triple bond of alkynes, silver salts lead to the formation of a silver-π-complex, facilitating the formation of C–X bonds (X = C, N, O, Halo, P, *etc*.) by nucleophilic attack on this activated multiple bond. For a terminal or silylated alkyne, the reaction pathway could involve a different conversion into silver acetylide *via* deprotonation/desiliconization in the presence of bases,[7] which itself reacts either as a nucleophile to be trapped by electrophiles or by engaging in cross-coupling reactions through the transmetalation process.[8] This ability of silver to induce π-activation is not the only factor responsible for its activity and effectiveness; additionally, the transformation exhibits good functionality in a number of important reactions such as alkynylation, cycloaddition, cycloisomerization of functionalized alkynes (enynes, multiynes, propargyl compounds, *etc*.), and hydrofunctionalization.[9] Moreover, in addition to the activation of carbon-carbon triple bonds, other functional groups, such as imines and carbonyls are also activated through coordination with silver, providing a useful and important method for facilitating many different organic transformations with high atom efficiency.[10]

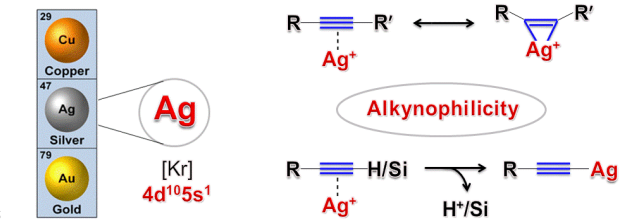


Fig. 1 Activation of the carbon-carbon triple bond by silver catalyst.

A survey of the literature related to the topic of silver-catalysed reactions of alkynes revealed a considerable number of alkyne-based reactions catalysed by this noble metal, particularly over the past decade (Fig. 2). A number of excellent reviews have incorporated the advances in the silver-catalysed reactions of alkynes from different aspects, particularly the special issue of "*Coinage Metals in Organic Synthesis*" in *Chem. Rev.* (2008),[11] "*The Organic Chemistry of Silver Acetylides*" by Pale *et al.* (2007),[12] and a book titled "*Silver in Organic Chemistry*" edited by Harmata (2010).[13] However, a review that focuses on the specific topic of silver-catalysed reactions of alkynes remains elusive.[14] Moreover, rapid development in this field since 2010 has been witnessed. Therefore, this review is timely in highlighting these advances to the chemical community.

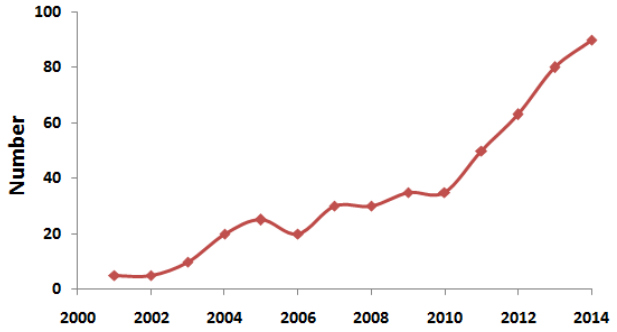


Fig. 2 A statistical analysis is made of the silver-catalysed reactions of alkynes through the survey of the articles published in *ACS*, *RSC*, *Wiley*, *Elsevier*, *etc*. during the past fourteen years.

Scope and Organization

This review presents an overview of the transformations of alkynes under silver catalysis over the past five years (*ca.* 2010–2014). A comprehensive review is an overwhelming task. Thus, this text will cover silver(I)-catalysed organic reactions of alkynes and their important derivatives *via* functionalization of the C–C triple bond and the formation of new C–C, C–N, C–O, C–Halo, C–P and C–B bonds (Fig. 3). To fully profile some specific reactions, a brief description of the background will be provided. Unless necessary, reactions with silver(I) salts as cocatalysts together with other metal salts have not been included in this review. The differences in reaction pathways resulting from diverse reagent combinations will be addressed with an emphasis on discussing the reaction mechanism, aiming to inspire new ideas for the further design and development of novel reactions.

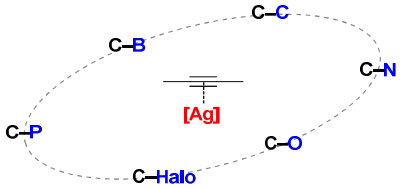
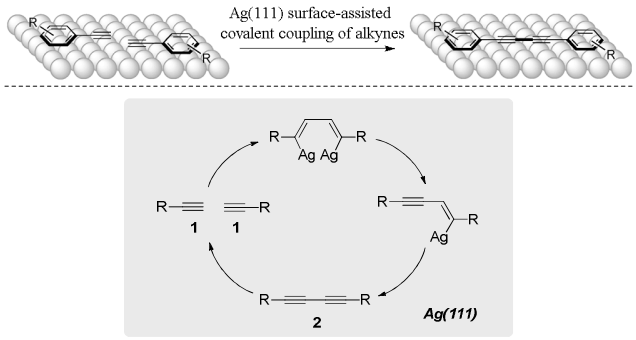


Fig. 3 Classification of the reactions by the types of bonds formed with acetylenic carbon.

2. Formation of Carbon−Carbon Bonds

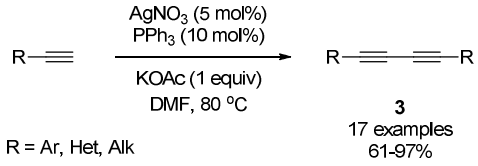
2.1 Alkynylation

Formation of Csp–Csp bonds: Glaser−Hay coupling, a well-known named reaction, proceeds identically through the dehydrogenation of a terminal alkyne with a Cu(I) ion and establishment of a Cu–acetylide intermediate.[15] Likewise, a related silver acetylide can be attained using a silver ion. However, research findings on Ag-related syntheses of butadiyne moieties remain scarce. Recently, the research groups of Klappenberger[16] and Studer and Fuchs[17] successively reported the homo-coupling of terminal alkynes **1** on the noble metal surface (Scheme 1). Alkyne homo-coupling occurs on the Ag(111) metal surface in *ultra*-high vacuum under mild conditions, leaving volatile H_2 as the sole by-product. The mechanism for the surface-assisted covalent coupling of terminal alkynes on Ag(111) was elucidated using density functional theory (DFT)-based transition state calculations,[18] suggesting a hierarchic reaction pathway that is fundamentally different from the classical coupling schemes in wet chemistry. The reaction is initiated by covalent coupling between two molecules rather than by single-molecule dehydrogenation. The resulting dimer undergoes two subsequent dehydrogenation processes, which are expected to be rate-limiting according to the comparatively large barriers. Notably, the Ag(111) surface is more efficient compared with Au(111) and Cu(111). The on-surface coupling reaction is formally reminiscent of classic Glaser−Hay coupling schemes, but is essentially different; this can be interpreted as a basic step of surface-confined acetylide chemistry. This reaction presents a new approach towards the realization of two-dimensional carbon-rich or all-carbon polymers.



Scheme 1

More recently, the Wen group reported a convenient $AgNO_3$-catalyzed efficient homocoupling of (hetero)aryl/alkyl alkynes using PPh_3 as a ligand, which afforded a wide range of 1,3-diynes **3** in excellent yields (Scheme 2).[19]



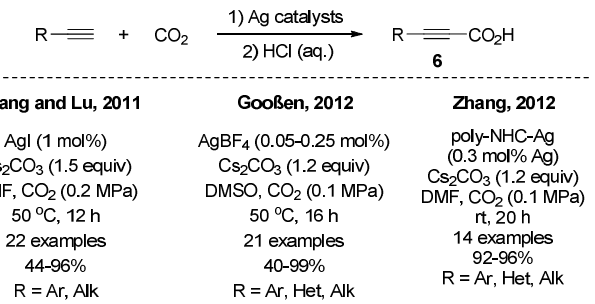
Scheme 2

Formation of Csp^2–Csp bonds: The transition metal-catalysed Sonogashira coupling of terminal alkynes with aryl and alkenyl halides has become one of the most efficient and straightforward methods to form Csp^2–Csp bonds in organic synthesis. This coupling reaction was first established in the 1970's.[20] So far, a great number of modifications for palladium catalyst systems have been developed to overcome the disadvantages of the reaction such as homocoupling products caused by CuI, expensive palladium complexes, and ugly smell of amines. However to date, only one report related to the silver(I)-catalysed Sonogashira-type coupling of terminal alkynes with aryl iodides or bromides **4** has been described by Wang and co-workers in 2006 (Scheme 3). This reaction proceeded in the presence of AgI (10 mol%), PPh_3 (30 mol%) and K_2CO_3 (2 equiv) in DMF at 100 °C for 8–12 h, affording the corresponding internal alkynes **5** in 62–99% yields. The mechanism for this silver-based Sonogashira reaction is not fully clear.[21]

Scheme 3

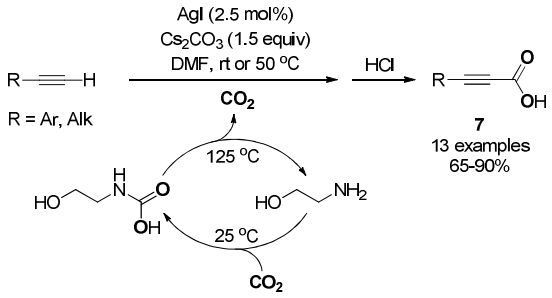
Carbon dioxide (CO_2) is one of the most abundant C1 feedstocks on earth.[22] In this respect, a high-energy active reagent, powerful catalyst, extra energy or high CO_2 pressure is generally required for successful CO_2 incorporation. Silver has been discovered to be a highly effective catalyst for the elegant and sustainable transformations that combine C−H bond functionalization and CO_2 incorporation. Remarkable progress related to the silver-catalysed C−H carboxylation of alkynes has been achieved over the past few years, which constitutes a convenient approach for propargylic acids and propiolates.[23]

As summarized in Scheme 4, in 2011 Zhang and Lu reported the Ag(I)-catalyzed carboxylation of aryl and alkyl terminal alkynes with CO_2 under ligand-free conditions. Various silver(I) salts as well as CuI all exhibited moderate to high activity. Diverse functionalized propiolic acids **6** were synthesized in moderate to excellent yields (44–96%). The addition of Cs_2CO_3 improved the yields to a large extent. The disadvantage of this method may be the use of CO_2 at a pressure of 0.2 MPa. Soon after, Gooßen and co-workers improved the methodology using considerably lower loadings of silver catalyst ($AgBF_4$, 0.05–0.25 mol%) in DMSO at ambient CO_2 pressure; using this methodology, heteroaryl alkynes also produced reasonable yields.[24] Additionally, heterogeneous silver catalysis for the carboxylation of terminal alkynes was reported by Zhang and co-workers, who employed *N*-heterocyclic carbene polymer-supported silver nanoparticles (poly-NHC-Ag) as reusable catalysts in this transformation, leading to production of the corresponding propiolic acids **6** in essentially quantitative yields at room temperature.[25]



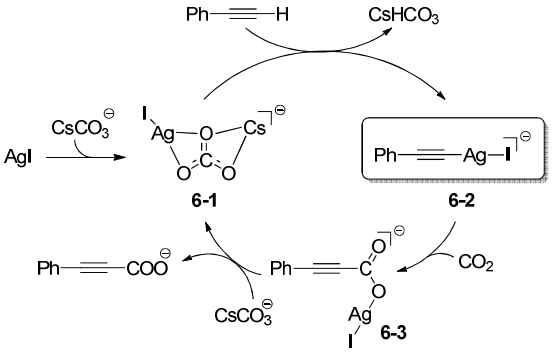
Scheme 4

Carbon dioxide capture from exhaust gases and direct consumption for organic transformations are of considerable interest for designing green reaction processes. Inspired by the CCU concept (recycle CO_2: Capture and Use), in 2013, Hong and co-workers reported the carboxylation of terminal alkynes with CO_2 from exhaust gas (candle or methanol combustion), which was captured using an aqueous ethanolamine (MEA) solution; this reaction was as efficient as that using commercial hyper-pure CO_2 gas (Scheme 5).[26] A variety of functionalized 2-propiolic acids **7** were obtained in the presence of 2.5 mol% AgI catalyst at room temperature or under heating conditions. Notably, the concentration of CO_2 and the purity of the combustion gas had significant impacts on the yields because the directly introduced gas did not work. Furthermore, the aqueous MEA solution could be continuously recycled without any decrease in the CO_2 capture and release efficiency, thus demonstrating the practicality of this protocol for CO_2 capture.



Scheme 5

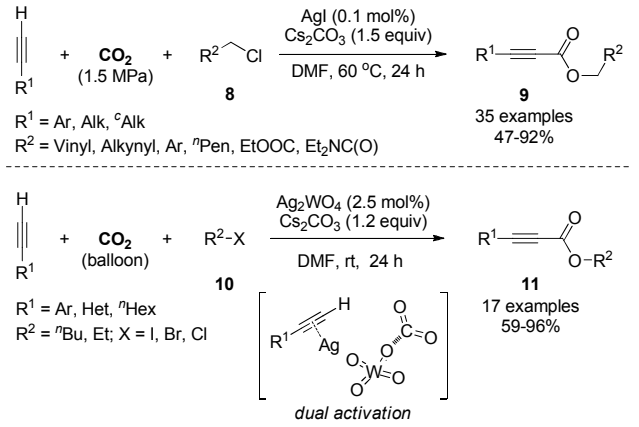
Silver(I) acetylide (R-C≡C-Ag) is generally proposed as the active catalytic species or the key intermediate in silver-catalysed alkynylation reactions. This point was also recognized in the above carboxylation of terminal alkynes with CO_2. However, the DFT studies performed recently by Luo and Zhang *et al*., disclosed an unexpected and new catalytically active species, the $[IAgCsCO_3]^-$ anion species **6-1**, rather than the conventionally considered Ph-C≡C-Ag or $AgCO_3^-$ anion (Scheme 6).[27] Aided by theoretical calculations, the authors found that the iodine anion functions as an inorganic anion ligand to promote the insertion of CO_2 into the alkyne−silver bond (**6-2**→**6-3**). The Cs_2CO_3 functioned with dual roles: as a base abstracting hydrogen from the terminal alkyne and a crucial player in generating the catalytically active species **6-1**. Thereafter, Jover and Maseras *et al*. reported similar theoretical calculation and discovered the crucial role of the solvent DMSO in acting as a ligand during the Ag(I)-catalysed carboxylation of terminal alkynes.[28]



Scheme 6

2-Alkynoates **9** could be obtained with high efficiency through a ligand-free AgI-catalysed three-component reaction of aryl- and alkyl-substituted terminal alkynes, CO_2, and various α-functionalized chloromethanes **8** such as allylic, propargylic and benzylic chlorides. Compared with the reported NHC-Cu(I) catalyst system,[29] the silver(I) catalyst exhibited substantially enhanced activity and selectivity, even at a considerably lower catalyst loading (0.1 mol% AgI) (Scheme 7).[30] Recently, Li and He *et al*. discovered Ag_2WO_4 to be an efficient Ag(I)-based bifunctional catalyst for improving the reaction under

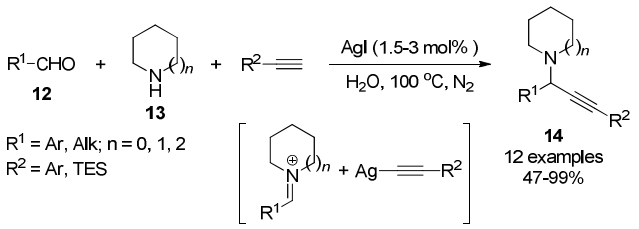
atmospheric CO_2 at room temperature.[31] Various alkynes bearing a (hetero)aryl or alkyl group with haloalkanes **10** were applized to produce 2-alkynoates **11** in good-to-excellent yields. Dual activation was proposed, *i.e.*, terminal alkyne activation by silver(I) and CO_2 activation by the tungstate anion, which was verified by nuclear magnetic resonance (NMR) spectroscopy.



Scheme 7

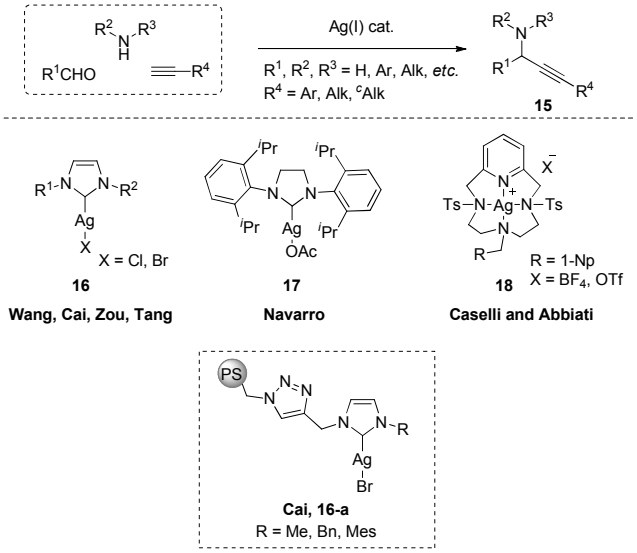
Formation of Csp^3–Csp bonds: A series of silver-catalysed reactions of alkynes using different approaches were reported with the aim of constructing Csp^3–Csp bonds. These approaches largely consist of the A^3 reaction, alkyne additions to carbonyl or imine compounds, cross-dehydrogenative-coupling (CDC) reactions and decarboxylative alkynylations with carboxylic acids. Alkynylated products resulting from these transformations have widespread applications as substrate precursors and intermediates in many synthetic derivatization reactions.

A^3-coupling, a three-component coupling reaction between aldehydes, alkynes and amines has been recognized as a convenient and general approach for producing propargylamines.[32] The coinage metals ($Cu^{I/II}$, Ag^{I}, $Au^{I/III}$) all have been investaged and efficiently promoted the A^3 reactions. In 2003, Li *et al.* successfully developed the first silver-catalysed A^3-coupling reaction (Scheme 8), which was particularly suitable for aliphatic aldehydes compared with the copper or gold catalyst syetems. This procedure was compatible with a wide variety of substrates, including aromatic/aliphatic aldehydes **12**, cyclic dialkylamines **13** and terminal alkynes, efficiently affording the propargylamines **14** in good yields (47–99%).[33] Mechanistically, the addition of silver acetylide to the iminium ion was assumed to be the key step. Shortly after, the same group improved this methodology by performing the reaction using an ionic liquid as the reaction medium, thus expanding the reaction scope to dialkyl and alkylaryl amines.[34]



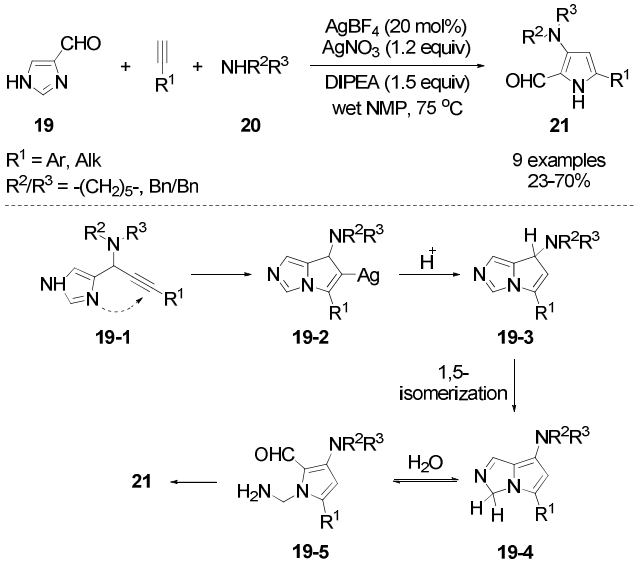
Scheme 8

Following Li's pioneering work, the silver-based A^3-coupling reaction was extensively studied by other research groups,[35] who primarily focused on elucidating the effects of other silver salts as catalysts (Scheme 9).[36] These endeavours have resulted in remarkable improvements in the A^3 reaction in terms of the substrate scope and reaction efficiency, as well as for catalyst recycling. Particularly, the silver(I)-NHC complexes **16** and **17** exhibited superior catalytic potency. For example, polystyrene-supported N-heterocyclic carbene–silver complexes [PS-NHC-Ag(I)] **16-a** reported by Cai *et al*. were highly effective for A^3 reaction under room temperature that could be easily separated and recycled for several runs without a significant decrease in catalytic activity. Recently, a class of the most robust catalyst tetraaza-macrocyclic silver complexes **18** were discovered by Caselli and Abbiati *et al.*; these catalysts were compatable with a much broader scope of substrates, even the challenging anilines and ketones.[37]



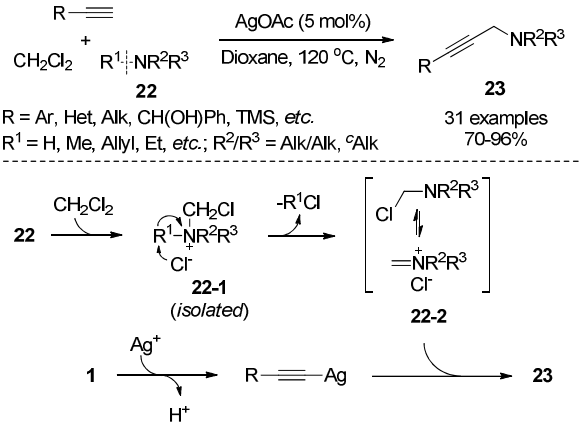
Scheme 9

To construct multi-functionalized molecules, the silver-based A^3-coupling reaction provided an attractive platform for developing tandem reactions, particularly for the synthesis of *N*-/*O*-containing heterocycles. Indeed, this was demonstrated by the successful synthesis of dihydrobenzofurans,[38] aminoindolizines,[39] chromeno[3,4-*c*]pyridin-5-ones,[40] and quinolines.[41] In 2011, Liu and co-workers described a silver-based A^3 reaction of imidazole aldehydes **19**, secondary amines **20** and terminal alkynes, which resulted in unexpected products, pyrrole-2-carboxyaldehydes **21** (Scheme 10).[42] The reaction likely occurred *via* the initial formation of A^3-coupling product **19-1** followed by an intramolecular annulation to produce intermediate **19-2**, which was then transformed into intermediate **19-3** by protonation. Subsequently, an unusual imidazole ring opening occurred *via* sequential 1,5-isomerization to afford **19-4** and hydrolysis to afford **19-5**. Finally, hydrolysis of **19-5** afforded the product **21**.



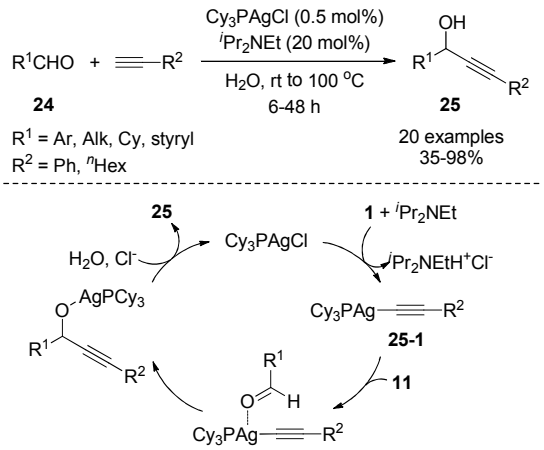
Scheme 10

Similar to the A^3 reaction, another three-component coupling reaction between terminal alkynes, dichloromethane (CH_2Cl_2) and secondary/tertiary amines **22** under silver catalysis was developed by Zhou and Yin in 2014, which allowed for the synthesis of propargylamines **23** in good to excellent yields (70–96%) without the use of exotic bases, co-catalysts or additives (Scheme 11).[43] Mechanistically, this three-component coupling reaction proceeded through the initial formation of a methaniminium chloride intermediate **22-1** *via* a substitution reaction of CH_2Cl_2 with a tertiary amine, the subsequent decomposition of **22-1** *via* R^1Cl dislocation to afford the methylene ammonium chloride **22-2**, and the final reaction with silver acetylide to afford the product **23**, with regeneration of the Ag(I) catalyst.



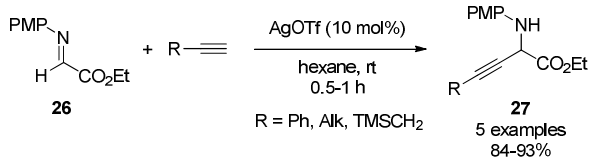
Scheme 11

In 2005, Li and co-workers discovered that a phosphine ligand could serve as a remarkable chemo-switch for the silver-catalysed A^3 reaction in water. Rather than regular A^3-coupling products, aldehyde-alkyne two-component addition products **25** were exclusively produced, in the presence of a phosphine ligand (Cy_3P) (Scheme 12).[44] It is already known that alkynyl silver reagents are typically too stable to participate in nucleophilic addition to carbonyl compounds. Consequently, the authors postulated that the coordination of the electron-donating P-ligand increased the electron density on silver to weaken the Ag–C bond of silver acetylide **25-1**. A variety of aldehydes **24** with aryl, alkyl and styryl substitutents were well-tolerated. The Li group later expanded this silver-catalysed nucleophilic addition of terminal alkynes to ketones, such as trifluoromethyl ketones, cyclic ketones and isatins in water.[45] Recently, Yao and co-workers prepared a TiO_2-supported silver nanoparticle that was shown to be an effective catalyst for the direct aldehyde-alkyne addition in the presence of catalytic amounts of phosphine ligand (PPh_3) and tertiary amine (Et_3N).[46] Notably, this methodology has been exploited in the construction of diverse heterocyclic frameworks by tandem alkynylation/cyclization reactions of *ortho*-amino/-hydroxyaryl aldehydes/ketones with terminal alkynes.[47]



Scheme 12

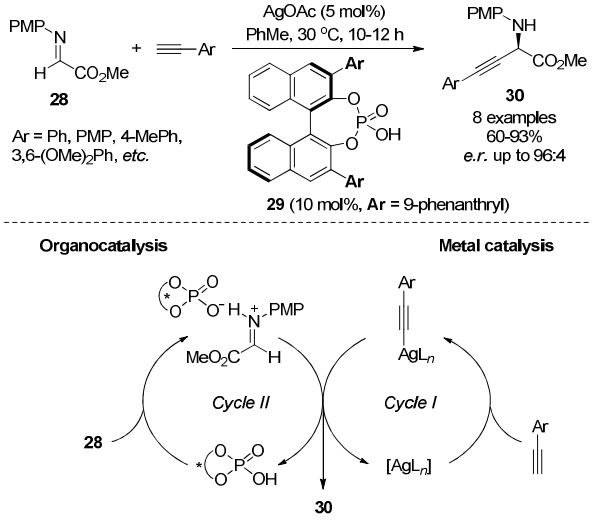
The nucleophilic addition of terminal alkynes to imines is an alternative pathway for producing propargylamines. The first silver-catalysed protocol for the direct alkynylation of *N*-PMP α-imino esters **26** with terminal alkynes was described by Chan and co-workers in 2004. This protocol provided an efficient and practical method for synthesizing β,γ-alkynyl α-amino acids **27** under mild reaction conditions (Scheme 13).[48] Among the silver salts tested, AgOTf, $AgPF_6$, $AgClO_4$ and $AgNO_3$ in hexane all produced considerable yields, whereas AgOAc only resulted in a small amount of products.



Scheme 13

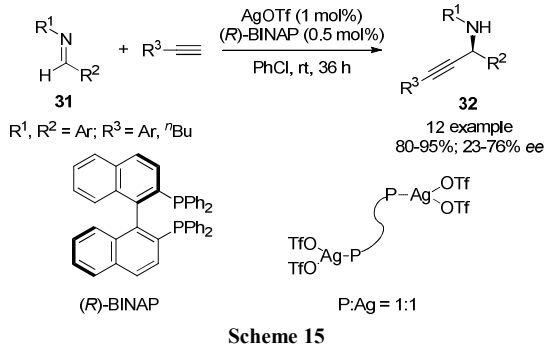
Chiral propargyl amines are important building blocks for the synthesis of natural products, plant pesticides, and pharmaceuticals.[49,33b] The asymmetric alkynylation of imines is an ideal route for producing these important compounds; however, available methods for their generation remain scarce. In 2007, Rueping *et al.* reported a silver-catalysed enantioselective alkynylation of α-imino esters **28** with aryl-substituted terminal alkynes using a chiral binol hydrogen phosphate **29** (binol = 1,1'-bi-2-naphthyl). The reaction afforded chiral propargylamines **30** with high yields (60–93%) and enantioselectivity (*e.r.* up to 96:4)

(Scheme 14).[50] This protocol represents the first addition of organometallic compound to aldimine under dual catalysis, leading to the further establishment of novel cooperative catalytic models based on chiral Brønsted acids and metal catalysts.[51] Nevertheless, this methodology still suffers from disadvantages, such as the limited substrate scope of electron-rich aryl-substituted alkynes. For the mechanism, the authors proposed an approach that combines two well-differentiated and parallel catalytic cycles, *i.e.*, the addition of metallic alkynylides to imines (cycle **I**) and the use of chiral Brønsted acids as chiral imine activators (cycle **II**).



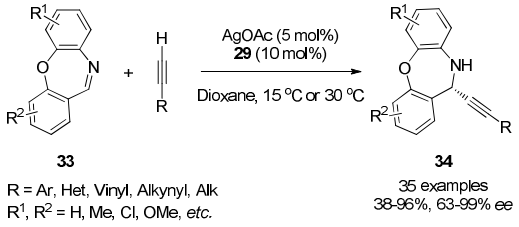
Scheme 14

Recently in 2014, Chen and Shi *et al*. reported another asymmetric version for propargylamines **32** from the more general imines such as Schiff bases **31**, using (*R*)-BINAP-AgOTf as a catalytic system (Scheme 15).[52] Interestingly, they discovered that the ligand-to-silver(I)-catalyst ratio (P:Ag = 1:1) played a crucial role in the reaction outcome, as no reaction was observed without ligand or with excess ligand. Although low to moderate enantioselectivity (23–76% *ee*) was obtained in most cases, their observation of a ligand effect may be important for further optimization.



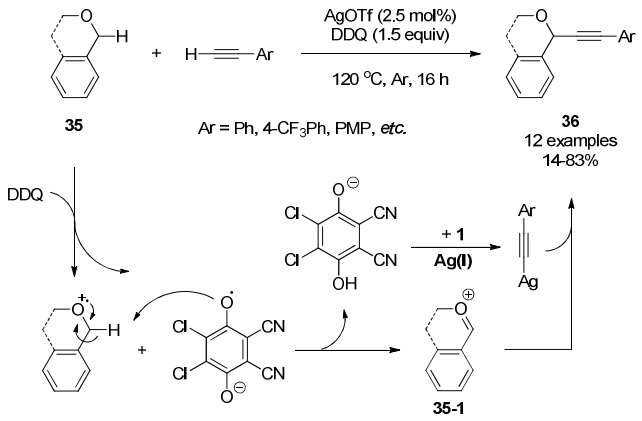
Scheme 15

Extension of the imine alkynylations to other challenging and unexplored alkynes was realized by Liu and co-workers, who demonstrated the asymmetric alkynylation of seven-membered cyclic imines **33**, catalysed by combining chiral phosphoric acid **29** and AgOAc as chiral catalysts (Scheme 16).[53] This approach provided optically active oxazepine derivatives **34** with excellent enantioselectivities. A broad scope of alkynes could be utilized in this protocol such as arylacetylenes, conjugated enynes, and 1,3-diynes.



Scheme 16

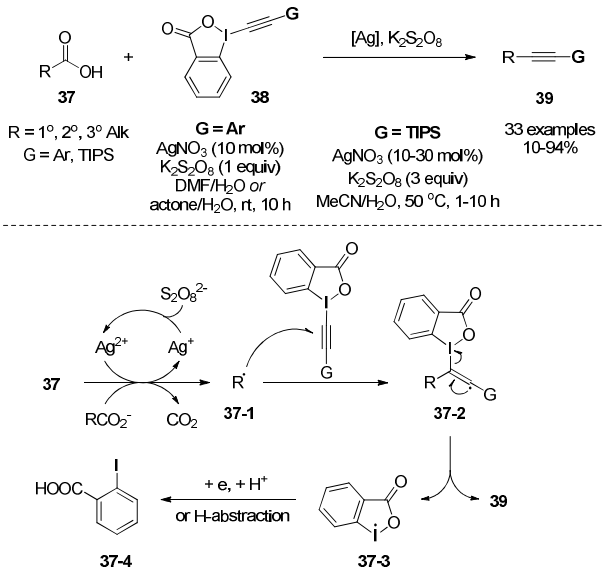
Transition metal-catalysed C–C bond formation through direct C–H bond activation has attracted considerable attention from organic chemists in recent years.[54] In 2010, the Li group developed the first silver-catalysed cross-dehydrogenative-coupling (CDC) protocol to access propargyl ethers **36** from terminal alkynes and benzylic ethers **35**. The reaction proceeded smoothly using 2,3-dichloro-5,6-dicyanoquinone (DDQ) as an oxidant at 120 °C under an argon atmosphere (Scheme 17).[55] Isochroman appeared to be the best benzylic ether substrate for this reaction, as acyclic methyl benzyl ether resulted in poor yields. In comparison with $Cu(OTf)_2$, AgOTf exhibited much better catalytic activity for different alkynes. A plausible reaction mechanism was proposed involving a benzoxy cation **35-1** derived from benzylic ether **35** by a single electron transfer with DDQ and H-radical abstraction.



Scheme 17

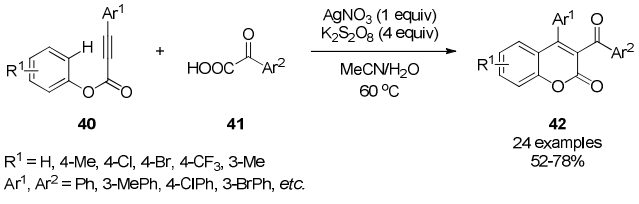
Compared with nucleophilic and electrophilic alkynylations,[1] the radical version of alkynylations has received substantially less attention. Furthermore, the reported radical methods rely heavily on the use of alkynylsulfones as alkynylating agents. A remarkable advance in this direction was achieved by Cheng and Li *et al*. in 2012, who described the silver-catalysed radical decarboxylative alkynylation of primary/secondary/tertiary aliphatic carboxylic acids **37** using commercially available ethynyl benziodoxolones **38** in an aqueous solution (Scheme 18).[56] This radical-type Csp^3–Csp cross-coupling was compatible with a variety of functional groups and exhibited high levels of chemo- and stereoselectivity. Mechanistically, the oxidation of Ag(I) by persulfate ($K_2S_2O_8$) occurred first to generate the Ag(II) ion, which then underwent single-electron transfer reaction (SET)

with a carboxylate to produce the carboxyl radical. Rapid decarboxylation of the carboxyl radical afforded the corresponding alkyl radical **37-1**. Addition of the alkyl radical **37-1** to the triple bond of **38**, followed by subsequent β-elimination of the adduct radical **37-2**, afforded the final products **39**, along with the formation of benziodoxolonyl radical **37-3**. 2-Iodobenzoic acid **37-4** was then produced from **37-3** *via* either hydrogen abstraction or a reduction−protonation sequence. Following this report, a double decarboxylative cross-coupling reaction of cinnamic acids or phenylpropiolic acid with aliphatic acids by cooperitive $AgNO_3$ and copper(0) catalystic system was reported by Mai, Sun and co-workers, who also proposed a radical mechanism.[57]



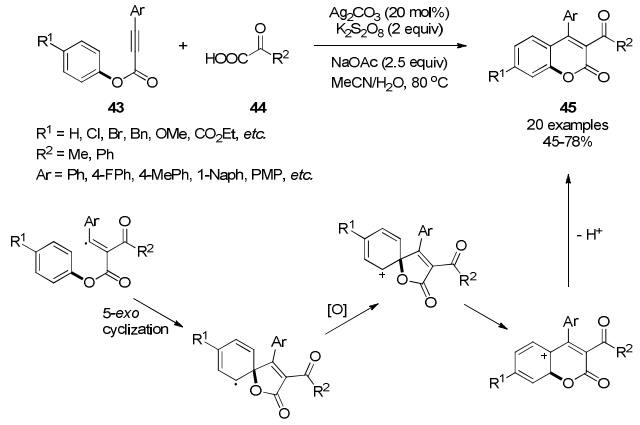
Scheme 18

Combination of the silver(I) salt and $K_2S_2O_8$ in decarboxylation reactions provides an efficient route to generate radical that could take part in radical cascade reactions. This methodology for radical insertion and 6-*endo* cyclization of alkynoates in a tandem manner has been established to produce coumarin derivatives. Following this strategy, the group of Yang and Wang recently reported the synthesis of coumarins **42** with high yields from alkynoates **40** and α-keto acids **41** *via* a $AgNO_3$-mediated, $K_2S_2O_8$-oxidized radical reaction, resulting in the formation of two C–C bonds in one operation (Scheme 19).[58]



Scheme 19

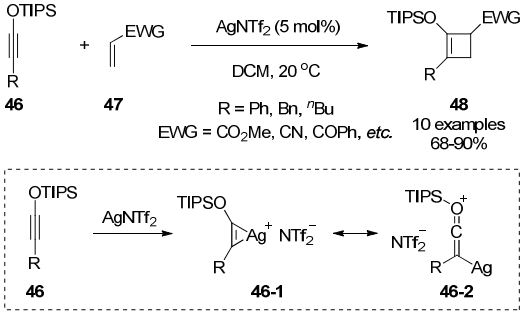
In contrast, Ding and Qiu *et al*. reported a Ag_2CO_3-catalysed radical tandem cyclization of alkynoates **43** with aryl- and alkyl-substituted 2-oxoacetic acids **44**, that involved sequential radical acylation, 5-*exo* cyclisation, ester migration and aromatization, delivering a series of 3-acylcoumarins **45** in 45–78% yields (Scheme 20).[59] Note that the presence of NaOAc resulted in significant increase of product yields.



Scheme 20

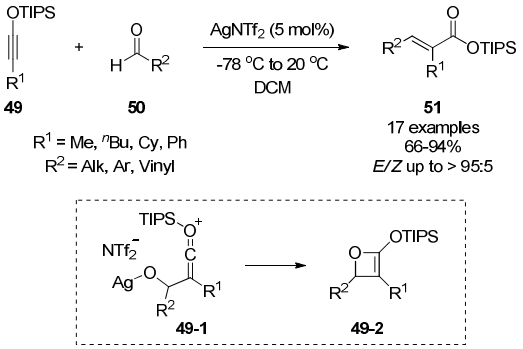
2.2 Cycloaddition and Cyclization

In 2004, Kozmin and co-workers discovered the first silver-catalysed [2 + 2] cycloaddition reaction between siloxy alkynes **46** and various α,β-unsaturated ketones, esters, and nitriles **47**, which resulted in the formation of cyclobutenes **48** (Scheme 21).[60] The authors identified $AgNTf_2$ (Tf = triflyl) as a unique catalyst for the activation of electron-rich siloxyalkynes **46**. The catalytic role of $AgNTf_2$ was likely due to complexation and activation of the siloxy alkyne **46** to form active silver–alkyne complex **46-1** and tautomer **46-2**, which were confirmed by low-temperature NMR, whereas AgOTf did not show the similar effect. The complex **46-1** and tautomer **46-2** could undergo various nucleophile-based transformations, such as cycloaddition[61] and hydrofunctionalization.[62]



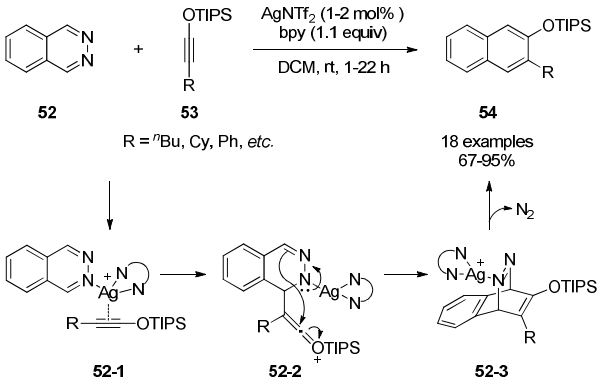
Scheme 21

For example, the chemo- and diastereoselective carbonyl olefination between aldehydes **50** and siloxy alkynes **49** was demonstrated by Kozmin *et al*. in 2010, which afforded trisubstituted unsaturated esters **51** in 64–94% yields in the presence of 5 mol% $AgNTf_2$ (Scheme 22).[63] This reaction represents an alternative to the widely utilized Horner–Wadsworth–Emmons reaction, and the mechanism may involve sequential [2 + 2] cycloaddition and conrotatory electrocyclic ring-opening reactions by intermediates **49-1** and **49-2**.



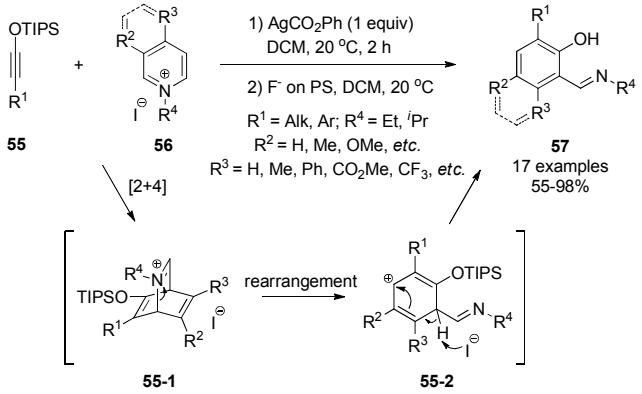
Scheme 22

As an extension, Kozmin and Rawal *et al*. developed a $AgNTf_2$-catalysed inverse electron-demanding Diels−Alder (IEDDA) reaction of 1,2-diazines **52** with siloxy alkynes **53** in the presence of 2-bipyridine (bpy) (1.1 equiv), which provided ready access to siloxy naphthalenes **54** (Scheme 23).[64] The IEDDA reaction of cyclic azadienes is a useful alternative to access heterocycles and carbocycles. However, thus far, the reported IEDDA reactions of azadienes are nearly all thermal processes and require high temperatures.[65] Very few examples of IEDDA reactions of cyclic azadienes catalysed by Lewis acids are known. Kozmin and Rawal's cycloaddition protocol proceeded under mild reaction conditions, using $AgNTf_2$ catalyst loadings as low as 1–2 mol%, affording naphthalenes **54** in 67−95% yields. Mechanistically, the coordination of Ag^+ with both phthalazine and siloxy alkyne first generates complex **52-1**; then the nucleophilic attack of the siloxy alkyne to phthalazine produces a diaza-enolate intermediate **52-2** bearing a highly reactive silyl-ketenium moiety. Following the intramolecular addition of diaza-enolate to the silyl-ketenium, a bicyclic azo intermediate **52-3** is produced, and upon spontaneous extrusion of N_2, the target naphthalene **54** is produced. Notably, a similar [4 + 2] reaction of 1,2-diazines and siloxy alkynes, using copper(I) or nickel(0) catalysis, were further developed by Rawal and co-workers. Compared with the silver catalysis, the latter protocol was less efficient and required increased catalyst loading, albeit with lower yields.[66]



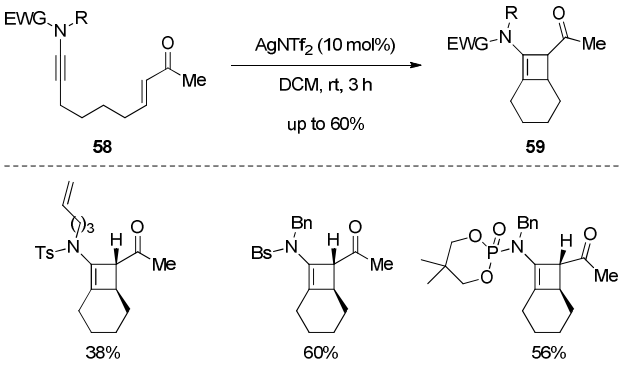
Scheme 23

In a Au(I)-catalysed [4 + 2] cyclization of isoquinoline *N*-oxides and siloxy alkynes to naphthols, pyridine *N*-oxides were unreactive.[67] Interestingly, silver salts proved to be effective and could efficiently catalyse the cyclization of various *N*-alkylpyridinium iodides and *N*-alkylisoquinolinium iodides **56** with siloxyalkynes **55**, which afforded the corresponding phenols and naphthols **57** in 55–98% yields (Scheme 24).[68] The reaction proceeded in the presence of a stoichiometric amount of silver(I) benzolate ($AgCO_2Ph$). Notably, $AgCO_2Ph$, rather than $AgNTf_2$, was shown to be effective in this reaction, which was probably due to the basity of $PhCOO^-$ ion that assisted the rearrangement of **55-1**. Similarly to the gold catalysis, a possible mechanism was proposed involving initial [2 + 4] cycloaddition and subsequent rearrangement by intermediates **55-1** and **55-2**.



Scheme 24

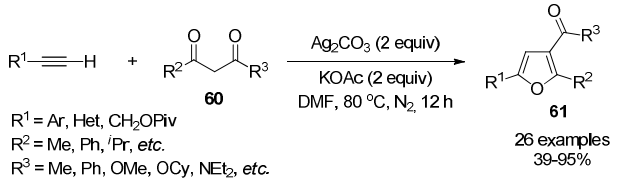
Following the previous copper(II)-catalysed intermolecular Ficini [2 + 2] cycloaddition of ynamides with α,β-unsaturated ketones,[69] the Hsung group succeeded in the first intramolecular type of *N*-sulfonyl substituted ynamide tethered to an enone motif **58** under silver catalysis, affording the thermo-induced cycloadducts bicyclo[4.2.0]oct-6-ene skeletons **59** in moderate yields (Scheme 25).[70] By screening several silver salts under identical conditions, both $AgNTf_2$ and $AgBF_4$ were effective and resulted in comparable yields.



Scheme 25

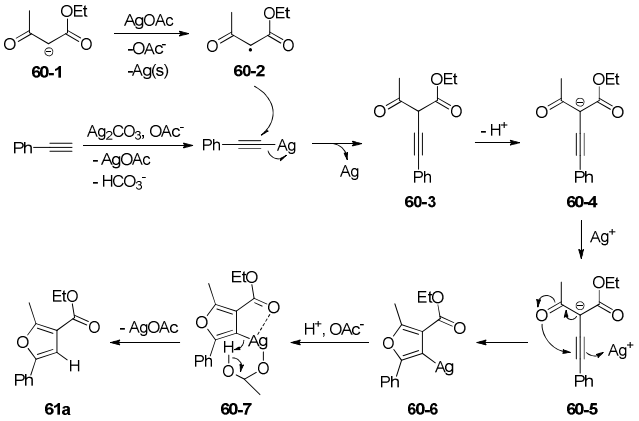
Furan is the most important member among the prevalent class of five-membered heterocycles, found in widespread available natural products, pharmaceuticals, and agrochemicals, and also represents a valuable intermediate in organic synthesis.[71] As efforts continued to develop oxidative C−C bond-forming reactions,[72] the Lei group in 2013 reported a silver-promoted oxidative C−H/C−H functionalization protocol for the construction of furan derivatives **61**, starting from the readily available 1,3-dicarbonyl compounds **60** and terminal alkynes (Scheme 26).[73] Importantly, the use of a silver(I) salt has avoided

the homocoupling of terminal alkynes that generally formed under copper catalysis. Comparing the yields of products formed with aryl alkynes, the majority of alkyl terminal alkynes did not perform well under identical conditions. Although the use of a stoichiometric amount of Ag_2CO_3 was one remarkable disadvantage of this method, Ag_2CO_3 could be recycled and reused several times without a significant loss of catalytic efficiency. Preliminary mechanistic investigations indicated that silver acetylide might be the key intermediate and that additional silver salts as oxidants are required. Nevertheless, the mechanism remained fully unclear at that time. Following this work, a silver(I)-promoted tandem addition/oxidative cyclization of 1,3-dicarbonyl compounds and alkynoates was reported by Zhang *et al*., which also produced furans.[74]



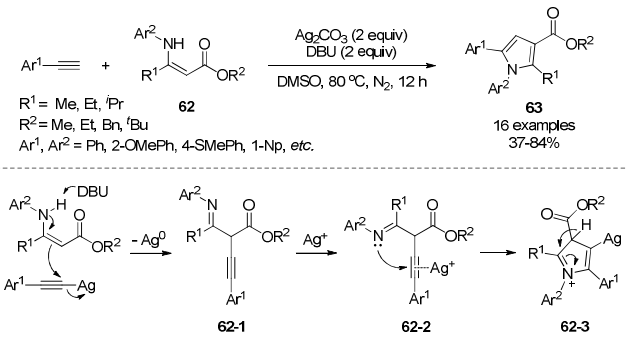
Scheme 26

To elucidate the mechanism of this intriguing silver-mediated formation of furan through oxidative coupling, Novák and Stirling *et al*. conducted DFT and experimental investigations (Scheme 27).[75] By comparing free-energy profiles, they proposed successive radical and ionic pathways: the first radical route featured the oxidation of enolate **60-1** to afford the radical intermediate **60-2** by a silver cation and subsequent radical coupling with the silver acetylide to generate the intermediate **60-3**; in the second ionic part, C–O bond formation occurred to produce the furan ring **61a** *via* intermediates **60-4** to **60-7**. In this reaction process, the silver acetylide played important roles in C–C coupling: its formation opened a favourable reaction channel for the coupling and provided the oxidizing partner (Ag^+), which transformed the radical mechanism to an ionic one, whereas in the following cyclization process, the Ag^+ only played a catalytic role. The calculations clearly confirmed the dual role of silver as both an oxidant and a catalyst, as previously postulated in Lei's report.



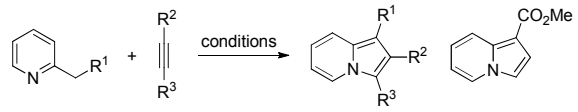
Scheme 27

This methodology of silver-mediated oxidative tandem cross-coupling and intramolecular cyclization was further expanded by Lei *et al*. to the reaction of terminal alkynes and β-enamino esters **62**, which led to the synthesis of pyrroles **63** (Scheme 28).[76] This protocol constituted an operationally simple and efficient method to produce poly-substituted pyrroles. Although little mechanistic information was known for this reaction, Lei and co-workers also proposed a plausible transformation process (intermediates **62-1** to **62-3**). However, an alternative radical mechanism that is similar to the formation of furan **61** as demonstrated by Novák and Stirling *et al*. described above, might be possible.



Scheme 28

Under similar conditions to Lei's furan synthesis, Liang and Pan *et al*. developed a silver-mediated sequential oxidative C–H functionalization and 5-*endo-dig* cyclization of 2-alkylazaarenes **64** with terminal and internal alkynes. This reaction provides a straightforward route to access biologically important indolizines **65** (Scheme 29).[77] Notably, the reaction of trimethylsilylacetylene and methyl 2-pyridylacetate resulted in the desiliconization product **65′** in 55% yield. Two different pathways were proposed that the 2-alkylazaarenes **64** underwent deprotonation and nucleophilic attack to silver acetylide intermediate, whereas the internal alkynes involved a successive radical and ionic pathway. Simultaneously, Agrawal *et al*. described the same reaction under similar conditions, focusing on terminal alkynes.[78] Notably, Ag_2CO_3 was also recycled and reused in these two reports.

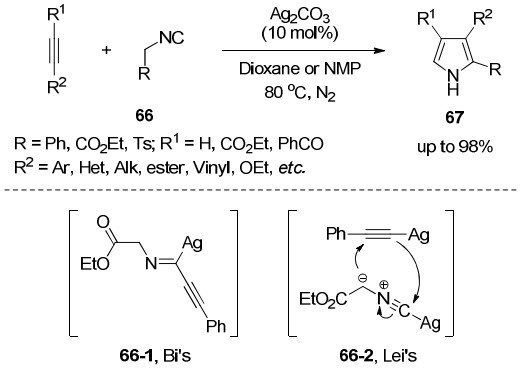


Liang, Pan, 2014	**Agrawal, 2014**
Ag_2CO_3 (2 equiv)	Ag_2CO_3 (2 equiv)
KOAc (2 equiv)	KOAc (2 equiv)
DMF, 120 °C, 12-18 h	DMF, 110 °C, 12 h
R^1 = CO_2Et, CO_2Me, CN, *etc.*	R^1 = CO_2Et, CO_2Me, CN
R^2 = H, Me, ^{n}Pr, Ph; R^3 = Ar, Het, TMS	***R*²** = ***H***; R^3 = Ar, Het
19 examples; 55-86%	15 examples; 45-89%

Scheme 29

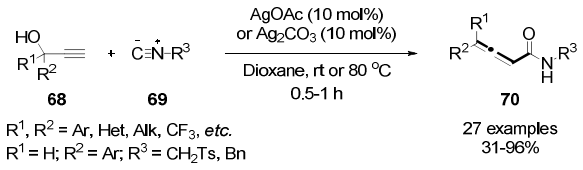
Isocyanides and alkynes are two important classes of fundamental chemicals, and their [3 + 2] cycloaddition is an ideal route to pyrrole syntheses. However, following the initial report in 1979,[79] there was a long period of silence. In 2005, a real breakthrough was achieved when effective copper catalysis was discovered independently by the groups of Yamamoto[80] and de Meijere,[81] who made this reaction more efficient and practical. Unfortunately, this protocol was not applicable to more abundant,

non-activated terminal alkynes. An attempt to address this issue was described by de Meijere *et al*. in 2009 using freshly prepared copper acetylides to react with isocyanides.[82] Obviously, this approach was not practical. In 2013, Lei's[83] and our groups[84] simultaneously reported the discovery of Ag_2CO_3 as a robust and unique catalyst for this isocyanide-alkyne [3 + 2] cycloaddition reaction for the synthesis of 2,3-disubstiotuted pyrroles **67**, which exhibited a broad substrate scope and was particularly suitable for diverse terminal alkynes (Scheme 30). This unexpected catalytic activity of Ag_2CO_3 was probably due to the basicity of counterions. Based on the experimental investigations, a plausible mechanism was proposed that involved two key steps: (1) catalytic cycling between Ag_2CO_3 and $AgHCO_3$, and (2) 1,1-insertion of isocyanides **66** to silver acetylide to afford intermediate **66-1**, thus accounting for the regioselectivity for carbon-carbon bond formation. In the meantime, Lei *et al*. described an alternative possible pathway involving the cycloaddition of two silver species **66-2**.



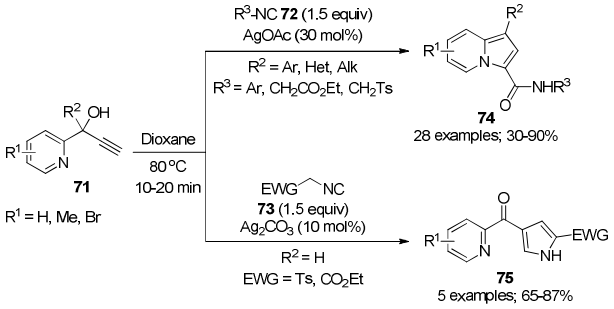
Scheme 30

Interestingly, using propargylic alcohols **68** rather than simple alkynes to react with isocyanides **69** under identical silver-catalysed conditions, our group further discovered an unexpected cross-coupling/rearrangement reaction, which generated 2,3-allenamides **70** in good to excellent yields (Scheme 31).[85] The choice of an appropriate silver catalyst appeared to be crucial for an efficient transformation, as AgOAc was found to be effective for tertiary propargylic alcohols, whereas Ag_2CO_3 was efficient for secondary propargylic alcohols. Some mechanistic investigations were performed such as ^{18}O-labeling experiment, indicating a plausible reaction sequence that involves intermolecular carbon-carbon coupling and intramolecular hydroxyl group transfer. However, the exact mechanism currently remains unclear.



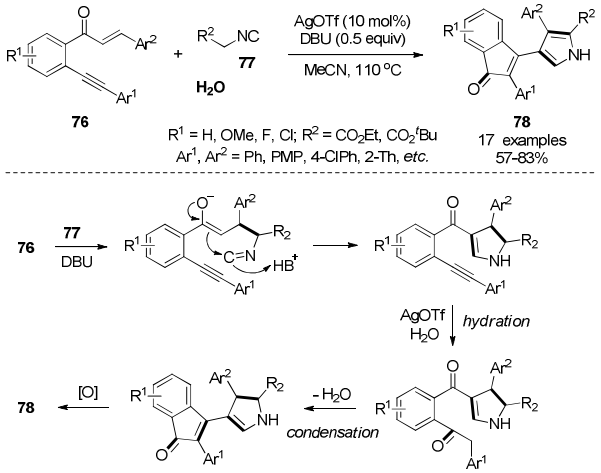
Scheme 31

By functionalizing the alkyne component, our group discovered a new silver-catalysed chemoselective cyclization reaction of 2-pyridyl alkynyl carbinols **71** with isocyanides **72** and **73**, which divergently afforded either indolizines **74** or 2,4-disubstituted pyrroles **75** by choosing appropriate terminal propargylic alcohols, *i.e.*, secondary or tertiary (Scheme 32).[86] Compared with the previous formation of 2,3-disubstituted pyrroles[83,84] the regioselective formation of 2,4-disubstituted pyrroles **75** directed by the 2-pyridyl group was noteworthy, as this proved to be a useful strategy for regulating the regioselectivity of alkynes.



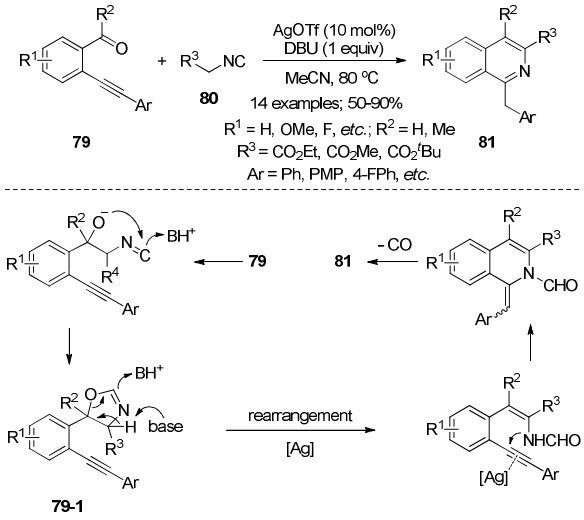
Scheme 32

In 2012, Wu *et al*. developed a DBU-promoted, AgOTf-catalysed three-component reaction of 1-(2-alkynylphenyl)-2-enones **76**, 2-isocyanoacetates **77** and H_2O, which allowed for the synthesis of 3-(1*H*-pyrrol-3-yl)-1*H*-inden-1-ones **78** in good yields (Scheme 33).[87] Several transition metal catalysts, such as palladium(II), copper(II), silver(I), gold(I), were tested and AgOTf afforded the highest yields. Notably, there are four new bonds formed *via* cascade reactions involving sequential Michael addition, intramolecular nucleophilic addition, intramolecular condensation and oxidation processes.



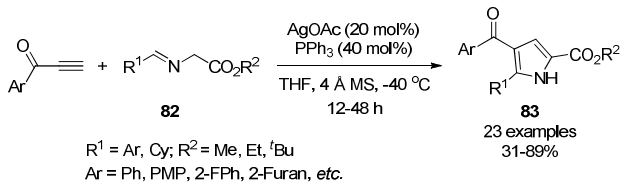
Scheme 33

The same group further extended this strategy to a tandem DBU-promoted condensation followed by a AgOTf-catalysed intramolecular cyclization reaction of 2-alkynylbenzaldehydes **79** and 2-isocyanoacetates **80**, allowing for the smooth preparation of isoquinoline derivatives **81** (Scheme 34).[88] The formation of an oxazole ring intermediate **79-1** was proposed as a key step in the reaction mechanism.



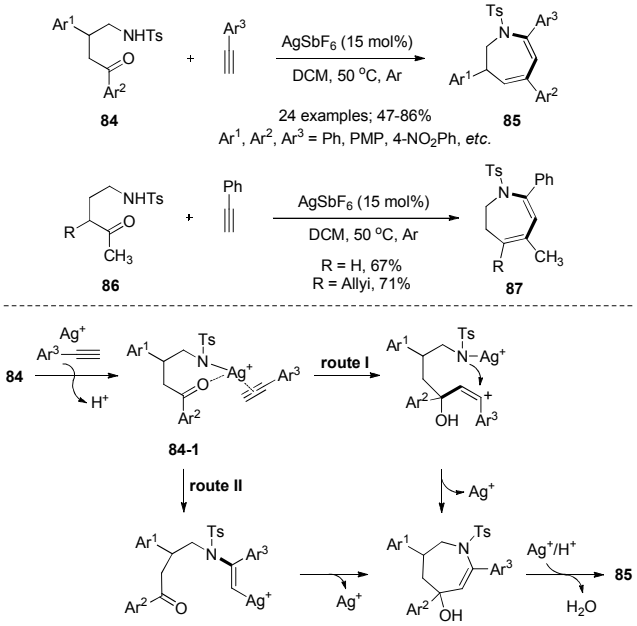
Scheme 34

In 2013, an intermolecular [3 + 2] cycloaddition of *in situ* formed glycine-derived azomethine ylide **82** with ynones was developed by Deng *et al*. using AgOAc (20 mol%) and Ph_3P (40 mol%) catalyst system, leading to the corresponding 2,3,5-trisubstituted pyrroles **83** in 31–89% yields (Scheme 35).[89]



Scheme 35

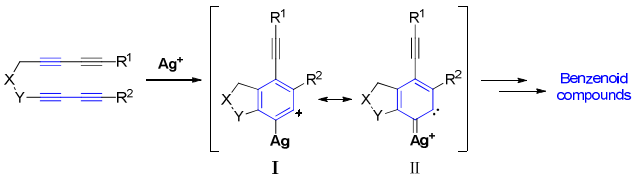
One-step construction of a seven-membered ring system *via* a two-component reaction is always a challenging task. Recently, Li *et al*. established an efficient method for the synthesis of 2,3-dihydro-1*H*-azepines **85** *via* the silver-catalysed [5 + 2] cycloaddition of γ-amino ketones **84** with alkynes (Scheme 36).[90] This protocol allowed the formation of seven-membered ring systems along with the release of H_2O as the only by-product. $AgSbF_6$ proved to be effective, whereas other examined silver salts, metal catalysts, and Brønsted acids resulted in trace amounts of products. The reaction was applicable to a range of γ-amino ketones, even the simple aliphatic γ-amino ketones **86**, which afforded azepines **87** in high yields. However, under identlcal conditions, the alkyne scope was mostly limited to aryl terminal alkynes; aliphatic alkynes did not participate in the reaction, whereas internal alkynes produced low yields. In addition, the *N*-Ts group appeared to be essential because other protecting groups, such as *N*-PhCO or -Me groups, did not exhibit any reactivity. Nevertheless, the significance of the azepine skeleton as an important structural element rendered this method particularly attractive to synthetic and medicinal chemists. The plausible reaction mechanism was proposed by Li *et al*., which involved two possible routes after the formation of complex **84-1**.



Scheme 36

2.3 Reactions *via* Arynes

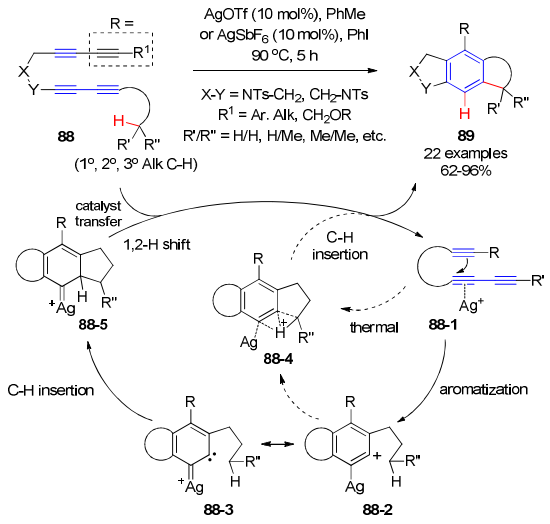
Hexadehydro-Diels–Alder reaction (HDDA): The HDDA reaction was initially termed by Hoye based on analogy to other dehydropericyclic reactions.[91] Over the past years, the Hoye and Lee groups have rapidly developed a host of reaction motifs that showcase both the unique reactivity of arynes and the potential of the HDDA reaction in arene synthesis.[92] One of the impressive advances in this area is the discovery by the Lee group of the unique activation effect of silver catalysts toward bis-1,3-diynes, which generates an intermediate viewed as a metal-stabilized aryl cation **I** or a 1,2-bis-carbene-carbenoid canonical form **II** (Scheme 37). Unlike free arynes, these metal-complexed arynes are subtly balanced between stability and reactivity, allowing them to effectively participate in a variety of inter- and intramolecular transformations, thus providing new approaches for producing valuable benzenoid compounds.



Scheme 37

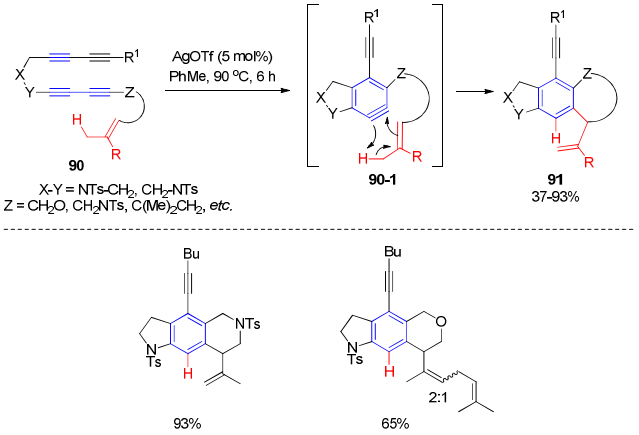
The first silver-catalysed HDDA reaction of ynamide-tethered bis-1,3-diynes **88** was developed by the Lee group in 2013 (Scheme 38).[93] They found that this approach constituted a new type of silver-catalyzed C–H bond functionalization by *in situ* generated aryne intermediates, in which unactivated 1°, 2° and 3° C–H bonds were effectively added across the π-bond of arynes. Both symmetrical and asymmetrical bis-1,3-diynes were suitable for the HDDA reaction. By screening Lewis acids catalysts in the presence of tetraynes containing secondary C–H bond, silver(I) salts such as AgOTf, $AgSbF_6$ and AgOAc afforded comparable yields. While other metal salts such as $Cu(OTf)_2$, $Zn(OTf)_2$ and $Sc(OTf)_3$ were less efficient, and $Au(PPh_3)Cl$ and $PtCl_2$ even

failed to yield the product. It was found that bis-1,3-diynes with secondary and tertiary C–H bonds participated in HDDA C–H bond insertion by AgOTf catalysis in toluene, whereas the reaction of bis-1,3-diynes with a primary C–H bond prefered by $AgSbF_6$ catalysis in iodobenzene, which was probably due to $AgSbF_6$ possessing higher Lewis acidity than AgOTf. The corresponding products **89** were obtained in 62–96% yields. Mechanistically, a sequence of bond-forming events from the initial silver-complex **88-1** leads to a key silver-complexed aryne intermediate **88-2** or its resonance form **88-3**, which then undergoes C−H insertion by intermediate **88-4** or [1,2]-hydride shift by another intermediate **88-5** to afford the product **89**.



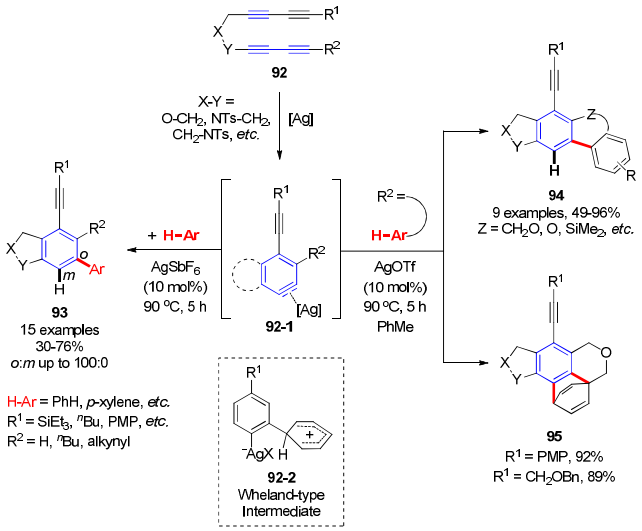
Scheme 38

The same group later extended this protocol by introducing an alkene moiety terminally into bis-1,3-diynes **90** and developed an intramolecular tandem HDDA/Alder-ene reaction by silver catalysis to produce benzenoids **91** in 37–93% yields (Scheme 39).[94] The position of the tethered heteroatom connecting both 1,3-diynes exhibited the greatest impact on the reactivity of the substrate **90**. Moreover, the tether size and the substitutent on the alkene moiety significantly affected both the HDDA reaction and the subsequent Alder-ene reaction of arynes **90-1**, thereby influencing the tandem ring closing effiency and the product yield.



Scheme 39

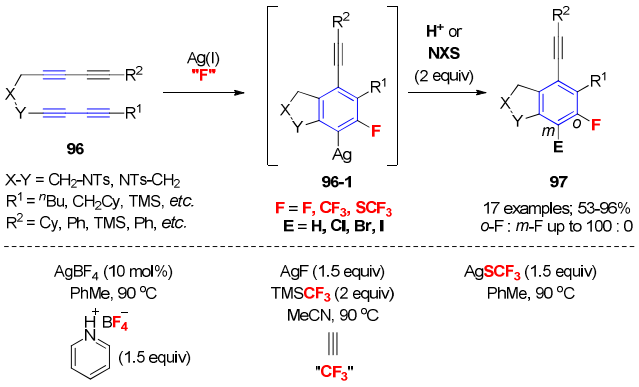
Xia and Lee further applied this silver-catalysed HDDA method towards the intra/intermolecular aromatic C–H bond functionalization reaction of bis-1,3-diynes **92**, which provided a new strategy for the synthesis of biaryls **93** and **94** (Scheme 40).[95] The regioselectivity of C–H insertion into aryne intermediates **92-1** in intermolecular hydroarylation was significantly directed by steric and electronic factors of the aryne intermediates, leading to biaryls **93**. Notably, the electronic factor in the arenes also played a crucial role in successful hydroarylation; for example, strongly electron-rich or electron-deficient arenes resulted in very low yields (*e.g.*, PhOMe: ~10%; PhCl: ~10%). The intramolecular Csp^2–H insertion was limited to products **94** with the formation of five- and six-membered rings, whereas an intramolecular Diels−Alder reaction occurred to afford products **95** if longer tether-containing systems were used. A plausible stepwise hydroarylation of arynes, involving electrophilic aromatic substitution rather than direct insertion of the Csp^2–H bond of arenes, was proposed from deuterium scrambling experiments. Furthermore, DFT calculations suggested that the reaction proceeded through a Wheland-type intermediate **92-2**, followed by water-catalysed proton transfer in the final step.



Scheme 40

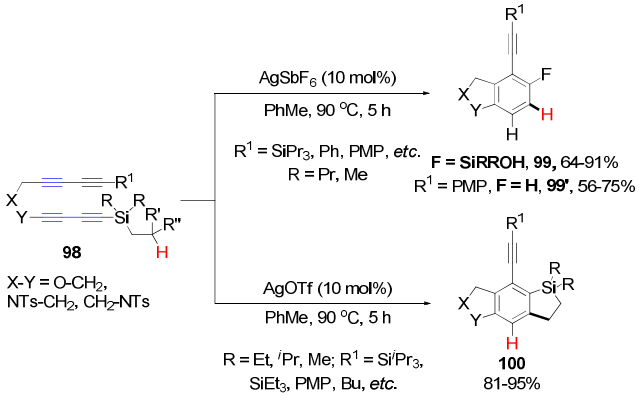
General approaches for fluorination, trifluoromethylation, and trifluoromethylthiolation were developed by Lee *et al*. based on

the electrophilic nature of the aryne. These transformations were successfully achieved through the addition of fluorine-containing nucleophiles onto aryne intermediates under either silver-catalysed or silver-promoted reactions of tetraynes **96** (Scheme 41).[96] Considering the substituent effect on the regioselectivity of fluorination, the electronic effect of silicon overrides its steric disadvantage to produce *ortho*-F/CF_3/SCF_3 substituted products **97**. In addition to protons (H^+), other appropriate electrophiles could also trap the organosilver intermediate **96-1**. For example, in the presence of $AgBF_4$ (1.5 equiv) and *N*-halosuccinimide (Cl, Br, I, 2 equiv), 1,2-bis-halogenated products **97** were obtained directly from tetraynes **96** in good yields. $AgBF_4$ played a vital role in the reaction, whereas other silver/copper/gold catalysts either produced poor yields or were ineffective. In contrast to previous methods requiring an aromatic precursor, the current method enabled the non-traditional synthesis of Ar–F, Ar–CF_3 and Ar–SCF_3 from nonaromatic building blocks under relatively mild conditions. Afterwards, the Hoye group revealed a HDDA/dichlorination reaction of acyclic triynes with excess Li_2CuCl_4, resulting in the dichlorinated aromatic compounds. They discovered the product yields heavily relied on the concentration of Li_2CuCl_4.[97]



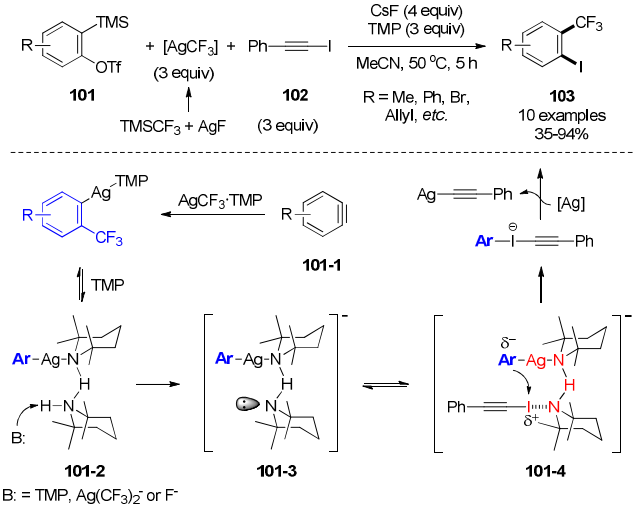
Scheme 41

Most recently in 2014, Lee *et al*. reported a novel silver-catalysed HDDA/alkylation protocol for silyl-substituted bis-1,3-diynes **98** (Scheme 42).[98] Interestingly, trialkylsilyl-bis-1,3-diynes **98** with silyl-attached 2°- and 3°-alkyl C–H moieties underwent hydride transfer reactions in the presence of $AgSbF_6$ (10 mol%) in toluene, affording hydrogenated products **99** in 64–91% yields, whereas bis-1,3-diyne-tethered primary silyl C–H bonds interestingly followed a C–H insertion pathway by AgOTf catalysis, providing fused tricyclic products **100** in 81–95% yields. Note that the unsymmetrical bis-1,3-diynes **98** afforded desiliconization products **99'**, due to the PMP substituent at R^1 enhanced the electron density of the initial generated aromatic ring. The reaction mechanism involved 1,5-hydride transfer from the β-carbon of the silyl group onto aryne intermediates.



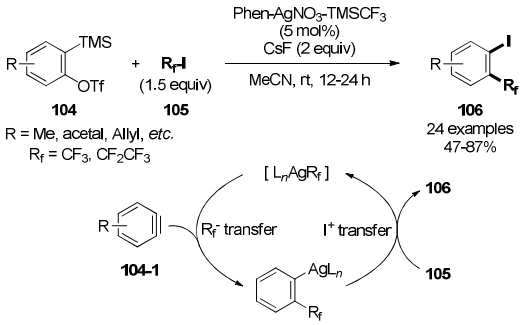
Scheme 42

1-Trimethylsilyl-2-Aryl Triflates: Compared with the HDDA pathway, the generation of aryne intermediates through the base-promoted elimination of 1-trimethylsilyl-2-aryl triflates is more general.[99] Recently, the Hu group reported a silver-mediated trifluoromethylation-iodination of arynes **101-1** *via* the reaction of 1-trimethylsilyl-2-aryl triflates **101**, 1-iodophenylacetylene **102** and $AgCF_3$, which was generated *in situ* from $TMSCF_3$ and AgF, in the presence of 2,2,6,6-tetramethylpiperidine (TMP) as a hindered ligand (Scheme 43).[100] Notably, instead of $AgCF_3$, other CF_3 sources such as $CuCF_3$ and $Zn(CF_3)_2$ all failed in the reaction. This method provided a convenient route for producing trifluoromethylated iodoarenes **103**, which were otherwise difficult to synthesize. A reaction mechanism was proposed by Hu *et al*. involving key transformations of intermediates **101-2**, **101-3** and **101-4** on a hydrogen-bonding-linked TMP dimer. The effects of TMP as a privileged ligand for the reaction was attributed to the following: (i) increasing the electron density on Ag and thus enhancing the nucleophilicity of $AgCF_3$; (ii) reducing the energy barrier of the iodination step *via* intermediate **101-4**, owing to the six-membered ring formed by hydrogen and halogen bonding; and (iii) enhancing the rigidity of the transition state and therefore increasing the proximity of the aryl group and the iodine atom. Apart from the efficient installation of CF_3 and I groups, significant disadvantages could still be observed, such as the use of excess amounts (3 equiv) of $AgCF_3$ and 1-iodophenylacetylene **102** and the release of large quantities of silver phenylacetylide as a by-product. These disadvantages left room for further improvement.



Scheme 43

Indeed, by using perfluoroalkyl iodides (R_fI) **105** as an iodine source, the Hu group later reported a catalytic process for the vicinal trifluoromethylation–iodination of arynes with catalytic amounts of silver species (Scheme 44).[101] This protocol provided easy access to *ortho*-perfluoroalkyl iodoarenes **106** from arynes precursors **104** under very mild conditions. Preliminary mechanistic investigations indicated that a radical or SET pathway was not likely. Consequently, an ionic atom-transfer reaction of R_fI **105** was proposed in this insertion step, whereas a silver-mediated metathesis process was involved in efficient transfer of the electropositive iodine atom. This protocol for the formal insertion of arynes **104-1** into R_f-I bonds under silver(I) catalysis represented the first example of ionic atom-/group-transfer reactions of both perfluoroalkyl and iodine groups from R_fI into a single molecule.



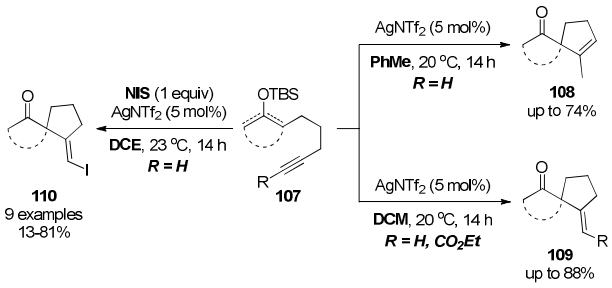
Scheme 44

2.4 Cycloisomerization

Silver-catalysed cycloisomerization reactions of alkynyl compounds represent an effective and straightforward methodology for forming carbocycles or heterocycles. Generally, the substrates utilized in the Ag(I)-catalysed cycloisomerization reactions structurally contain an alkyne-tethered unsaturated moiety, such as aryl, alkenyl, allenyl and alkynyl groups.[102]

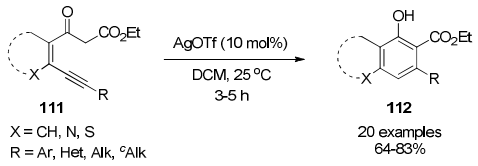
Conia-ene Reaction: The Conia-ene cyclization is a pericyclic reaction of an enolizable carbonyl group with an alkyne, leading to the formation of a quaternary carbon center.[103] However, the need for elevated temperatures limits the synthetic utility of this reaction. Alternatively, the transition metal-catalysed version of such reactions proceeds at lower temperatures, as reported by research groups such as the Toste, Davies and Detty-Mambo groups, largely based on gold catalysis;[104] however, few effective silver-catalysed protocols have been developed.

In 2012, Miesch *et al*. described an efficient $AgNTf_2$-catalysed cycloisomerization reaction of alkynylsilyl enol ethers **107**. This reaction allowed the diastereoselective synthesis of a variety of *spiro* compounds **108** and **109** *via* regioselective cyclization (Scheme 45).[105] The solvent greatly influenced both the yields and the product type. In most cases, the use of DCM as the solvent favoured the formation of 5-*exo*-regioisomers **109**, whereas the use of toluene allowed for the generation of *endo*-regioisomers **108**. The potential of this spirocyclization protocol was further highlighted by trapping an alkenyl-silver intermediate with electrophilic iodine through a one-pot reaction with *N*-iodosuccinimide (NIS), leading to *E*-alkenyl iodide derivatives **110**.



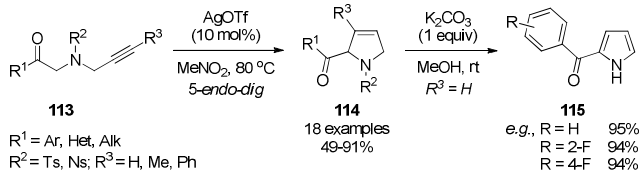
Scheme 45

Later, Verma and co-workers reported a silver-catalysed cyclization of 3-(2-alkynyl)aryl-β-ketoesters **111** for the facile and efficient synthesis of medicinally useful derivatives of acridinols, quinolinols and naphthalenols **112** at room temperature. Among the Lewis acids examined, silver salts were efficient and AgOTf afforded the best result, whereas CuOTf was not effective. The reaction proceeded *via* regioselective 6-*endo*-*dig* electrophilic cyclization (Scheme 46).[106]



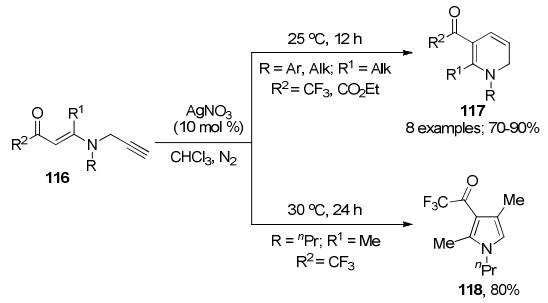
Scheme 46

In 2013, Wang and co-workers extended the protocol to monocarbonyl compounds, α-ketopropargylamines **113**, which underwent 5-*endo*-*dig* carbocyclization, affording 3-pyrrolines **114** in 49–91% yields with good functional group tolerance (Scheme 47).[107] Similar to AgOTf, $AgSbF_6$ and $AgNTf_2$ proved to be effective, whereas other Lewis acids such as Au(I), Cu(I, II), and Fe(III) did not result in the pyrrolines. The reaction was found to be compatible with both tosyl and nosyl substituents at the R^2 position but not with alkyl, aryl and acyl groups. Furthermore, the transformation of products **114** into 2-substituted pyrroles **115** was realized under base-mediated conditions.



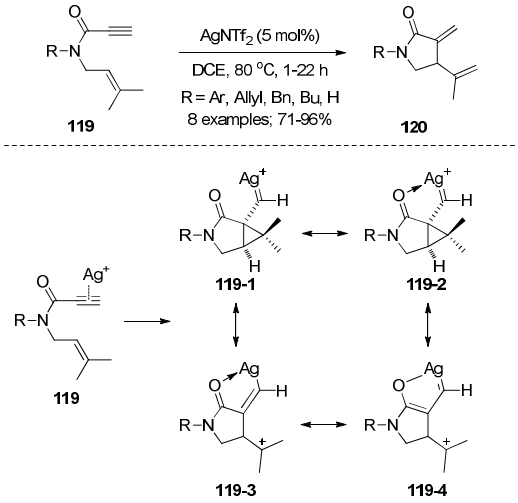
Scheme 47

Inspired by reports in the literature on transition metal-catalysed intramolecular cyclocondensation reactions, in which *N*-propargylic-β-enaminones could serve as potential precursors, Martins *et al*. investigated the possibility of the silver-catalysed Conia-ene reaction of *N*-propargylic-β-enaminones **116** (Scheme 48).[108] This reaction was successfully catalysed by $AgNO_3$ (10 mol%). The authors discovered that the terminal carbon of the triple bond was more reactive than the internal one, and it underwent nucleophilic attack by the α-carbon of the carbonyl group, thereby resulting in 1,2-dihydropyridines **117**. Interestingly, the reaction of *N*-propargylic β-enaminone **116** with subtle variation in the substituents (R = ^{n}Pr, R^1 = Me, R^2 = CF_3) resulted in the formation of a pyrrole **118** in 80% yield.



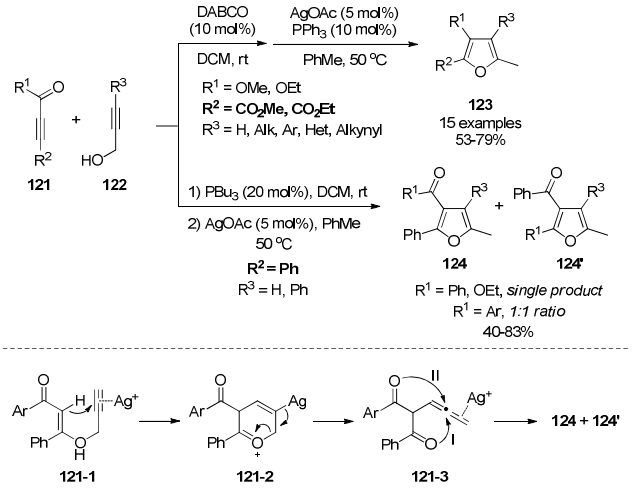
Scheme 48

Enynes: Enynes could serve as prototypical substrates for transition metal-catalysed (such as by Ru, Rh, Pd, Pt, Ir and Au) atom-economical construction of numerous new chemical entities.[102a,109] The electrophilic activation of alkyne moieties could lead to Alder-ene-type dienes.[110] In this direction, in 2012, Shin and co-workers explored the silver-catalysed cycloisomerization of propiolamide-derived 1,6-enynes **119**, leading to the selective formation of Alder-ene-type 1,4-dienes **120** at room temperature (Scheme 49).[111] Improved catalytic performance of $AgNTf_2$ compared with expensive gold or platinum salts was found. The presence of a carbonyl group in combination with silver salts was essential for the selective formation of 5-*exo-dig* 1,4-diene products. Based on the reaction profile, β-oxo-coordinated silver carbenoids **119-1~119-4** were proposed as possible intermediates.



Scheme 49

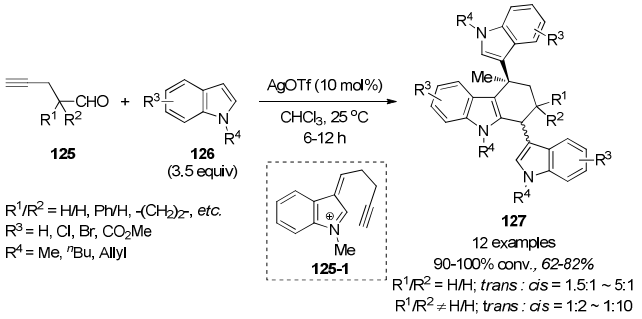
Following the previous report on the synthesis of α-carbonyl furans *via* copper-catalyzed three-component reaction of diethyl but-2-ynedioate, propargylic alcohols and oxygen molecule under open-air conditions,[112] in 2009, Jiang *et al*. reported a one-pot synthetic methodology for producing polysubstituted furans **123** by the domino reaction of DABCO-catalysed Michael addition and silver(I)-catalysed intramolecular cyclization reactions of electron-deficient alkynes **121** and ethynyl carbinols **122** (Scheme 50).[113] For the reaction scope, in contrast to but-2-ynedioates, which afforded single isomers **123**, aryl alkynyl ketones ($R^1 \neq$ Ph, OEt) afforded a pair of regioisomeric furans **124** and **124'** catalysed by PBu_3 and AgOAc. A plausible reaction mechanism was proposed, as an eneyne adduct **124-1** underwent sequential 6-*endo-dig* cyclization and rearrangement through intermediates **124-2**~**124-3**. If the two ketone carbonyls were different, annulation of the allene intermediate **124-3** occurred in two possible ways, I and II, accounting for the generation of regioisomeric furans **124** and **124'**.



Scheme 50

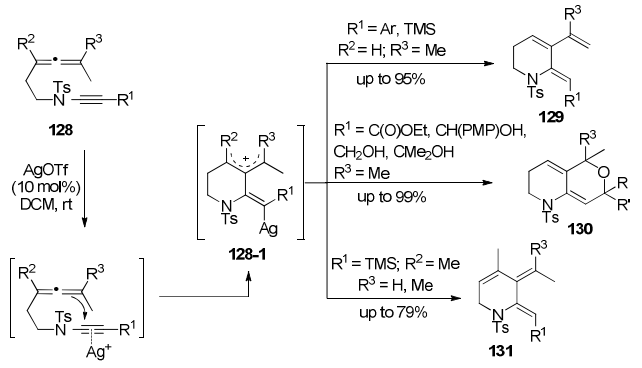
The auto-tandem catalysis of two or more mechanistically different transformations in a one-pot method has attracted a surge of interest for the development of complex molecules from simple starting materials in a highly atom-economical manner.

Carbophilic and oxophilic Lewis acid versions of silver salts that slightly prefer to form σ-coordination over π-coordination render silver salts as a class of good catalysts for auto-tandem catalysis involving the dual activation of C–O and C–C unsaturated bonds. In this context, Che and co-workers demonstrated that AgOTf efficiently catalysed the cascade reaction of acetylenic aldehydes **125** with an excess amount of indoles **126** (3.5 equiv), affording highly substituted tetrahydrocarbazoles **127** in high yields (62–82%) (Scheme 51).[114] Based on the experimental results, they determined that AgOTf catalysed the initial aldol condensation between the aldehyde moiety and indoles, leading to formation of the 3-alkylidene-3*H*-indolium cation intermediate **125-1**, which is a key intermediate, and then to the incorporation of two additional indoles during the cyclization process.



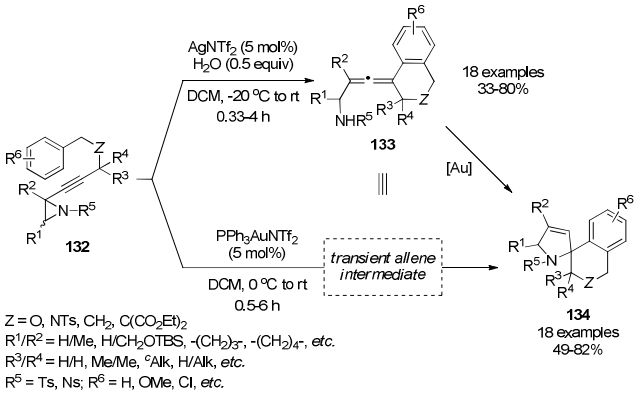
Scheme 51

Allenynes: Considering the preferential activation of the alkyne moiety in allenynes in the presence of a π-acid transition metal catalyst, Malacria, Fensterbank and Aubert *et al*. explored the cycloisomerization of 1,*n*-allenynamides, *i.e*., 1,6-allenynamides **128** by silver catalysis and obtained diverse piperidine derivatives **129**~**131** in good yields, which contained triene moieties (Scheme 52).[115] Among the π-acid transition metals tested, such as gold(I), silver(I), copper(II) and platinum(II), silver salts were shown to be the most efficient. The intermediate **128-1** evolved differently, according to the substitution patterns of both ynamide and allene units. A complete conversion of intermediate **128-1** into *Z*-Alder-ene products **129** occurred if the allenynamides **128** contained steric hindrance groups, *e.g.*, aryl group, whereas substrates bearing propargylic alcohol or ester moieties afforded fused piperidines **130**. A simple methyl substitution at the internal position (R^2 = Me) or a mono-substituted group at the external allene carbon prioritized the production of isomeric cross-conjugated trienes **131** with an exocyclic 1,2-diene moiety.



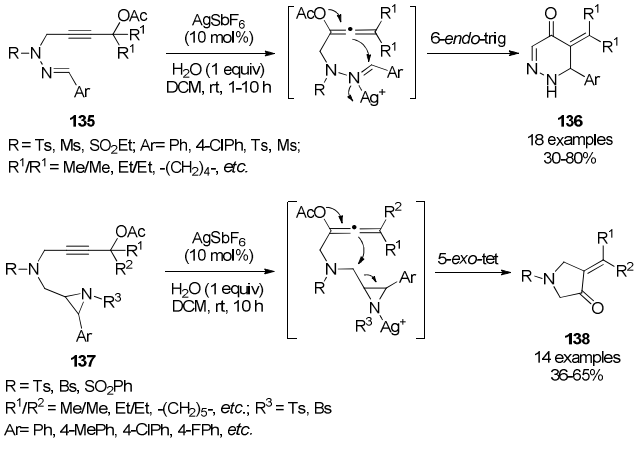
Scheme 52

Propargyl Compounds: Silver-catalysed tandem cyclization of alkynylaziridines **132** was reported by Pale and co-workers, allowing for the stereoselective synthesis of aminoallenylidene-fused heterocycles **133**, including isochromans, isoquinolines and tetrahydronaphtalenes (Scheme 53).[116] In contrast, with a gold catalyst, PPh_3AuNTf_2, 1-azaspiro[4.5]decanes **134** were obtained in 49–82% yields. Mechanistically, both Ag- and Au-catalysed reactions all proceeded *via* the initial Friedel−Crafts-type intramolecular reaction to afford allenes such as **133**, and the cyclization of such aminoallenes subsequently required gold catalysis to produce the corresponding spirocyclic products **134**. This result highlighted the duality between the oxo- or azaphilicity and alkynophilicity of silver and gold catalysts, as well as their complementarity in terms of reactivity.



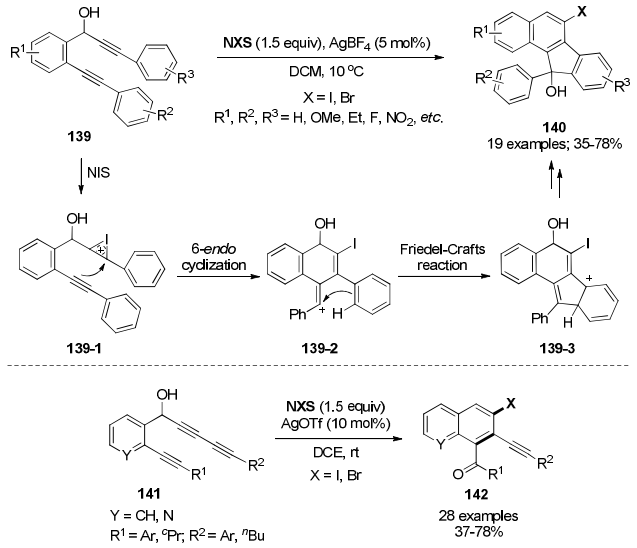
Scheme 53

Propargylic esters have versatile reactivity to undergo 1,2- or 1,3-acyloxy migration, leading to allenic intermediates.[117] Further transformations from these 1,3-migrations by the selective coordination of transition metal catalyst with other functional group moieties rather than allene moieties remain a formidable challenge. Innovations in this direction by research groups such as the Toste and Chan groups are available but are all either limited to gold catalysis or diynyl esters.[118] Silver-catalysed transformations without the use of diynes remains unknown. In light of these discoveries, Shi and co-workers recently described a silver-catalysed route to produce 5,6-dihydropyridazin-4-ones **136** from *N*-sulfonylhydrazone-propargylic esters **135** *via* the tandem 1,3-acyloxy migration and Mannich-type addition and elimination pathways (Scheme 54).[119] The same group then expanded the silver(I)-catalysed protocol to the intramolecular cyclization of *N*-activated aziridine-propargylic esters **137** through the 5-*exo-tet* process, leading to the production of pyrrolidin-3-ones **138** in fair yields (36–65%).[120] This reaction proceeded *via* tandem 1,3-acyloxy migration, 5-*exo-tet* cyclization, and an unprecedented carbon–carbon bond cleavage.



Scheme 54

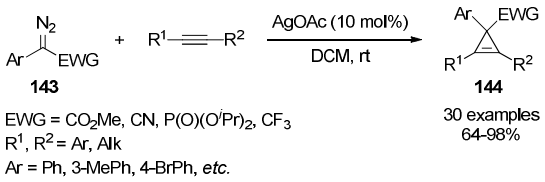
Cascade cyclization reactions of tethered alkynes have proven to be more convenient for the selective synthesis of architecturally complex cyclic compounds that are generally not easily accessible *via* conventional pericyclic reactions. In the context of continuous efforts to perform transition metal-catalysed tandem reactions and electrophilic cyclization reactions, in 2012, Peng *et al*., disclosed a novel $AgBF_4$-catalyzed, NXS (X = I, Br)-promoted electrophilic cascade cyclization of 1,6-diyn-4-en-3-ols **139** for the facile synthesis of halo-substituted benzo[*a*]fluorenols **140** under mild reaction conditions (Scheme 55).[121] $AgBF_4$ showed the best catalytic activity compared with $Cu(OTf)_2$, PPh_3AuCl and other silver salts. The reaction was proposed to proceed through sequential iodonium-mediated triple bond activation to intermediate **139-1**, intramolecular 6-*endo*-*dig* cyclization to intermediate **139-2**, Friedel–Crafts cyclization to intermediate **139-3**, and final intramolecular rearrangement to afford products **140**. Similarly, the Wu group recently examined the reactivity of acyclic triynols **141** with NXS in the presence of a silver catalyst and developed a tandem electrophilic cyclization reaction that resulted in the formation of trisubstituted naphthalenes and quinolines **142** in 37–78% yields.[122]



Scheme 55

2.5 Carbenoids

One of the most general approaches for the synthesis of cyclopropenes involves the reaction of alkynes with metal carbenoids generated *in situ* from diazo compounds.[123] The outcome of the reaction is dependent on whether the alkyne is a terminal alkyne or an internal alkyne. In 2011, Davies *et al*. discovered that silver catalysis was an excellent approach for the cyclopropenation of internal alkynes with donor/acceptor carbenoids (Scheme 56).[124] This was the first cyclopropenation of internal alkynes, participating with donor-/acceptor substituted diazo compounds **143**.[125] The carbenoid structure had a great impact on this cyclopropenation reaction, due to the acceptor- and acceptor-/acceptor-substituted diazo compounds all failed to react with internal alkynes. The generality of the silver-catalyzed cyclopropenation was demonstrated with a range of disubstituted alkynes, affording substituted cyclopropenes **144** that had not been previously synthesized. Thereafter, the same group reported an enantioselective variant of this cyclopropenation reaction by combining the (*S*)-xylylBINAP$(AuCl)_2$ and $AgSbF_6$; however, poor enantioselectivity was obtained using $AgSbF_6$ alone with chiral ligands.



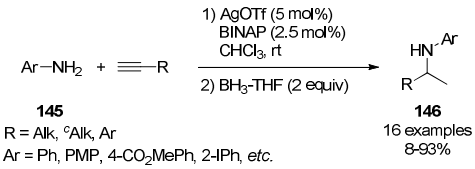
Scheme 56

3. Formation of Carbon–Nitrogen Bonds

3.1 Intermolecular Hydroamination

The intermolecular hydroamination of alkynes can be described as the formal addition of an amine source, such as ammonia or primary or secondary amines, across the C–C triple bond to produce enamines. Although such transformations have been continuously developed by means of transition metal catalysis,[126] silver-catalysed protocols remain rather rare.

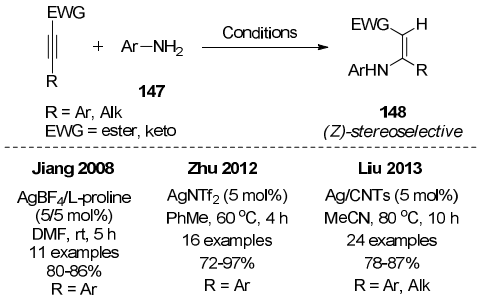
Encouraged by the ligand-controlled, highly efficient Ag(I)-BINAP catalyst system for the A^3 reaction, Shi *et al*. extended the catalyst system to the hydroamination reaction of terminal alkynes with aryl amines **145**, affording products **146** in 8–93% yields (Scheme 57).[52] A complex prepared using AgOTf and BINAP ligand in a ratio of Ag:P = 1:1 effectively promoted this reaction, whereas no reaction occurred using the silver salt without ligand or with excess ligand under identical conditions.



Scheme 57

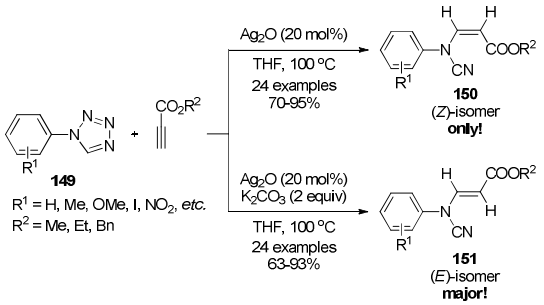
In contrast to the rare reports on the intermolecular hydroamination of unactivated alkynes, many reports in the literature discuss the reaction of activated alkynes. In this category, in 2008, Jiang and co-workers[127] reported $AgBF_4$-catalysed hydroamination of electron-deficient alkynes with various substituted amines **147** in the presence of L-proline

ligand, which stereoselectively afforded only (*Z*)-isomers **148**; this result was attributed to the low steric hindrance and the formation of a hydrogen bond that stabilized the (*Z*)-products **148** (Scheme 58). Moreover, the effectiveness of L-proline as a ligand in silver catalysis was notable, as it previously performed well in the Cu(I)-catalysed Ullmann reaction.[128] This silver-catalyzed protocol was then further developed by the Zhu[129] and Liu[130] groups. For example, simpler $AgNTf_2$ without a ligand and Ag/carbon nanotubes (CNTs) as a catalyst were utilized. In Liu's work, the aryl and alkyl alkynes were all applicable. However, only aryl amines **147** were applicable in these protocols, which require further improvement.



Scheme 58

Rather than directly using amines as the amino source in alkyne hydroamination, the search for other simple-to-use surrogates remains of interest. 1-Aryl-1*H*-tetrazoles **149** were recently employed by Zhang and Wang *et al*. as the amino source in the silver-catalysed hydroamination of alkyl propiolates, enabling the stereoselective synthesis of *N*-cyanoenamines **150** and **151** (Scheme 59).[131] Notably, the easy interchange between *Z* and *E* isomers can be simply regulated by K_2CO_3. This is the first example of the application of tetrazole as a potential synthetic equivalent of cyanamide. Compared with other precursors of cyanamides, tetrazoles are more stable and less toxic.

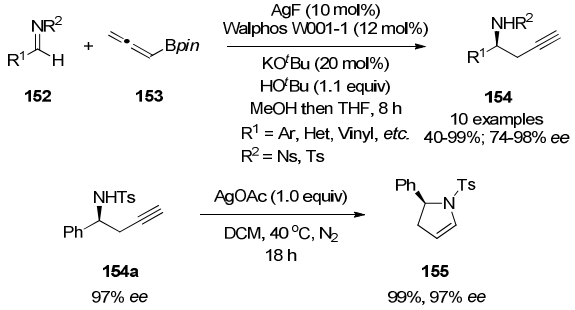


Scheme 59

3.2 Intramolecular Hydroamination

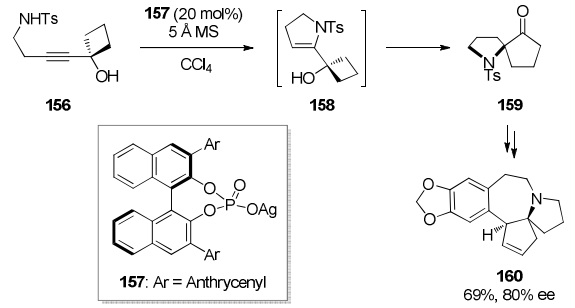
The cyclization reactions of aminoalkynes in either an *exo* or *endo* manner provide efficient methods for the synthesis of *N*-containing heterocycles.[132] The hydroamination products generated from aminoalkynes bearing primary amine moieties typically undergo isomerization to cyclic imines. Generally, hydroamination can be accomplished by amine group or C–C triple bond activation with the aid of acids, bases or transition metal salts, among others.[133] In contrast, silver has received less attention as a catalyst for hydroamination for a long period of time. However, over the past five years, this situation has changed enormously. As commonly observed, amine, carbamate, amide and imino functional groups are capable of participating in nucleophilic attack in these types of cyclizations.[134]

In 2011, Jarvo and co-workers developed a silver-catalysed, enantioselective propargylation reaction of aldimines **152** with allenyl boronic acid pinacol ester (B*pin*) **153**, generating homopropargylic sulfonamide products **154** in good yields and with high *ee* values (Scheme 60).[135] To demonstrate their synthetic utility, they performed the silver-catalysed intramolecular hydroamination of one product **154a**, which undergoes an 5-*endo-dig* cyclization resulting in *anti*-Markovnikov adduct. Importantly, the cyclization reaction did not affect the newly formed stereogenic centre and provides enantiomerically enriched 2-pyrroline **155** in 99% yield with 97% *ee*.



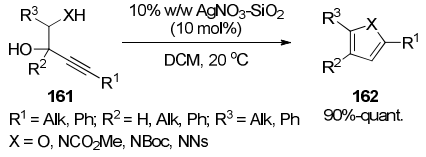
Scheme 60

The pyrrole ring is often found as a key structural unit in natural products. Indeed, the silver-catalysed 5-*endo-dig* cyclization of homopropargylic sulfonamide **156** shown above was employed by Tu and co-workers in the catalytic asymmetric formal synthesis of (−)-cephalotaxine **160** (Scheme 61).[136] In the presence of a chiral silver phosphate catalyst **157**, the key product azaspirocycle **159** was obtained from cyclobutanols **156** through intermediate **158** *via* a tandem hydroamination and semipinacol rearrangement reaction.



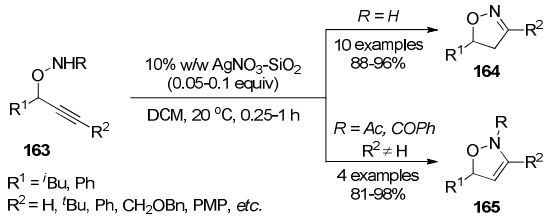
Scheme 61

Silver nitrate supported on silica gel could be employed as a recoverable and reusable heterogeneous catalyst. Using such a catalyst system, Knight *et al*. reported the 5-*endo-dig* cyclization of 3-alkyne-1,2-diols and 3-alkynyl-hydroxyalkanamines **161**, affording furans and pyrroles **162** in essentially quantitative yields (Scheme 62).[137]



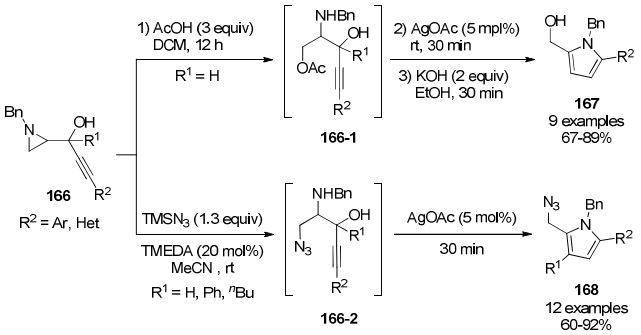
Scheme 62

Using the same efficient silver catalyst, Knight *et al*. developed a relatively brief but certainly efficient route for producing both 4,5- and 2,5-dihydroisoxazoles **164** and **165** from unprotected or *N*-protected *O*-propargylic hydroxylamines **163**, respectively (Scheme 63).[138] Given that the initial precursors, secondary propargylic alcohols, could be easily obtained as single enantiomers using a number of approaches, this chemistry should be amenable to the synthesis of optically pure products of both types.



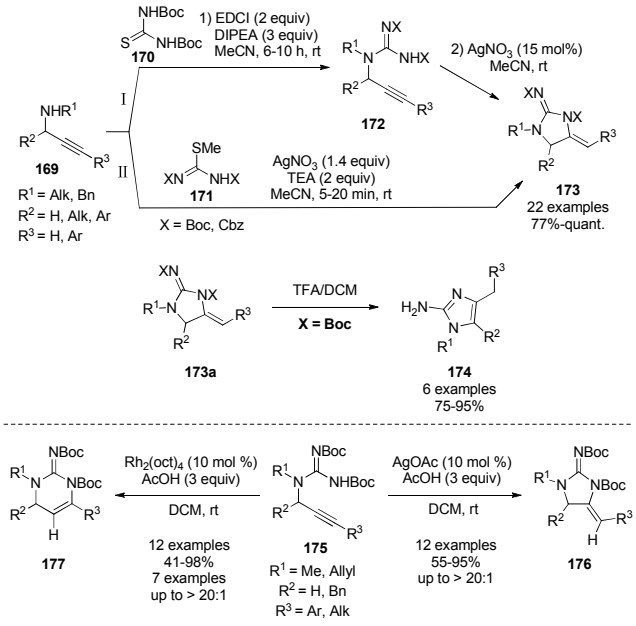
Scheme 63

The aziridine group is capable of functioning as a masked amino group in the hydroamination of alkynes. Lee and Ha *et al*. described the ring-opening/recyclization reaction of 1-(aziridin-2-yl)propargylic alcohols **166** (Scheme 64).[139] In the presence of nucleophiles such as HOAc and $TMSN_3$, intermediates **166-1** and **166-2** could be generated under mild conditions, and Ag(I)-catalysed intramolecular hydroamination subsequently occurred, resulting in the formation of 1,2,5-tri- and 1,2,3,5-tetra-substituted pyrroles **167** and **168** in good yields.



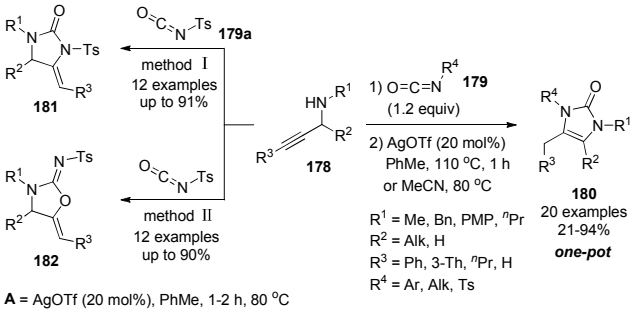
Scheme 64

In 2010, Eycken and co-workers discovered a novel silver-mediated cyclization of propargylguanidines **172** derived *in situ* from propargylamines **169** and thioureas **170** or **171**. The cyclization reaction proceeded either in a stepwise manner (path **I**) or in a one-pot process (path **II**), affording 2-iminoimidazolines **173** in excellent yields (Scheme 65).[140] Furthermore, the *Boc*-protected 2-iminoimidazolines **173a** could be easily converted to 2-aminoimidazoles **174** in excellent yields under acidic conditions. Thereafter, directly starting from *Boc*-protected propargylguanidines **175**, Looper *et al*. developed a silver-catalysed, acid-promoted hydroamination that produced 5-*exo*-*dig* products **176** in high yields.[141] Moreover, 6-*endo*-*dig* products **177** were obtained with high levels of regioselectivity and moderate-to-excellent yields with $Rh_2(oct)_4$ (10 mol%) as the catalyst.



Scheme 65

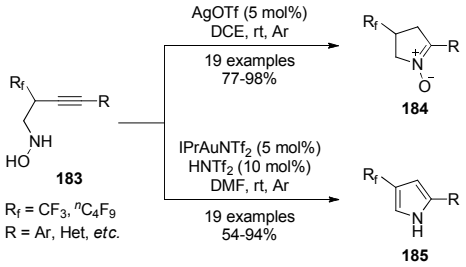
Isocyanates can be incorporated into silver-catalysed cyclizations with propargyl amines. As summarized in Scheme 66, in 2011, Ermolat'ev and Eycken *et al.* developed a one-pot protocol for the synthesis of 2-imidazolones **180** from secondary propargylamines **178** and a variety of isocyanates **179** *via* the tandem acylation and AgOTf-catalysed cyclization of *in situ*-generated propargylic urea intermediates.[142] Subsequently, Eycken and co-workers reported a catalyst-dependent selective *O*- and *N*-cyclization reactions[143] of propargylic urea, which were generated *in situ* from secondary propargylic amines **178** and tosyl isocyanate **179a**. Imidazolidin-2-ones **181** were obtained with AgOTf catalysis (method **I**), whereas in the presence of a gold(I) complex, *i.e*., $Au(PPh_3)Cl$, oxazolidin-2-imines **182** were produced as the major product (method **II**).[144]



Scheme 66

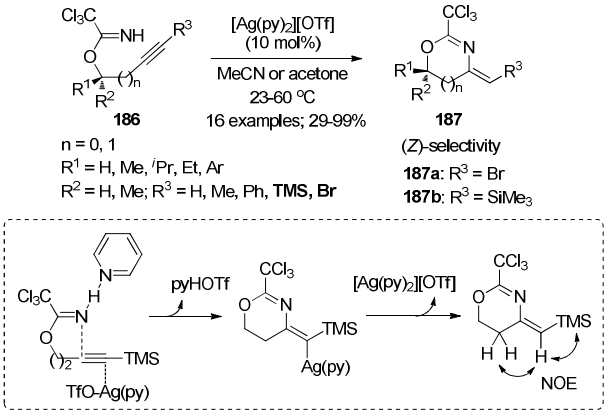
N-(2-perfluoroalkyl-3-alkynyl) hydroxylamines **183** are easily prepared from terminal alkynes, 2-bromo-2-perfluoroalkyl-1-ene and hydroxylamine hydrochloride *via* a simple two-step procedure. The intramolecular hydroamination of **183** has been

investigated by Zhang and Xiao *et al*., resulting in the formation of 4-perfluoroalkyl cyclic nitrones **184** in the presence of AgOTf as a catalyst (Scheme 67).[145] In contrast, with $IPrAuNTf_2$ and $HNTf_2$ cooperative catalysis, the pyrroles **185** were obtained in 54–94% yields. These two chemoselective reactions provided a divergent method for the synthesis of fluoroalkylated five-membered azaheterocycles.



Scheme 67

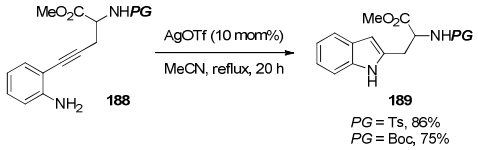
The first intramolecular hydroamination of (homo)propargylic trichloroacetimidates **186** was reported by Hii and co-workers with the aid of a silver catalyst (Scheme 68).[146] Methylene-substituted heterocycles **187** were obtained through 5- and 6-*exo-dig* annulations with 29–99% yields and (*Z*)-selectivity. Notably, the $[Ag(py)_2][OTf]$ complex was found to be highly effective for the cyclisation of internal alkynes to produce vinyl-bromide and -silane products **187a** and **187b**, respectively. The ability of one of the pyridines to dissociate from the metal during the reaction appeared to be key to the reactivity, as the reaction did not proceed if a chelating ligand, *i.e*., [(phen)Ag][OTf] (phen = phenanthroline), was used. The primary role of the liberated pyridine was to serve as a Brønsted base to abstract the imine hydrogen and sequester the released triflic acid, thereby preventing competitive side reactions, *e.g.*, protodesilylation of the substrates and products.



Scheme 68

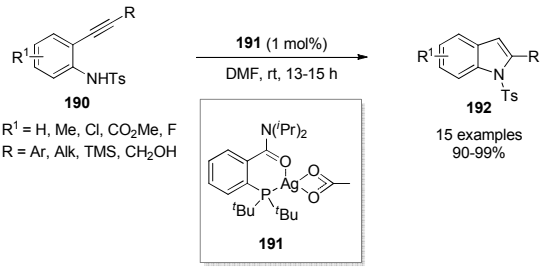
The cyclization reaction of *ortho*-alkynylanilines and their derivatives is a general, efficient and direct method for the construction of indole rings that is triggered by a base, fluoride, ammonium or transition metal salts.[147] Silver salts have been demonstrated to be robust catalysts for cyclizations of *ortho*-alkynylanilines towards indoles in recent years.

In 2004, Rutjes *et al*. reported the formation of isotryptophan products **189** *via* the AgOTf-catalysed cyclization of *ortho*-alkynylanilines **188** (Scheme 69).[148] Notably, *ortho*-NH_2 has priority to form 2-substituted indoles, which even interferes with the carbamate nitrogen in the cyclization process.



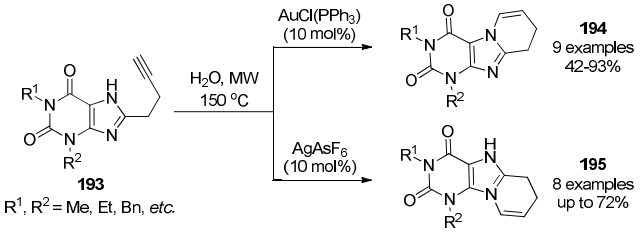
Scheme 69

Recently, this silver-catalysed protocol was further developed by McNulty *et al*., who described the first example of the intramolecular hydroamination of *N*-tosyl-2-alkynylanilines **190**, employing a well-defined homogeneous *P,O*-ligand-Ag(I) complex **191**, leading to the production of indoles **192** in excellent yields (90–99%) with low catalyst loading (1 mol%) under mild conditions (Scheme 70).[149] The reactions were shown to be first order in terms of the catalyst, and a mechanism was postulated that highlighted the role of the hemilabile ligand in promoting cyclization. In addition, the enhanced thermal and chemical stability of these silver(I) complexes make them ideal for probing chemical reactivity (π-acidity) in the area of homogeneous catalysis without fear of silver metal or halide precipitation, which is a problem that has plagued the development of silver catalysis in general.



Scheme 70

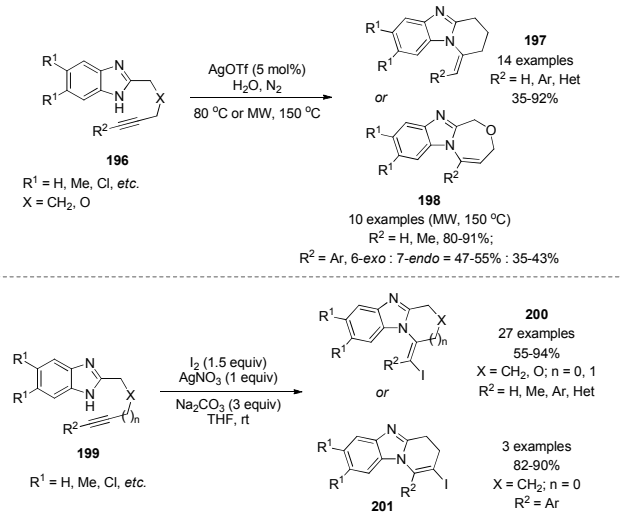
In the process of studying the transition metal-catalysed hydroamination of alkynes towards *N*-heterocycles, in 2009, the Liu group reported the first examples of the synthesis of N7-annelated xanthines **194** in high yields *via* the gold(I)-catalysed intramolecular hydroamination of 8-(but-3-ynyl)-xanthines **193** under microwave heating in water, whereas under silver(I) catalysis, N9-annelated xanthines **195** were mainly obtained through an isomerization-hydroamination reaction (Scheme 71).[150] From labelling studies using D_2O or deuterated starting materials, a gold or silver vinylidene intermediate was found to be formed *via* 1,2-H migration.



Scheme 71

Furthermore, the same group reported a transformation of 2-

alkynyl-1*H*-benzo[*d*]imidazoles **196** under AgOTf catalysis, leading to fused benzimidazoles **197** and **198**. Interestingly, the 6-*exo*-*dig* or 7-*endo*-*dig* ring-closing pathway could be regulated by changing the heteroatom linker between the benzimidazole and the alkyne units (Scheme 72).[151] When introducing aryl groups into the R^2 position, regioisomers of oxa-fused benzimidazoles could be formed, because of the π–π conjugation effect between the acetylene bond and the aryl group. Several tested Ag(I) salts, such as AgOTf, $AgNO_3$, $AgSbF_6$ and $AgSO_3Me$, were all effective. A simple and regioselective route to produce diverse fused heterocyclic polycyclic compounds with vinyl iodo moieties **200** and **201** was also developed by the same group; this reaction occured *via* $AgNO_3/I_2$-promoted iodocyclization of benzoimidazoles **199** under mild conditions.[152] $AgNO_3$ acted as a vital additive because of its great impact of eliminating the interference of iodine ions (I^+) that would result in bisiodine by-products.



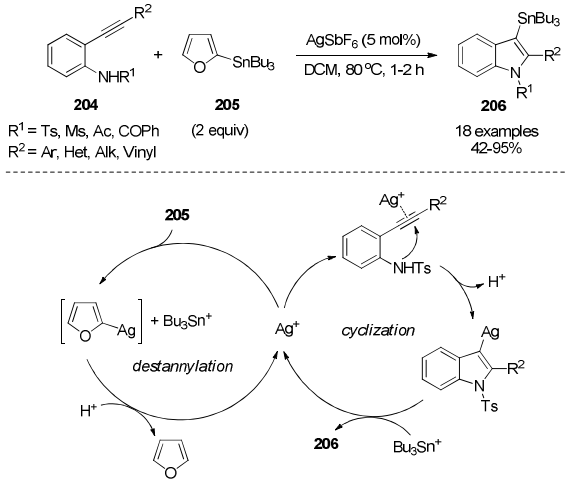
Scheme 72

Recently, Hu and co-workers developed the silver-catalysed heterocyclization of enyne-substituted pyrimidines **202** derived by Heck−Sonogashira reaction of 6-*N*,*N*-di-Boc-amino-5-iodo-2-methyl pyrimidin-4-ols with aryl acetylenes or trimethylsilylacetylene, affording pyrido[2,3-d]pyrimidines **203** in 77–95% yields (Scheme 73).[153] The chemoselective azacyclization was proposed involving a tandem deprotection of Boc group, cyclization-aromatization step. Note that a free phenolic hydroxyl group of pyrimidines was well tolerated.

Scheme 73

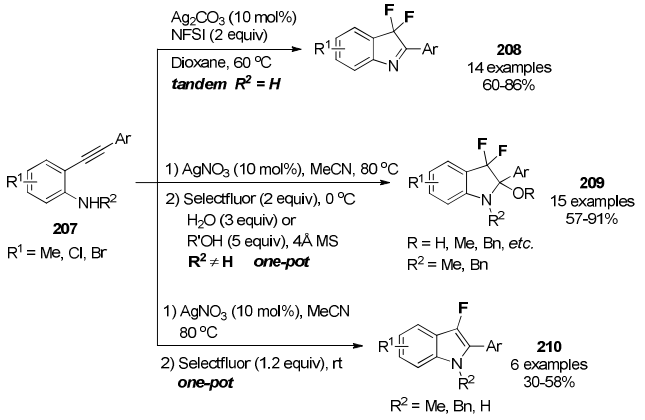
3.3 Cyclization

Over the past few years, remarkable developments in sequential reactions have been achieved by incorporating the hydroamination reaction into a rationally designed cascade of transformations, providing a step-economic route for producing diversely functionalized molecules *via* a one-pot reaction.[154] Such a strategy has been employed in the silver-catalysed tandem annulations of *ortho*-alkynylanilines, which allowed for the synthesis of diverse functionalized indoles, particularly 3-substituted indoles. For example, in 2013, Liu and co-workers reported a silver-catalysed tandem cyclization/stannylation of *N*-protected *ortho*-alkynylanilines **204** with 2-tributylstannylfuran **205**, which afforded 3-tributyltin substituted indoles **206** in fair to excellent yields (42–95%) (Scheme 74).[155] This work represented the first example of a silver-catalysed metalative benzannulation reaction. Notably, the presence of *N*-electron-withdrawing protecting groups was crucial for the reaction, because the reaction of *N*-methyl substituted substrate afforded 1-methyl-1*H*-indole without a stannyl group. Furthermore, the resulting (3-indolyl)stannanes **206** could be derivatized into various functionalized indoles. A plausible reaction mechanism was proposed that involved parallel destannylation and cyclization processes.



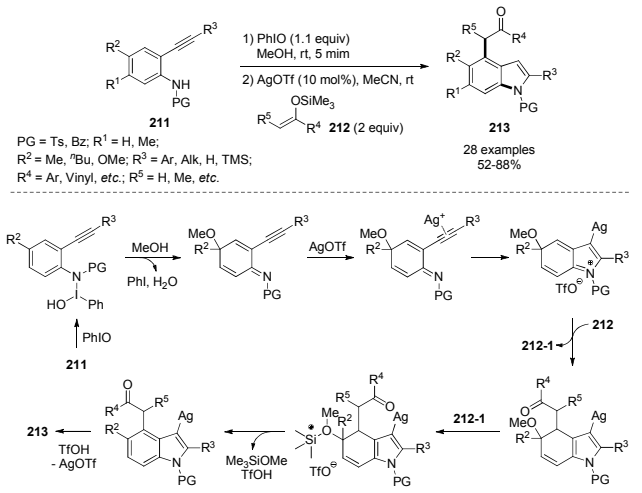
Scheme 74

Fluorinated indoles are of considerable interest for medicinal research.[156] However, most of the available methods primarily rely on direct fluorination of the ''preformed'' indole ring. Following the report of Arcadi *et al.*, on the gold(III)-catalysed aminofluorination of 2-alkynylanilines,[157] You and co-workers studied the silver-catalyzed reaction of 2-alkynylanilines **207**, *i.e.*, tandem cyclization/fluorination reaction of *N*-unprotected 2-alkynylanilines with an electrophilic fluorinating reagent, *N*-fluorobenzenesulfonimide (NFSI), which afforded 3,3-difluoro-3*H*-indoles **208**, whereas 2-substituted 3,3-difluoroindolines **209** and 3-fluoroindoles **210** were produced through a one-pot, two-step strategy in the presence of $AgNO_3$ as a catalyst and Selectfluor (Scheme 75).[158] These protocols conveniently afforded structurally diverse fluorinated indole derivatives **208**~**210** under mild conditions. Notably, the scope of 3-fluoroindoles **210** was limited to substrates **207** bearing an electron-deficient aryl group.



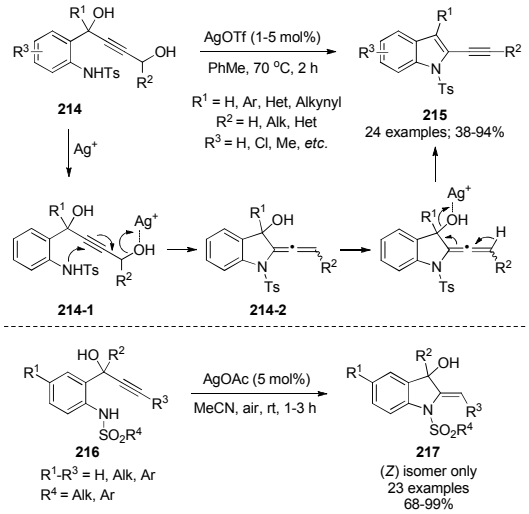
Scheme 75

The dearomatization of aromatics provides a useful strategy for constructing complex molecules.[159] In 2014, Yang and Fan *et al.* applied this strategy to synthesize 4-acetonylindoles **213** *via* the silver-catalysed tandem cyclization of 2-alkynyl anilines **211** with silyl enol ethers **212** (Scheme 76).[160] AgOTf was superior to AuCl as a π-acid catalyst in this reaction as verified by the higher product yields. By comparison, iodosylbenzene (PhIO) proved to be the best oxidant for this one-pot synthesis. Mechanistically, the reaction proceeded by the initial oxidative dearomatization of 2-alkynylanilines **211**, followed by the silver-catalysed sequential heterocyclization, Michael-type addition with silyl enol ethers **212** to install the 4-acetonyl group onto the indole ring and the final tandem rearomatization/protodemetalation to reconstruct the indoles. The *in situ*-generated Me_3SiOTf **212-1** promoted the rearomatization.



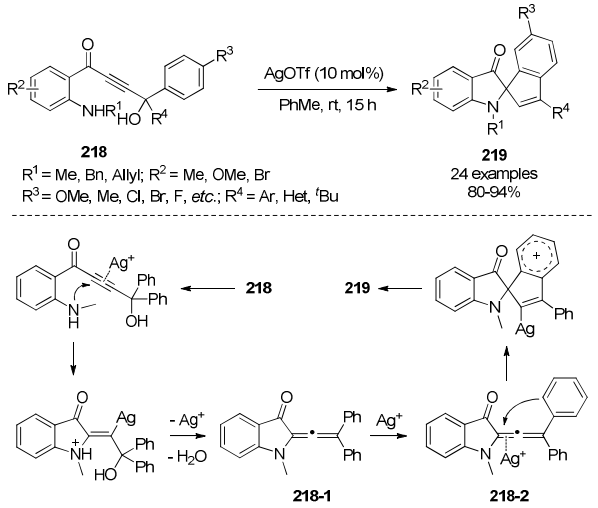
Scheme 76

Propargylic alcohols are readily available functionalized alkynes;[161] additionally, the close proximity of the hydroxyl group to the carbon-carbon triple bond in one molecular scaffold imparts these molecules with extraordinary potential to undergo reactions that are distinct from those of alkynes alone.[162] A number of methodologies have been developed based on the silver-catalysed cascade reactions of propargyl alcohols that allowed for the generation of indole and indoline derivatives. For example, in 2012, Chan and co-workers reported an intramolecular tandem heterocyclization and alkynylation reaction of propargylic 1,4-diols **214**, which resulted in the synthesis of 2-alkynyl indoles **215** (Scheme 77).[163] Notably, previous routes to such indoles primarily relied on the Sonogashira reaction at the C-2 position.[164] A plausible mechanism was proposed with the initial coordination of silver(I) catalyst and the sterically less hindered secondary alcohol moiety to afford complex **214-1**. Following the dehydration/5-*exo*-*dig*-cyclization cascade, intermediate **214-2** was generated, and the subsequent silver-catalysed sequential dehydration/isomerization afforded the product **215**. By slightly varying the substrate structure, the same group demonstrated a chemo- and stereoselective reaction of propargyl alcohols **216**, yielding (*Z*)-2-methyleneindolines **217** through a silver(I)-catalysed hydroamination reaction.[165] The reaction proceeded rapidly with catalyst loadings as low as 1 mol% under ambient conditions.



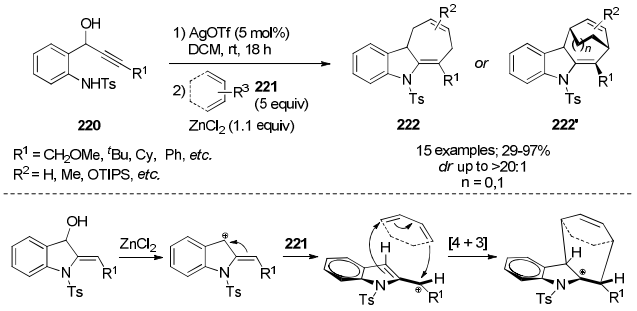
Scheme 77

Very recently, the authors further expanded this hydroamination methodology catalysed by silver salts to other multifunctionalized propargyl alcohols, such as 1-(2-allylamino)-phenyl-4-hydroxy-but-2-yn-1-ones **218** (Scheme 78).[166] Under the catalysis of AgOTf (10 mol%), the efficient tandem hydroamination and hydroarylation of propargyl alcohols **218** occurred, resulting in highly functionalized spirocyclic products **219** in high yields (80–94%). Notably, the *N*-tosyl-protected alkynes resulted in allenamides, without further cyclization. If the substrates contained different (hetero)aryl groups on the carbinol carbon centre, a mixture of regioisomers was obtained. Mechanistically, the indene ring was assumed to be formed *via* silver-catalysed 5-*endo*-*trig* hydroarylation of the allenic intermediate (**218-1**→**218-2**).



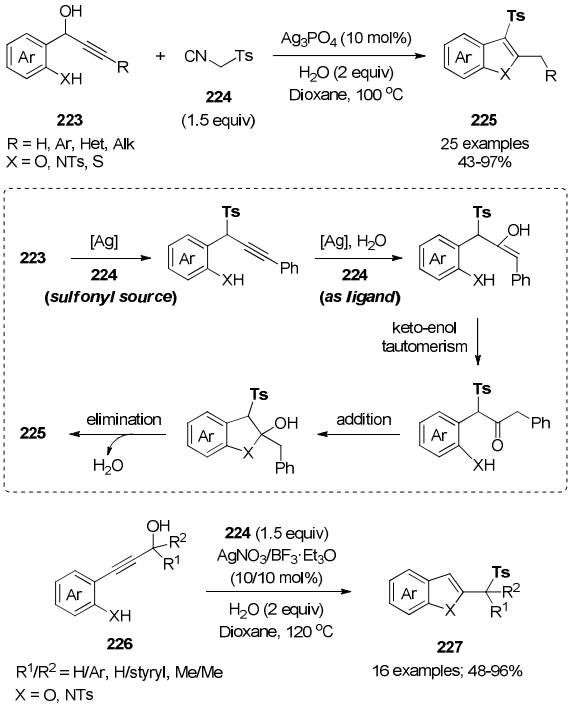
Scheme 78

The silver-catalysed hydroamination of propargyl alcohols **220** was utilized by Xue and Li *et al*. as a primary step in the tandem hydroamination/[4 + 3] cycloaddition reaction with dienes **221**, which afforded multitudinal indole-containing 5,7,6-tricyclic skeletons **222** or **222′**, depending on the type of dienes (Scheme 79).[167] Silver catalysis first resulted in the formation of hydroamination product **220-1**, and following the transformation into a cation intermediate **220-2** promoted by $ZnCl_2$, a more stable **220-3** was generated. Subsequently, the cycloaddition between **220-3** and dienes **221** *via* the *endo*-cycloaddition transition state occurred, affording a 6,5,7-skeleton **220-4** *via* a stepwise-like electron transfer process, which was eventually converted into cyclohepta[*b*]indoles by proton elimination.



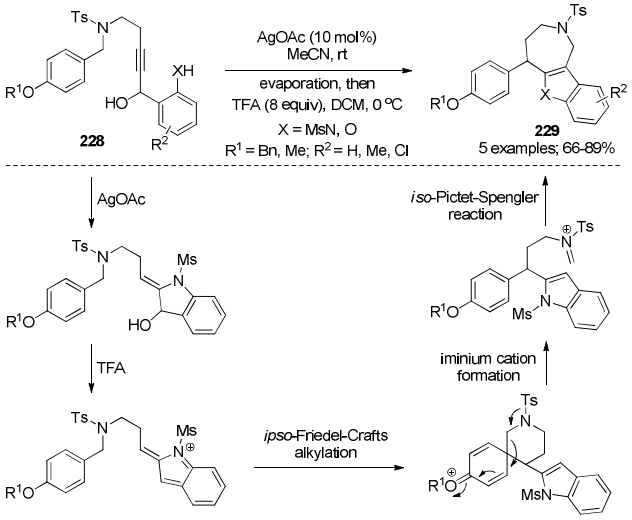
Scheme 79

Continuing our efforts towards the development of silver-catalysed reactions between alkynes and isocyanides, our group recently reported a novel heteroaromatization of secondary propargylic alcohols **223** with *p*-toluenesulfonylmethyl isocyanide (TosMIC) **224**, which allowed for the modular synthesis of diverse sulfonyl benzoheteroles **225**, such as benzofurans, indoles and benzothiophenes in good to excellent yields (Scheme 80).[168] Unlike the well-recognized coordination of the π-acidic transition metal catalyst to the C–C triple bond to induce the subsequent attack by nucleophilic moieties, mechanistic investigations indicated that the current annulations proceeded through a deoxysulfonylation, hydration, and condensation cascade, in which TosMIC played dual roles as the sulfonyl source and the ligand. Furthermore, the substrate scope was expanded to propargylic alcohols **226**, which structurally interchanged the positions of the hydroxyl group and the C–C triple bond, thereby resulting in benzoheteroles **227** in 48–96 yields. The reaction took place through a cooperative $AgNO_3$ and $BF_3{\cdot}Et_2O$ system.



Scheme 80

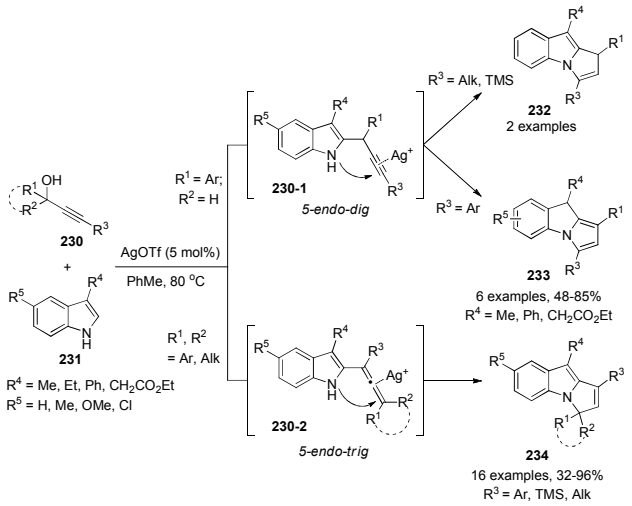
A cascade cyclization process was developed by Hamada *et al*. using aryl-substituted propargyl alcohols possessing a *p*-hydroxybenzylamine unit **228**, resulting in the formation of fused-tricyclic heterocycles **229** in 66−89% yields (Scheme 81).[169] This reaction proceeded by AgOAc-catalysed hydroamination and subsequent acid-promoted skeletal rearrangement.



Scheme 81

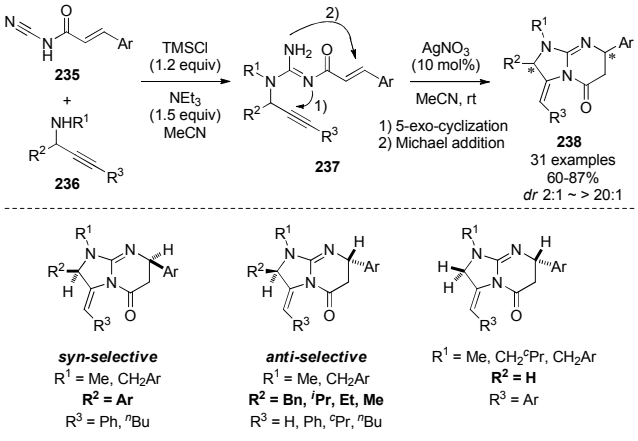
The highly reactive propargylic or allenic carbocation, based on resonance conversion, is easily generated from propargyl

alcohols simply by Brønsted or Lewis acid catalysis.[170] By utilizing this property, Zhan and co-workers developed a AgOTf-catalysed tandem Friedel–Crafts reaction/N–C bond formation reaction of propargyl alcohols **230** with 3-substituted 1*H*-indoles **231**, leading to the production of diverse *N*-fused heterocycles **232**~**234** (Scheme 82).[171] The reaction proceeded smoothly under mild conditions, without bases and ligands, and tolerated a broad scope of functional groups. Two distinct routes, depending on the use of secondary or tertiary propargyl alcohols **230**, including C2-propargylation/N–C 5-*endo-dig* cyclization and C2-allenation/N–C 5-*endo-trig* cyclization, to these heterocyclic frameworks were verified through the isolatable intermediates **230-1** and **230-2**.



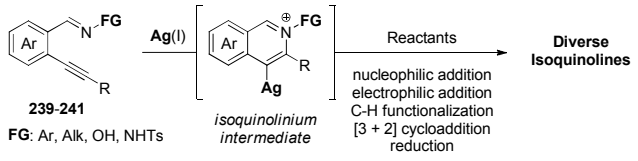
Scheme 82

Following the discovery of the chlorotrimethylsilane (TMSCl) activation of acylcyanamides as an efficient method for the synthesis of mono-*N*-acylguanidines,[172] Looper and co-workers continued to investigate silver-catalysed cyclizations.[173] As shown in Scheme 83, the acryloyl guanidines **237** generated from the reaction of TMSCl-activated *N*-cyanoacylamides **235** with propargylamines **236** smoothly underwent an expected $AgNO_3$-catalysed tandem hydroamination and Michael addition sequence to afford geometrically and constitutionally stable ene−guanidines **238**. Substituent variations could deliver products with high diastereoselectivity despite the newly formed stereocentre being five atoms removed and spanned by an almost planar heterocyclic core.



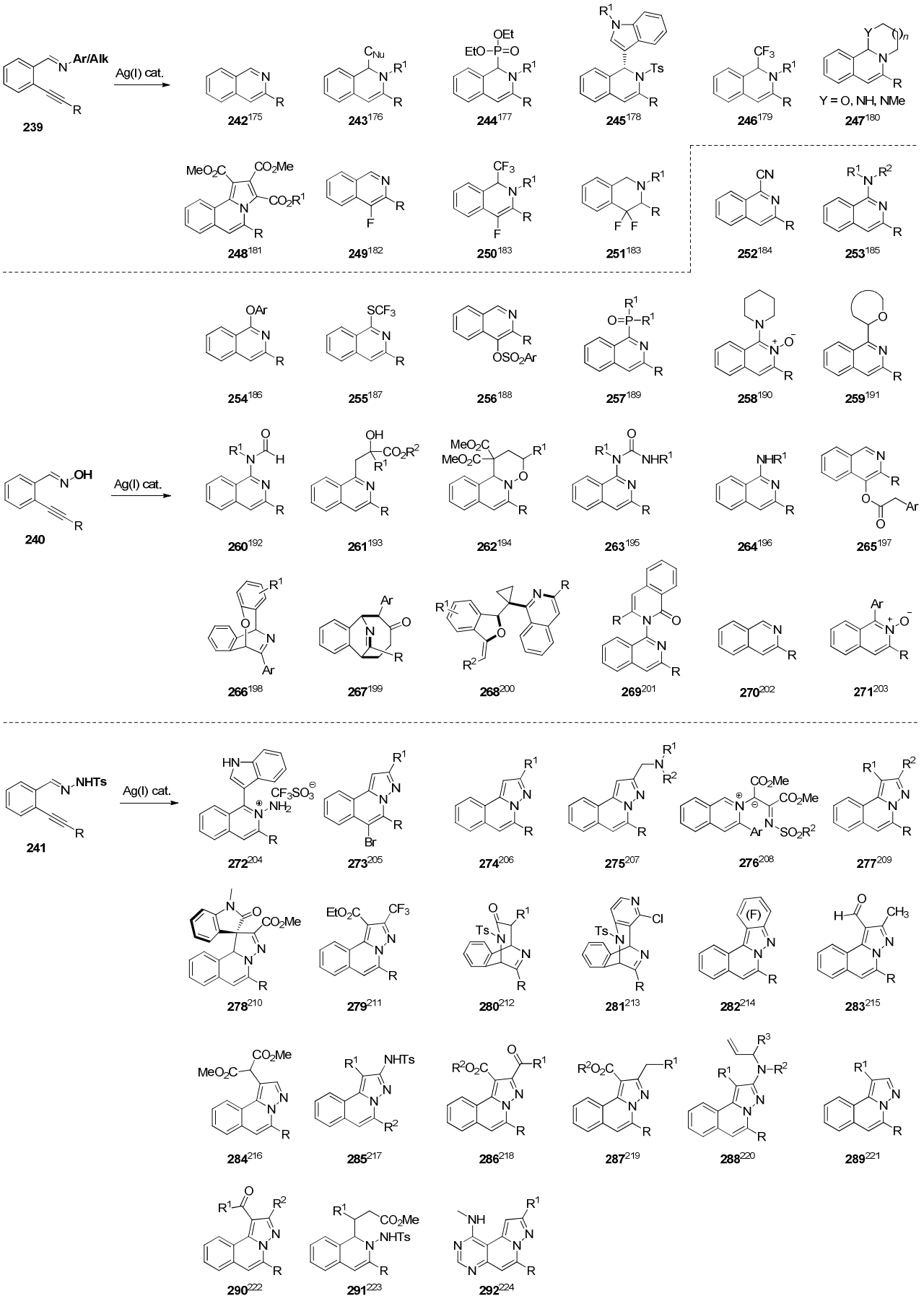
Scheme 83

Cycloisomerization of *ortho*-alkynylaryl aldimines: The *ortho*-alkynyl benzaldimines **239**~**241**, derived from the corresponding substituted benzaldehydes, could be cyclized in the presence of silver salts (Scheme 84). Cleverly, the isoquinolinium intermediate produced in such cyclizations could be trapped by various nucleophiles, electrophiles or reducing agents, thereby allowing for the synthesis of diverse functionalized isoquinolines (Table 1). Over the past few years, this strategy has been intensively explored and has resulted in numerous transformations that have become some of the most powerful methodologies for accessing isoquinoline frameworks. These achievements were summarized in 2012 and 2014 by Wu *et al*.,[174] who also made a major contribution to this field. Consequently, in the current review, we only present a tabulated summary for this class of silver-catalysed transformations.



Scheme 84

Table 1 Silver-catalysed cycloisomerization of *ortho*-alkynylaryl aldimines to isoquinolines


Ar/Alk
Ag(I) cat.
239
242[175]
243[176]
244[177]
245[178]
246[179]
247[180]
Y = O, NH, NMe
248[181]
249[182]
250[183]
251[183]
252[184]
253[185]
254[186]
255[187]
256[188]
257[189]
258[190]
259[191]
OH
Ag(I) cat.
240
260[192]
261[193]
262[194]
263[195]
264[196]
265[197]
266[198]
267[199]
268[200]
269[201]
270[202]
271[203]
NHTs
Ag(I) cat.
241
272[204]
273[205]
274[206]
275[207]
276[208]
277[209]
278[210]
279[211]
280[212]
281[213]
282[214]
283[215]
284[216]
285[217]
286[218]
287[219]
288[220]
289[221]
290[222]
291[223]
292[224]

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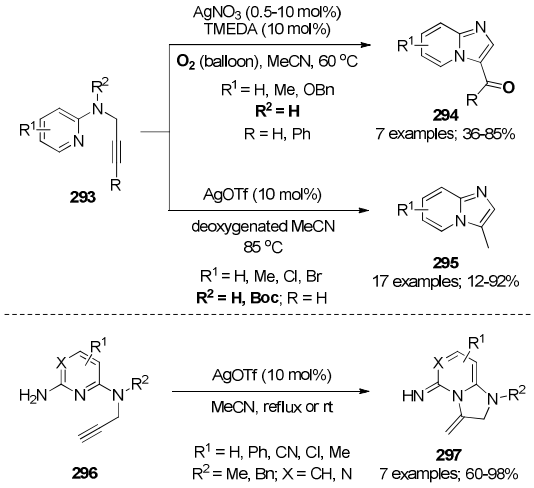
CRITICAL REVIEW

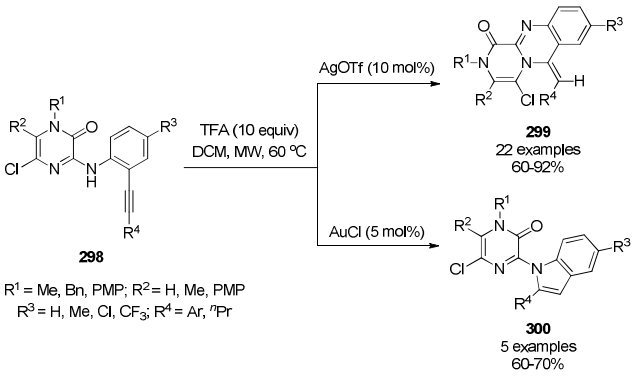
***N*-Heterocycle cycloisomerization**: Although silver-based heterocyclization reactions of alkynes are well documented, few examples are known for the silver-catalysed cyclizations of *N*-heterocyclic propargylamines.

In 2013, the Adimurthy group reported a Ag-catalysed intramolecular aminooxygenation of *N*-(prop-2-yn-1-yl)pyridin-2-amines **293** under an oxygen atmosphere, which primarily afforded the imidazo[1,2-*a*]pyridines **294** in 36–85% yields (Scheme 85).[225] Moreover, using deoxygenated MeCN as a solvent, Chioua and Marco-Contelles *et al*. obtained 3-methylimidazo[1,2-*a*]pyridines **295** as the major product from *N*-propargylaminopyridines **293** (R^2 = H, Boc).[226] Furthermore, the Marco-Contelles group investigated the scope, limitation, and mechanism of the AgOTf-catalysed cycloisomerization of 2-amino-6-propargylamineazines **296**, which bear a free amino group at the C-2 position. A completely different reaction was observed, which led to iminoimidazoazines **297** in 60–98% yields and with excellent regioselectivity.[227]



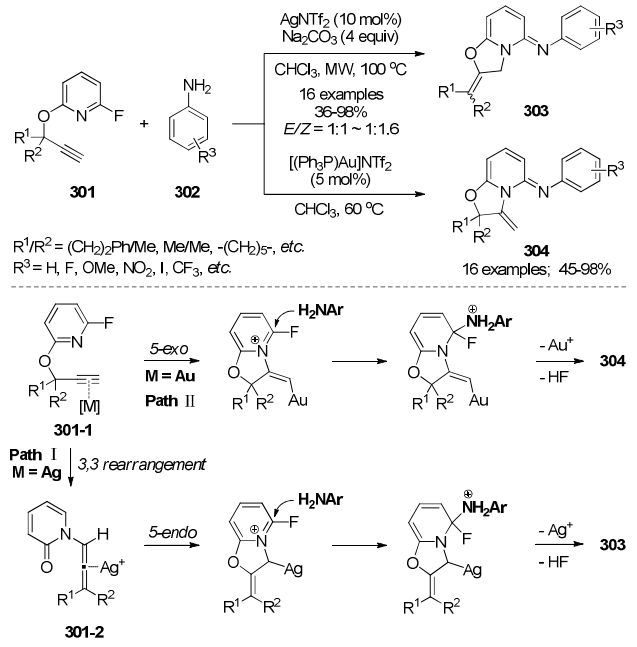
Scheme 85

Similar to the aromatic *N*-heterocycles such as the pyridyl group, 3-(*ortho*-alkynylated anilino)-2(1*H*)-pyrazinones **298** could also be transformed into the annulated pyrazino-quinazolines **299** under microwave irradiation conditions, through regioselective 6-*exo*-*dig* cyclization in the presence of AgOTf (10 mol%) and TFA (10 equiv) (Scheme 86).[228] While using AuCl instead of AgOTf as a catalyst, 3-indolyl-2(1*H*)-pyrazinones **300** were obtained *via* 5-*endo*-*dig* hydroamination.



Scheme 86

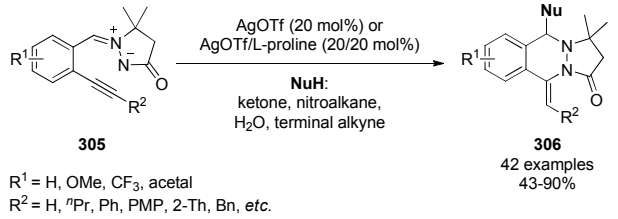
Rather than a nitrogen linker between the 2-pyridyl and the propargyl groups, Gagosz *et al*. studied the reaction of the readily available 2-propynyloxy-6-fluoropyridines **301** with arylamines **302** under gold or silver catalysis (Scheme 87).[229] Two sets of oxazolopyridine derivatives **303** and **304** with unusual heterocyclic motifs could be selectively formed in moderate to excellent yields, depending on the nature of the metal catalyst employed. Mechanistically, the use of a silver catalyst, $AgNTf_2$, appeared to favour the formation of **303** *via* path **I**, which featured a 3,3-rearrangement of **301-1** to *N*-allenyl 2-pyridone intermediate **301-2**, whereas the use of a gold catalyst, $[(Ph_3P)Au]NTf_2$, allowed for the formation of **304** *via* 5-*exo*-cyclization (path **II**).



Scheme 87

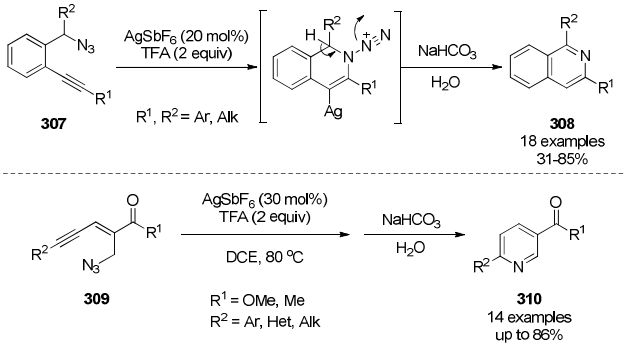
Miscellaneous: Azomethine imines that possess versatile reactivity have been explored by Li *et al*. under the rhodium(III)-

catalysed oxidative C–H functionalization.[230] Recently, the authors described a silver-catalyzed nucleophilic addition-cyclization reaction of alkynyl-azomethines **305** with soft nucleophiles such as ketones, nitroalkanes, water, and terminal alkynes (Scheme 88).[231] This reaction proceeded through 6-*exo-trig* cyclization and produced a range of polycyclic amides **306** in 43–90% yields. Given its broad scope and operational simplicity, this method may be applicable in the synthesis of related azaheterocyclic structures in the future.



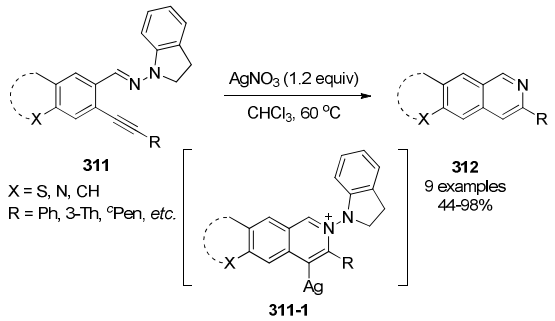
Scheme 88

2-Alkynyl benzyl azides **307** underwent an 6-*endo-dig*-type cycloisomerisation reaction, affording the substituted isoquinolines **308** in 31–85% yields, with the release of N_2 molecule (Scheme 89).[232] Ag(I) salts displayed high efficiency, whereas other metal catalysts such as Cu(II), Au(III), and Pt(II) did not result in the desired product. Recently, Reddy and co-workers reported a novel route for efficiently producing 3,6-disubstituted pyridines **310** from (*E*)-2-en-4-ynyl azides **309** with good functional group tolerance *via* a silver-catalysed aza-annulation reaction.[233] In addition, enynyl azides **309** were readily available from acetylenic aldehydes and acetates *via* sequential MBH reaction, esterification, and azidation steps.



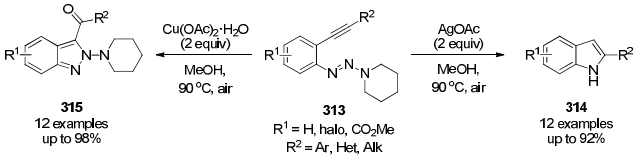
Scheme 89

In 2010, Ghavtadze and Würthwein *et al*. described a $AgNO_3$-mediated cyclization reaction of hydrazones **311** leading to the annulated pyridine derivatives **312** in 44–98% yields (Scheme 90).[234] $AgNO_3$ was essential due to other silver salts and metal compounds, such as AgOAc, CuI, $AuCl_3$, $PdCl_2$ were unefficient. Mechanistically, the silver(I)-assisted 6-*endo-dig* ring-closure process of substrates **312** led to the formation of an intermediate pyridinium cation **311-1**, which released indole as unusual but efficient neutral leaving group after N–N bond cleavage.



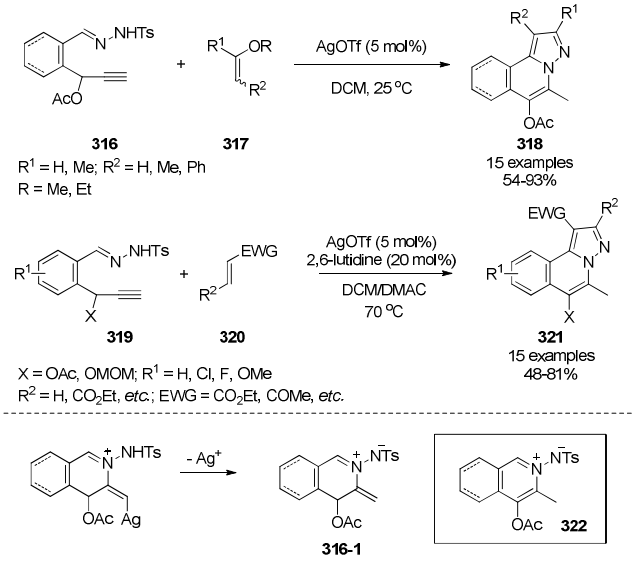
Scheme 90

Following the initial discovery of triazene-directed C–H annulations with various internal alkynes towards indoles promoted by Rh/Ag/Cu salts,[235] the Huang group recently developed the AgOAc-promoted aza-annulation of *ortho*-alkynyl aryltriazenes **313**, which produced indoles **314** *via* the unprecedented N–N cleavage of alkynyl triazenes (Scheme 91).[236] Replacement of AgOAc with $Cu(OAc)_2$ as the catalyst, a different cyclization pattern was observed that produced 2*H*-indazoles **315** *via* an oxidative cyclization. DFT-calculation suggested that AgOAc primarily was a π-acidic catalyst, whereas copper(II) salt functioned as a Lewis acid in the reaction.



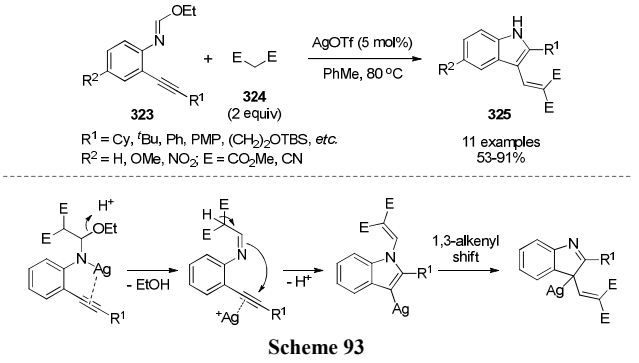
Scheme 91

Liu *et al*. recently studied the reaction of substituted 1-tosylhydrazon-4-oxy-5-ynes with alkenes by silver catalysis. A cascade 6-*exo-dig* azacyclization followed by [3 + 2] cycloaddition reactions were observed, which afforded a variety of fused azoheterocycles **318** and **321** in good yields. Both non-benzenoid and benzenoid substrates **316** and **319** were suitable for the cascade cyclization, and the applicability of this reaction to the alkenes **317** and **320** bearing electron-donating and electron-withdrawing groups was particularly notable (Scheme 92).[237] Acetoxy (OAc) and methoxymethyl (MOM) ethers presumably exerted an electron-withdrawing effect on the adjacent alkyne to enhance the 6-*exo-dig* cyclization step. A plausible mechanism was proposed involving the non-aromatic zwitterionic intermediate **316-1** rather than aromatic iminium species **322**, which exhibited high activity for dipolar cycloaddition with small energy barriers.



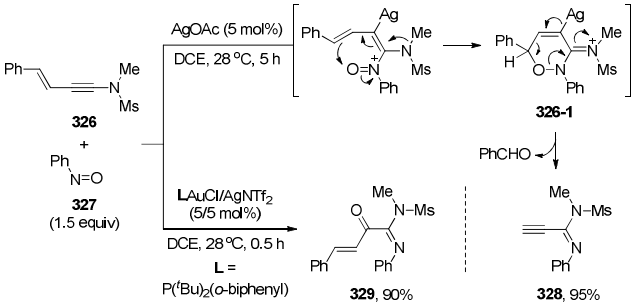
Scheme 92

The silver-catalysed cycloisomerization of *ortho*-alkynylaryl iminoethers **323** with active methylene compounds **324** was investigated by Oh *et al*. and was shown to be an efficient approach for the synthesis of 2,3-disubstituted indoles **325** (Scheme 93).[238] As a new route for synthesizing indoles, the reaction mechanism was quite interesting, involving a consecutive two-component condensation, cycloisomerization and 1,3-alkenyl shift sequence. This method represents an ideal protocol for the *in situ* metal-mediated synthesis of olefin and its regioselective migration to the metal-activated site and should be highly effective in constructing 3-alkenylated indoles, which are substructures found in many biologically active synthetic and natural compounds.[239]



Scheme 93

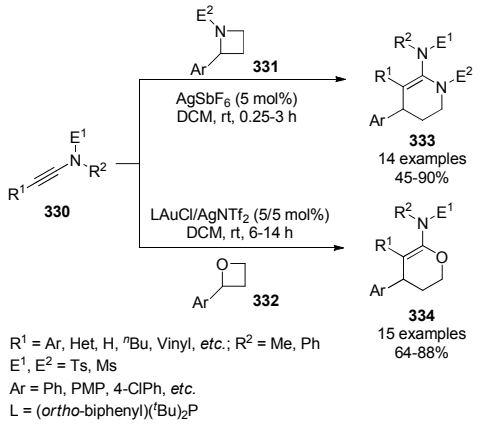
Previously, the metal-catalysed metathesis reactions between alkynes and double-bond species (*e.g.*, C=C, C=O, and C=N) producing various diene, enone, and enimine compounds were limited to a 1,2-metathesis route.[240] However, Liu *et al*. recently developed a catalyst-dependent, chemoselective metathesis reaction of 3-en-1-ynamide **326** with nitrosoarene **327** (Scheme 94).[241] The authors found that $LAuNTf_2$ catalysis resulted in the 1,2-metathesis product **329** in a 90% yield, whereas the corresponding silver salt, *i.e.*, $AgNTf_2$, implemented an unprecedented 1,4-metathesis process to generate 2-propynimidamide **328**, in which the yield could be further improved to 95% by AgOAc catalysis. Mechanistically, due to the weak N−O bond, the initial [4 + 2] cycloaddition was capable of proceeding to afford cycloadduct **326-1**, and subsequent molecular fragmentation led to 2-propynimidamide **328** and benzaldehyde. The difference might be due to the LAu^+ being more electron-rich than Ag^+, thereby directing a 1,2-shift of the neighbouring group through a hyperconjugation effect.[242]



Scheme 94

3.4 Cycloaddition

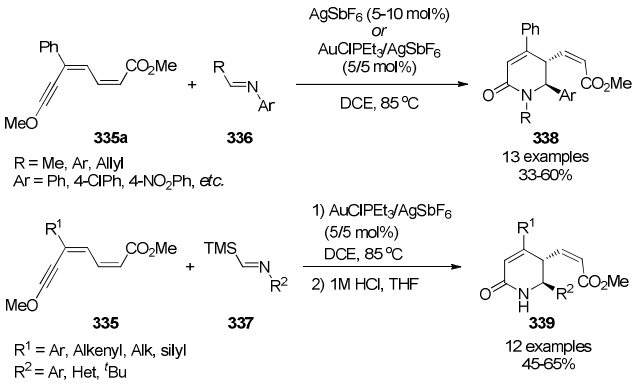
Ynamides are a class of versatile synthetic intermediates.[243] In 2014, Liu and co-workers developed a [4 + 2] cycloaddition reaction of azetidines **331** with ynamides **330**. It was found that $AgSbF_6$ sufficiently to catalyze this cycloaddition, affording 2-amino-1,4,5,6-tetrahydropyridines **333** in 45–90% yields. In constrast, the reaction of ynamides **330** and aryl oxetanes **332** required the gold(I)/silver(I) bimetallic catalyst system, and afforded 6-amino-3,4-dihydro-2*H*-pyran derivatives **334** with excellent regioselectivity. Notably, only using silver or gold catalyst, the product yields decreased dramatically. In these two cycloaddition reactions, azetidines **331** and oxetanes **332** functioned as nucleophiles, whereas metal-π-ynamides functioned as electrophiles (Scheme 95).[244]



Scheme 95

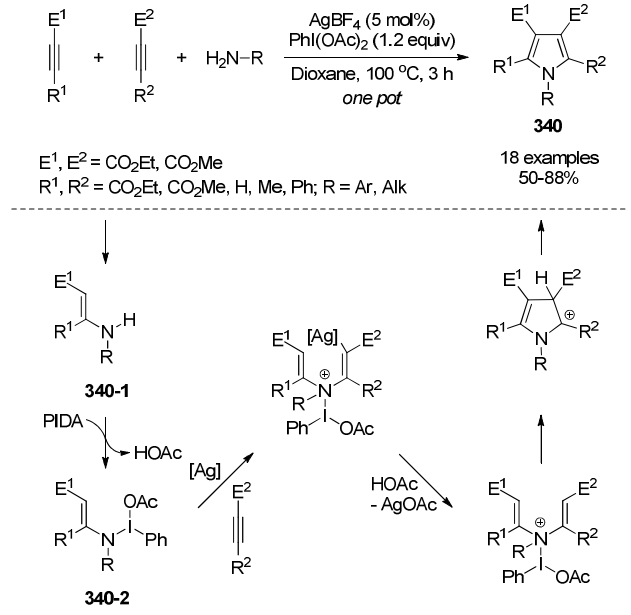
Another [4 + 2] cycloaddition of push-pull 1,3-dien-5-ynes **335** and aldimines **336** or silyl aldimines **337** was described by Aguilar *et al*. (Scheme 96).[245] This reaction could be mediated either by the catalytic amount of $AgSbF_6$ alone or by the $AuClPEt_3/AgSbF_6$ bimetallic catalyst system, thereby allowing for the regio- and diastereoselective formation of *trans*-5,6-dihydropyridin-2-ones **338** and **339** in moderate yields. In contrast to push-pull 1,3-dien-5-ynes **335**, the neutral, electron-deficient or electron-rich enynes did not result in dihydropyridones. This result demonstrated that the electronic

nature of the conjugated system was crucial and that a push-pull system was required for the intermolecular Hetero-Dehydro-Diels-Alder reaction.



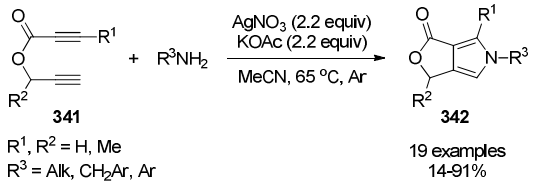
Scheme 96

Multicomponent reactions constitute a step-economic route to access molecules with a high degree of complexity. In 2010, Jiang and co-workers developed a three-component reaction of two activated alkynes and primary amines in the presence of $AgBF_4$ as a catalyst and $PhI(OAc)_2$ (PIDA) as an oxidant to afford fully substituted pyrroles **340** (Scheme 97).[246] Mechanistically, the oxidative activation of the enamine intermediate by PIDA played a crucial role in initiating the reaction cascade (**340-1**→**340-2**). In the case of different alkynes, the successive addition of alkynes and PIDA was required to achieve the selective formation of asymmetrically substituted pyrroles.



Scheme 97

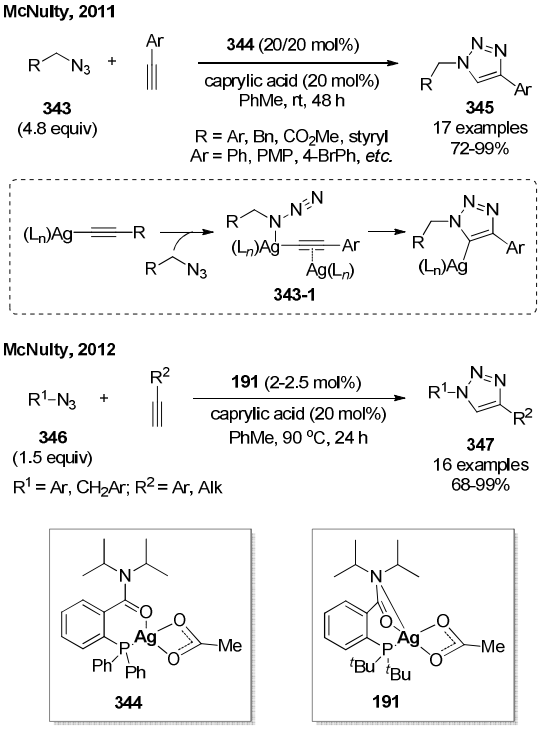
Ester-tethered diynes, *i.e.*, propargyl alkynoates **341**, were explored by Wan and co-workers in the silver-mediated tandem conjugate addition and cyclization reaction with primary amines, which resulted in the one-step synthesis of pharmaceutically relevant fused pyrroles **342** in 14–91% yields (Scheme 98).[247]



Scheme 98

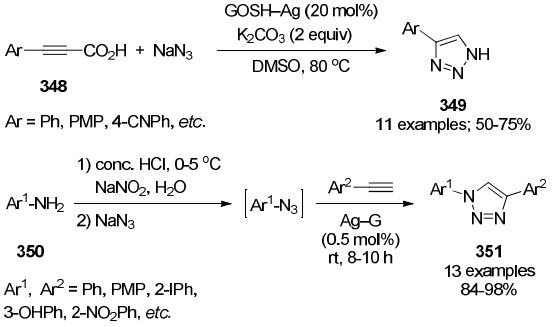
Azide-Alkyne Cycloaddition: Since the copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC) reaction was independently reported by the Sharpless and Meldal groups in 2002,[248] this reaction has been deployed across the fields of chemistry, materials science, and life sciences.[249] With the exception of copper salts, however, other transition metal-catalyzed AAC reactions have rarely been developed.

In 2011, McNulty and co-workers discovered the first synthetically useful Ag(I)-catalysed AAC (AgAAC) reaction of azides **343** with alkynes towards 1,4-disubstituted-1,2,3-triazoles **345** with the aid of a well-defined *P,O*-type silver(I) complex **344** (Scheme 99).[250] Among the set of Ag(I) salts tested, only the silver complex **344** induced the AAC reaction, indicating that the hemilabile *P,O*-type ligand played an important role. Mechanistically, the AgAAC reaction proceeded *via* a bimetallic pathway that involved the generation of silver acetylide and further activation of the acetylide–azide intermediate **343-1**, which was in accordance with the generally accepted mechanism of the CuAAC reaction.[251] However, the alkynes were limited to aryl alkynes. Soon after, the same group extended the substrate scope to aliphatic alkynes and aryl azides **346** with another well-defined silver(I) complex **191**, which only slightly varied the substituent of phosphine.[252] This reaction could be performed at 90 °C and exclusively afforded 1,4-disubstituted 1,2,3-triazoles **347** in 68–99% yields. More recently, this AgAAC reaction was further improved by Cuevas-Yañez *et al*. using a simple silver(I) salt, *e.g.*, AgCl, in an aqueous solution or a NHC-Ag(I) complex with a low Ag(I) catalyst loading.[253]



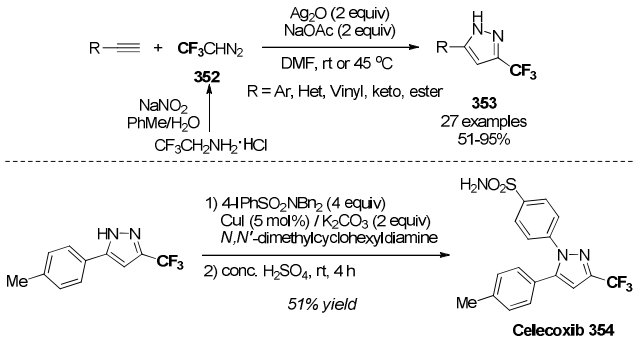
Scheme 99

In 2012, a reusable graphene-oxide-based silver-catalyst (GOSH–Ag) was prepared by Choi and co-workers and applied for the decarboxylative cycloaddition reaction of aryl propiolic acids **348** with NaN_3, allowing for the formation of 1-aryl-1,2,3-triazoles **349** in 50–75% yields (Scheme 100).[254] Recently, Jana and Islam *et al*. expanded this concept by preparing a recyclable graphene-based composite using silver nanoparticles (Ag–G) as a heterogeneous catalyst that was successfully utilized to synthesize 1,4-disubstituted 1,2,3-triazoles **351** starting from anilines **350** in a one-pot reaction.[255]



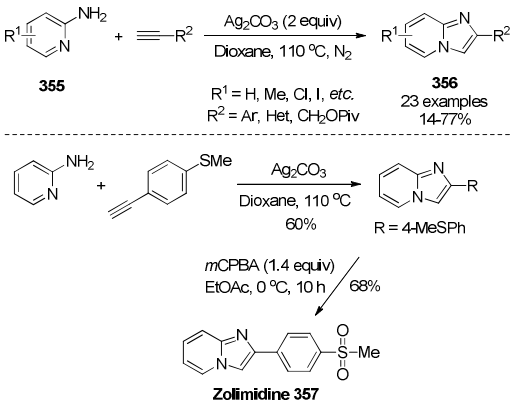
Scheme 100

Diazomethane-Alkyne Cycloaddition: To address the limitations of intermolecular 1,3-dipolar cycloaddition between alkynes and diazo compounds developed by groups such as Fields and Tomlinson in 1979 using 2,2,2-trifluorodiazoethane as a 1,3-dipole,[256] and, more recently, by the Li, Ready, Liang, and Legros groups using other diazocarbonyl compounds as 1,3-dipoles,[257] the Ma group in 2013 reported the Ag_2O-mediated cycloaddition of terminal alkynes with *in situ*-generated 2,2,2-trifluorodiazoethane (CF_3CHN_2) **352** from $CF_3CH_2NH_2{\cdot}HCl$ by diazotization, as a 1,3-dipole to construct functionalized 3-trifluoromethylpyrazoles **353** in a regioselective manner (Scheme 101).[258] Among the examined copper, silver, and gold salts/complexes, silver salts resulted in the best results. Remarkably, electron-deficient alkynes efficiently underwent the desired transformation, even at room temperature, within one hour. Furthermore, the group demonstrated the potential application of this protocol as a key step in organic synthesis, *i.e.*, the formation of anti-arthritis drug Celecoxib **354**.



Scheme 101

2-Aminopyridine-Alkyne Cycloaddition: Following previous work,[73,76] in 2012, Lei *et al*. demonstrated a novel method for the synthesis of 2-(hetero)aryl-imidazo[1,2-*a*]pyridines **356** *via* Ag_2CO_3-mediated tandem intermolecular and intramolecular oxidative C–N bond formation reactions of 2-aminopyridines **355** with terminal alkynes (Scheme 102).[259] Moreover, from controlled experiments such as the use of silver acetylides and internal alkynes rather than terminal alkynes, the authors envisioned that silver acetylide might be the key intermediate in the reaction. Using this protocol, they developed a concise route to synthesize the well-marketed antiulcer drug Zolimidine **357**.

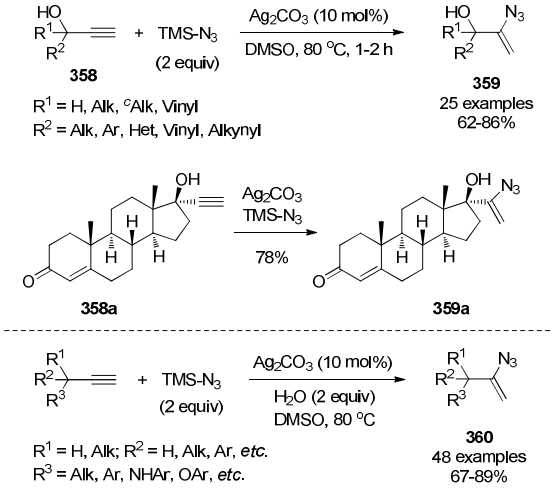


Scheme 102

3.5 Azidation

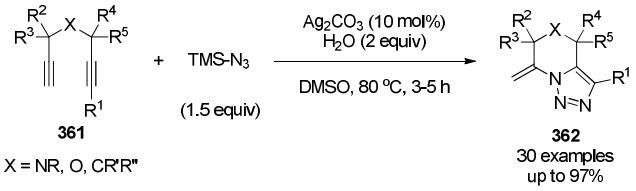
The hydroazidation of alkynes is a direct route to form Csp^2–N bonds, resulting in the formation of synthetically useful vinyl azides.[260] However, the general method for the hydroazidation of alkynes remains elusive. As shown in Scheme 103, our group recently discovered the first chemo- and regioselective conversion of ethynyl carbinols **358** into vinyl azides **359** by silver catalysis.[261] Among different transition metal catalysts examined, silver salts were effective and Ag_2CO_3 showed the best catalytic activity. This Ag_2CO_3-catalysed hydroazidation

protocol represents a highly efficient reaction for the convenient synthesis of a wide array of 2-azidoallyl alcohols **359**. This method was further utilized in the chemoselective modification of Ethisterone **358a**, an orally active progestin, thereby leading to the corresponding vinyl azide derivative **359a**, without changing the chiral centre. Our group further realized the general hydroazidation of terminal alkynes by combining TMS-N_3 and H_2O, which eliminated the dependence on the hydroxyl group in the substrates.[262] This reaction had a broad substrate scope of terminal alkynes, affording the corresponding vinyl azides **360** in 67–89% yields. Easy access to these highly functionalized vinyl azides has paved the way in organic synthesis to explore their synthetic potency in the future.



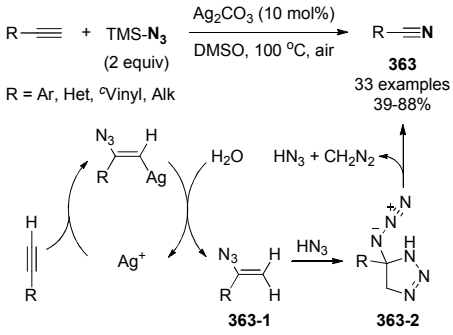
Scheme 103

To exploit the synthetic utilization of this novel reaction, our group further developed a silver-catalyzed tandem hydroazidation/alkyne−azide cycloaddition reaction of diynes **361** with TMS-N_3, which constituted an extremely simple route to access diverse pharmaceutically relevant 1,5-fused 1,2,3-triazoles **362**, including the fused heterocyclic units of piperidine, piperazine, morpholine, diazepine and isoquinoline (Scheme 104).[263] This work has paved the way in medicinal chemistry to explore the pharmaceutical potency of these fused heterocyclic frameworks in the future.



Scheme 104

Interestingly, in the absence of a stoichiometric amount of H_2O, Jiao and co-workers in 2013 reported a direct transformation of terminal alkynes into nitriles **363** through C≡C triple bond cleavage (Scheme 105).[264] This novel nitrogenation reaction of acetylenes, affording nitriles, was catalysed by Ag_2CO_3, utilizing $TMSN_3$ as the nitrogen source under aerobic conditions, whereas less yield was obtained in argon atmosphere. This functional group transformation was general, aliphatic/(hetero)aryl alkynes could be smoothly converted into the expected nitriles in good to excellent yields. Vinyl azide **363-1**, generated by the silver-catalysed functionalization of alkyne moieties, was the key intermediate in this transformation. Vinyl azide cyclized with *in situ*-generated hydrazoic acid (HN_3) to form the unstable intermediate **363-2**, which underwent a rapid rearrangement process to afford the nitrile product, along with the release of HN_3 and CH_2N_2. Additionally, the same group described the chemoselective conversion of aryl alkynes into amides by Au/Ag cocatalysis.[265]

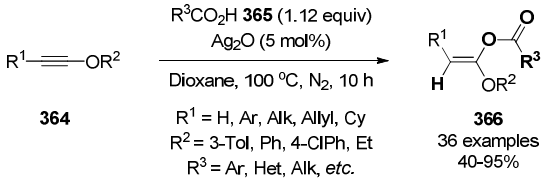


Scheme 105

4 Formation of Carbon–Oxygen Bonds

4.1 Hydrofunctionalization

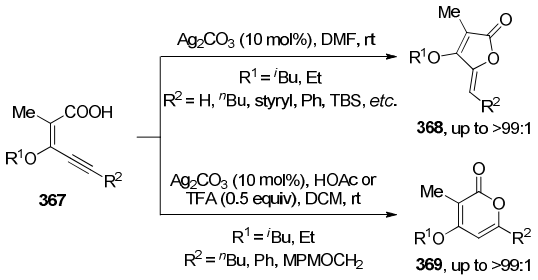
Hydrocarboxylation: Enol esters are versatile building blocks in organic synthesis.[266] The addition of carboxylic acids to alkynes is a straightforward and highly atom-economical protocol for the synthesis of enol esters. Although a number of transition metal-catalysed transformations using this protocol have been reported, the regio- and stereoselectivity issues have still restricted most of the applicability to terminal alkynes and asymmetric internal alkynes. Recently in 2014, Zhu and co-workers achieved the regio- and stereoselective *trans*-addition of carboxylic acids **365** to ynol ethers **364** using Ag_2O as a catalyst, which afforded (*Z*)-α-alkoxy-enol-esters **366** in 40–95% yields (Scheme 106).[267] Notably, in the evaluation of a variety of metal catalysts such as copper(I, II), silver(I), and gold(I), silver(I) salts were usually effective and Ag_2O afforded the best result, whereas other metal catalysts produced poor yields. However, this reaction still requires the use of a functionalized alkyne to realize regio- and stereo-selectivity.



Scheme 106

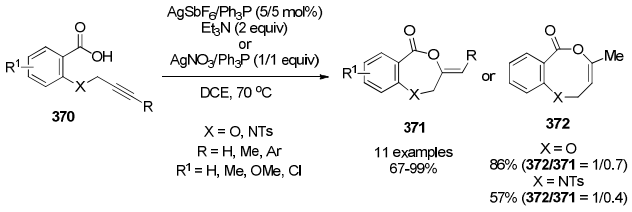
The intramolecular annulation of alkynoic acids enables direct access to lactones which have exhibited their synthetic potential and wide spread presence in biologically active natural products. Several transition metal salts, such as Pd, Cu, Ag and Au, could promote these transformations, producing five- and six-membered lactones, whereas reports presenting examples of seven-membered ring are scarce.[268] Since the 1960s, silver catalytic systems have been utilized for the cyclization of 4-

alkynoic acids and particularly in the cyclization of *ortho*-carboxytolanes and 2-en-4-ynoic acids.[132a] In 2009, Shindo and Yoshikawa *et al*. described the remarkable switching effect of Brønsted acids (HOAc or TFA) in the Ag_2CO_3-catalysed intramolecular cyclization of (*E*)-2-en-4-ynoic acids **367** (Scheme 107). A conventional 5-*exo-dig* cyclization occurred, producing tetronic acids **368**,[269] whereas with 0.5 equiv acid, the reaction was switched to a 6-*endo-dig* cyclization, affording 2-yrones **369** (Scheme 107).[270]



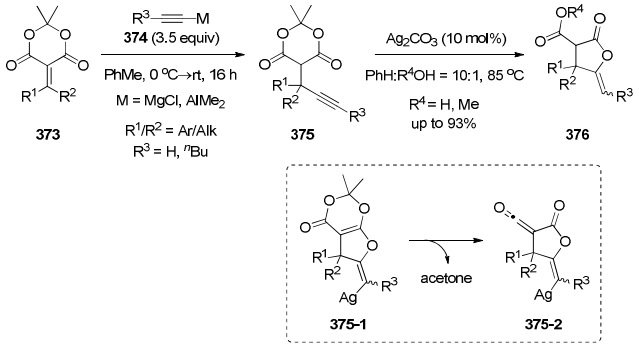
Scheme 107

Recently, in 2014, Porcel and co-workers reported the silver-mediated 7-*exo-dig* cycloisomerization of *ortho*-alkyne-tethered benzoic acids **370** into seven-membered alkylidene lactones **371**, along with the formation of 8-*endo-dig* cycloisomerization products **372**, which was dependent on the substituents in some cases (R^1 = H, R^2 = Me) (Scheme 108).[271] In contrast, with a gold(I) catalyst, seven-membered ring lactones **371** were obtained from terminal alkynoic acids more efficiently.



Scheme 108

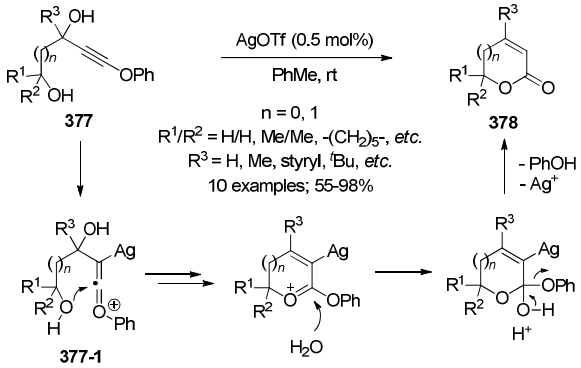
Propargyl-Meldrum's acids **375** were easily synthesized by the 1,4-conjugate alkynylation of alkylidene Meldrum's acids **373** using either dimethyl aluminium or Grignard alkynylides **374**, which constituted a general 1,4-conjugate alkynylation strategy for the formation of propargylic all-carbon quaternary centres. Subsequently, Fillion and co-workers realized the silver(I)-catalyzed intramolecular cyclization of alkynes **375**, thereby offering a two-step entry into complex γ-alkylidene butyrolactones **376** that contained an all-carbon quaternary centre at the C-4 position (Scheme 109).[272] Among the tested silver(I) and gold(I, III), Ag_2CO_3 showed the highest catalytic activity and afforded the products with high regio- and stereoselectivity. The mechanism for the formation of **376** primarily involved attack of the carbonyl-*O* onto the alkyne-coordinated Ag(I) complex, affording the 5-*exo-dig* intermediate **375-1**. The thermally induced cycloreversion of **375-1** resulted in the acylketene intermediates **375-2**, followed by nucleophilic attack of the corresponding solvent to produce the γ-alkylidene butyrolactones **376**. This work has laid a foundation for the further development of enantioselective versions.



Scheme 109

Hydro-Alkoxylation: Little progress has been made regarding the intermolecular hydro-alkoxylation of alkynes with alcohols. Thus far, the only example of such a reaction, which was catalysed by a silver-based system, was reported by Tani *et al*. in 1996.[273] However, the intramolecular hydro-alkoxylation reaction of hydroxy alkynes has been more thoroughly investigated. This reaction is important because it provides a straightforward method for the construction of pharmaceutically demanding oxygen-containing heterocycles, such as furan, pyran, and benzofuran derivatives, among others.[274]

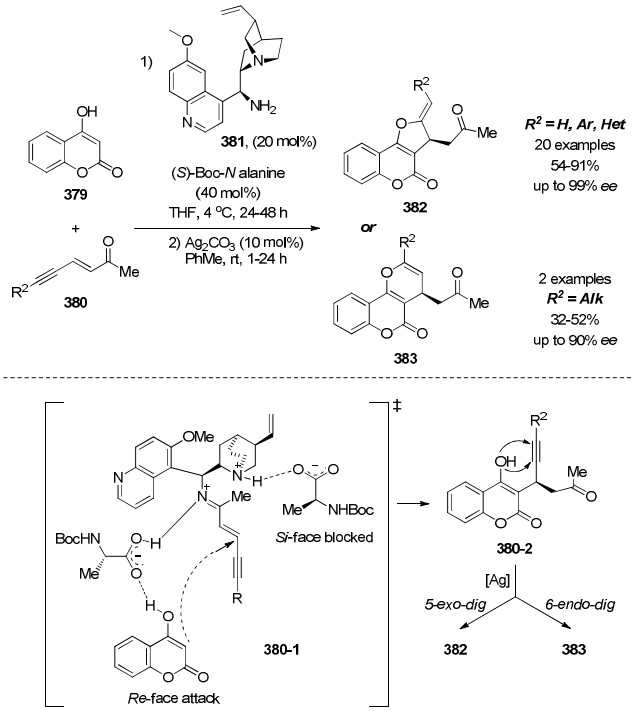
In 2013, Akai *et al*. reported a AgOTf-catalysed intramolecular cyclization of phenoxyethynyl diols **377** into α,β-unsaturated-γ-lactones and δ-lactones **378** in 55–98% yields at room temperature with an extremely low AgOTf loading of 0.5 mol% (Scheme 110).[275] This reaction started with the generation of an electrophilic oxonium intermediate **377-1**, which afterwards underwent an intramolecular annulation reaction with hydroxyl group and subsequently converted to the corresponding lactones **378**, accompanied by the release of a phenol molecule.



Scheme 110

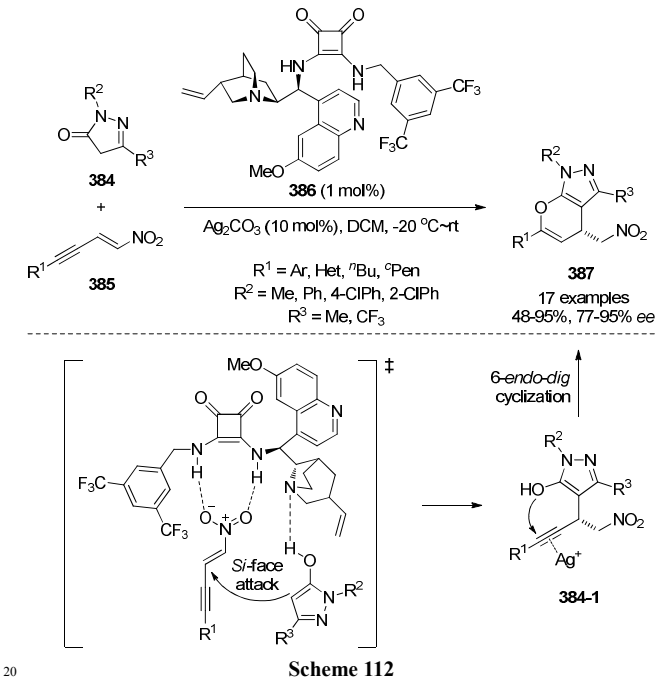
By combining organocatalysis, *i.e.*, cinchona-derived primary amine **381** with silver(I) catalysis, Enders and co-workers in 2014 developed a convenient one-pot stereoselective procedure for the asymmetric synthesis of five- and six-membered annulated coumarin derivatives **382** and **383** from 4-hydroxycoumarins **379** with enynones **380** (Scheme 111).[276] 1,4-Enynes **380-2**, *in situ*-generated by primary amine-catalysed stereo-controlled Michael addition of **379** to **380**, underwent silver-catalysed intramolecular hydroalkoxylation reaction *via* 5-*exo-dig* or 6-*endo-dig* mode to afford products **382** and **383**, which was controlled by the substituent on the alkyne moeity. Notably, *Boc*-protected amino acids as an additive could enhance the reactivity of the iminium

intermediate **380-1** and *ee* value for the reaction.



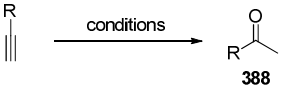
Scheme 111

Following this work, the same group further developed an asymmetric cycloaddition of pyrazolinones **384** and alkyne-tethered nitroolefins **385** for the novel synthesis of chiral pyrano-annulated pyrazoles **387**, by combining squaramide **386** and silver(I) catalysis (Scheme 112).[277] As drawn in the transition state, squaramide **386** acted as a bifunctional catalyst that gave rise to the preorientation and activation of **384** and **385** *via* hydrogen bonding. Simultaneously, the nucleophile could be directed to the *Si*-face of nitroolefin **385**, thus accounting for the observed enantioselectivity. After the asymmetric Michael addition for yielding **384-1**, the silver-catalysed electrophilic activation of the internal alkyne induced the subsequent hydroalkoxylation. The 6-*endo-dig* cyclization of **384-1** proceeded *via* stereoselective *anti*-addition of the enol to the alkyne, thus affording the *Z*-products **387**.



Scheme 112

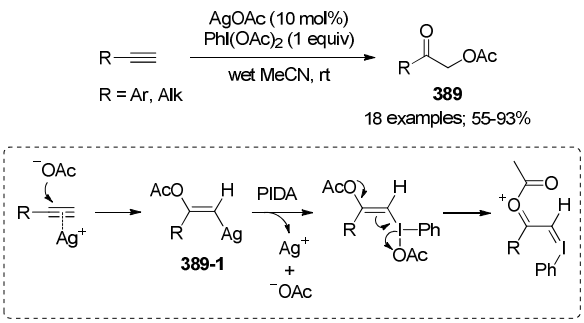
Hydration: A variety of transition metal salts are able to catalyse the addition reactions of water to alkynes (*i.e.*, hydration), producing valuable carbonyl compounds.[4a,278] Very few studies,[279] such as those by Dillard and co-workers in 1965 and Marsella and colleagues in 1993 could lead one to suspect that silver salts are inclined to induce the hydration of unactivated alkynes. A remarkable achievement in the silver-catalysed hydration of terminal alkynes was reported by Wagner *et al*. in 2012, who discovered that $AgSbF_6$ could efficiently and chemoselectively catalyse the hydration of a wide range of terminal alkynes into methyl ketones **388** under mild conditions (Scheme 113).[280] The reaction proceeded smoothly without the aid of co-catalysts, acids or ligands. However, heteroaryl alkynes, such as 2-ethynylpyridine, were not applicable. Meanwhile, a more practical protocol was developed by Lingaiah *et al*., who synthesized and examined several silver-exchanged silicotungstic acids (AgSTAs) as a catalyst under solvent-free conditions in the hydration reactions of mainly non-activated alkynes, in which Ag_3STA efficiently afforded the corresponding methyl ketones **388** in 79–97% yields.[281] One advantage of this method was that the catalyst could be recovered by simple filtration and was reusable without loss of activity and selectivity. Additionally, 2-ethynylpyridine was reactive such conditions. Then, by using HOAc as a solvent and $AgBF_4$ as a catlyst, Chen and Liu *et al*. significantly expanded the reaction scope to a range of (hetero)aryl and alkyl terminal alkynes.[282]



Wagner, 2012	Lingaiah, 2012	Chen, Liu, 2013
$AgSbF_6$ (10 mol%)	Ag_3STA (25 g/mol)	$AgBF_4$ (5 mol%)
MeOH:H_2O = 10:1	H_2O (3 equiv)	H_2O (2 equiv)
75 °C, 24 h	100 °C, 6-14 h	HOAc, 110 °C, 10 h
R = Alk, Ar	R = Alk, Ar, 2-Py	R = Alk, Ar, Het
17 examples	14 examples	22 examples
78-94%	79-97%	58-99%

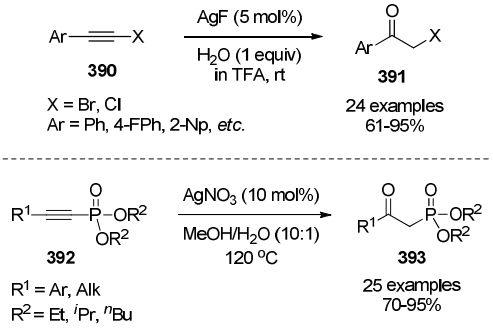
Scheme 113

In 2013, Deng *et al*. reported the formation of α-acetoxy ketones **389** *via* the AgOAc-catalysed reaction of alkynes with $PhI(OAc)_2$ in wet acetonitrile at room temperature (Scheme 114).[283] They proposed a mechanism that involved a β-acetoxyvinyl silver intermediate **389-1**; however, this hypothesis lacked suffcient experimental support.



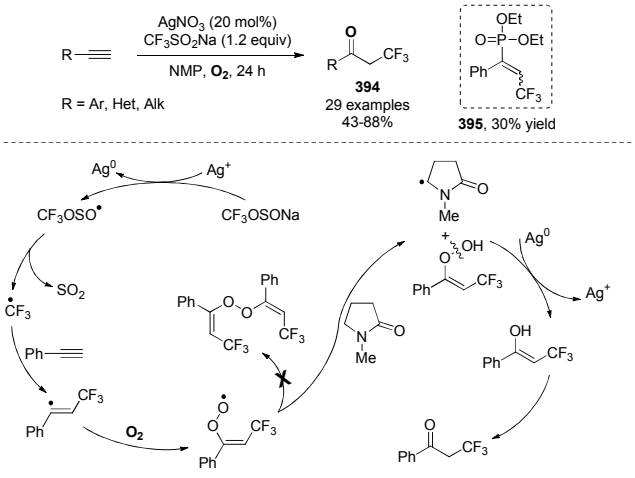
Scheme 114

In addition to terminal alkynes, the silver(I)-catalysed hydration reaction has been extended to other functionalized internal alkynes. For example, Liu and Chen *et al*. recently reported a AgF-catalysed hydration of haloalkynes **390** in TFA solvent, allowing for the synthesis of α-haloketones **391** in 61–95% yields (Scheme 115).[284] Among the tested silver catalysts, AgF proved to be optimal, and other catalysts such as gold(I) and copper(I) salts were not effective. The transition metal-catalysed hydration of alkynylphosphonates provides a direct and efficient route to β-ketophosphonates. In contrast to the use of expensive gold complex,[285] the cheap $AgNO_3$ as a catalyst could efficiently catalyse the conversion of alkynylphosphonates **392** into β-ketophosphonates **393** in a mixture solvent of MeOH and H_2O. This method was simple and atom-economical, and applicable to a variety of substrates **392**.[286]



Scheme 115

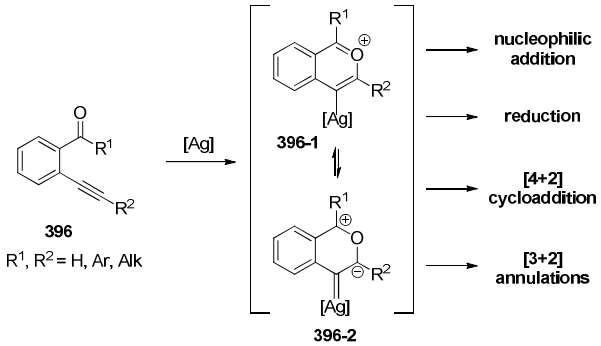
Rather than H_2O, dioxygen (O_2) is an alternative oxygen source used for oxygenation reactions of alkynes.[287] Recently, Maiti *et al*. described a $AgNO_3$-catalysed protocol for the direct conversion of acetylenes into α-trifluoromethyl ketones **394**, utilizing Langlois reagent (CF_3SO_2Na) as a CF_3 source under an oxygen atmosphere (Scheme 116).[288] Notably, this procedure was suitable for heteroaryl alkynes that were incompatible with earlier strategies. The solvent 1-methyl-2-pyrrolidinone (NMP) played a key role because it served as the source of hydrogen. Mechanistic investigations suggested a radical process, which was supported by trapping of the α-styrenyl radical intermediate with $P(OEt)_3$ to afford vinylphosphonate **395**.



Scheme 116

4.2 Carbonyl-yne Cycloisomerization

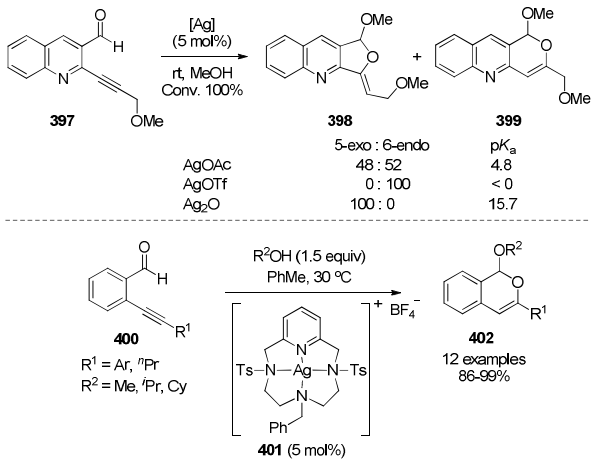
Carbonyl-yne cycloisomerization reactions were intensively investigated by Yamamoto and co-workers, who focused mainly on copper and gold.[289a,b] Silver-catalysed such kinds of reactions were further developed and represented a powerful method for synthesizing diverse oxygen-containing heterocycles, particularly isochromenes and their analogues. As a π-activator of the carbon−carbon triple bond, silver salts can generate highly reactive isobenzopyrylium cations **396-1** and their silver−carbene tautomers **396-2** by the intramolecular cyclization of enynal or enyone substrates **396**, which is then followed by different types of reactions: nucleophilic addition, reduction, [4 + 2] cycloaddition, and [3 + 2] annulations (Scheme 117).[174a,289]



Scheme 117

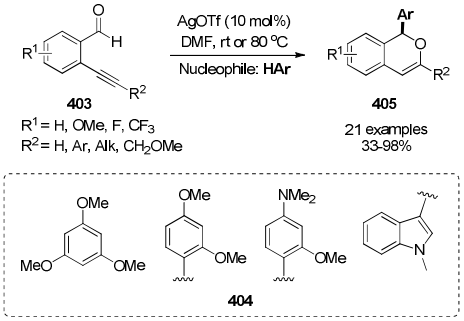
Belmont *et al.* reported a versatile cyclization reaction of 1-alkynyl-2-carbonylquinoline **397** by tandem cycloisomerization providing various furoquinoline **398** and pyranoquinoline **399** products (Scheme 118).[290] In the presence of either $AgSbF_6$ or $Au(PPh_3)SbF_6$ that was derived from $Au(PPh_3)Cl$ and $AgSbF_6$, excellent yields were obtained. In a control experiment, $AgSbF_6$ was proved to be essential because $Au(PPh_3)Cl$ alone resulted in a poor yield. Surprisingly, the pK_a of the Ag(I) catalyst, a type of silver counterion and extra additive/ligand, had a significant impact on the regioselectivity of the annulation, resulting in the 5-*exo*-*dig* product, the 6-*endo*-*dig* product or both. They proposed that furoquinoline **398** were obtained *via* sequential acetalization

and intramolecular cyclization, whereas 6-*endo*-*dig* products **399** were generated *in situ* from the pyrylium intermediates, in which silver(I) salt functioned as a Lewis acid and a π-activator, respectively. In addition, in a recent report in 2014 by Caselli and Abbiati co-workers, the 6-*endo*-*dig* products **402** could be obtained with absolute regioselectivity from enynals **400** using the silver(I) complex **401** as the catalyst which contained a macrocyclic pyridine-containing ligand.[291]



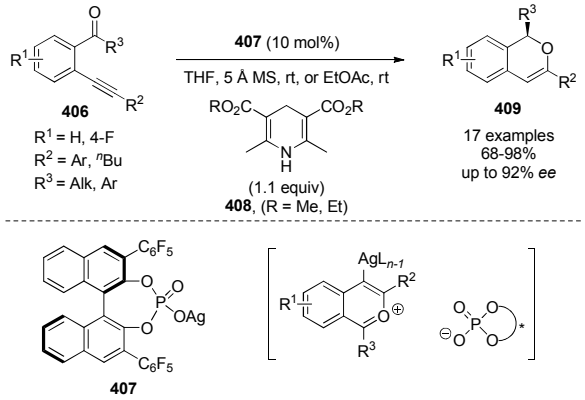
Scheme 118

The application of aromatic nuclei as external nucleophiles is rare and limited to indoles in the presence of silver complexes.[292] In 2014, Belmont *et al*. expanded the scope of this silver-catalysed nucleophile-triggered cycloisomerization of *ortho*-alkynylaldehydes **403** to electron-rich aromatics and heteroaromatics **404**. By using di-/tri-methoxybenzene, dimethylaminobenzene or *N*-methylindole as the nucleophile, they developed a AgOTf-catalysed domino reaction of *ortho*-alkynyl benzaldehydes **403**, leading to the production of functionalized 1*H*,1-arylisochromene derivatives **405** in 33–98% yields (Scheme 119).[293] Furthermore, the reactivity of diverse metallic salts such as Cu-, Au-, Pd-, and Pt-based catalysts were studied showing either no conversion or lower isolated yields.



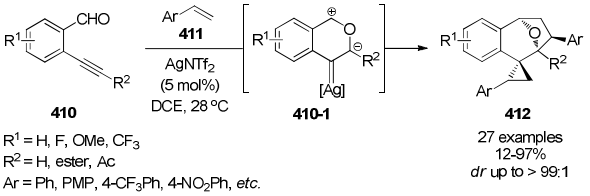
Scheme 119

The development of enantioselective transformations involving carbonyl ylide intermediate remains largely unexploited and a longstanding challenge in synthetic organic chemistry.[294] Within recent years, chiral counteranion-induced enantioselective transformations, *i.e.*, asymmetric counterion-directed catalysis (ACDC) have emerged as powerful tools in asymmetric synthesis.[295,51] By using the strategy of ACDC, Terada and co-workers successfully developed an enantioselective transformation of *ortho*-alkynylaryl ketones **406** into 1*H*-isochromene derivatives **409** in 68–98% yield and high enantioselectivity (up to 92% *ee*) (Scheme 120).[296] This reaction proceeded through a tandem cyclization/enantioselective-reduction reaction pathway with a chiral silver phosphate catalyst **407** as well as a Hantzsch ester **408** as the reductant. Notably, both Ag(I) and Cu(II) catalysts were capable of affording the 1*H*-isochromenes **409** in excellent yields, whereas gold(I) catalyst afforded poor yields. Compared with $Cu(OTf)_2$, AgOTf showed slightly improvement on the selectivity and efficiency for 6-*endo* cyclization of the *ortho*-alkynylaryl ketones **406**. Simultaneously, Akiyama *et al.* reported another enantioselective approach for synthesizing isochromenes under chiral copper(II) phosphate catalysis.[297] In this protocol, the alkyne moiety of the substrates bearing an aryl group were applicable.



Scheme 120

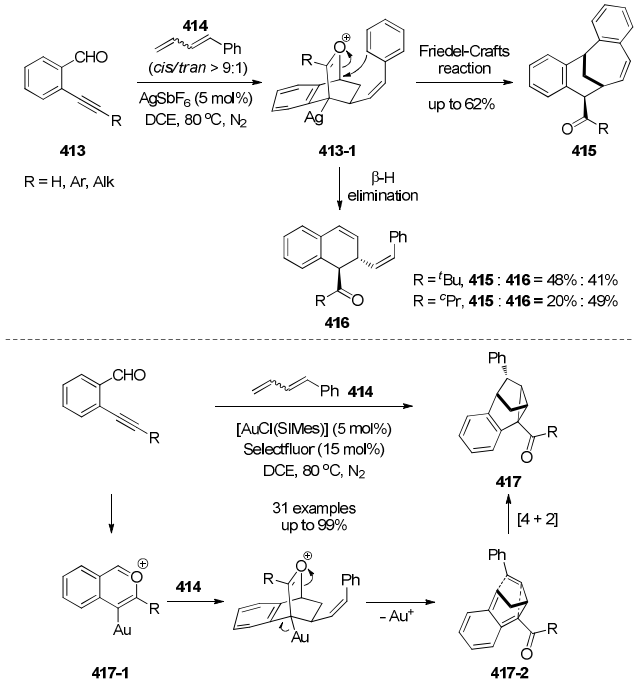
Compared with its common use in diazo chemistry, the silver−carbene process in carbonyl-yne cycloisomerization reactions has rarely been employed. Recently, a $AgNTf_2$-catalysed cycloisomerization reaction of *ortho*-alkynylbenzaldehydes **410** and alkenes **411** was developed by Zhu *et al*., leading to the synthesis of a series of complex polycyclic molecules **412** (Scheme 121).[298] In contrast, other metal catalyts such as Au(I), Fe(III), Cu(II), and Pt(II) were not effective. The reaction occurred smoothly, utilizing a variety of *ortho*-alkynylbenzaldehydes with electron-deficient or terminal alkyne units **410**. Both the electron-rich and electron-poor styrene derivatives **411** could give satisfactory yields; however, in the case of styrenes substituted with strong electron-withdrawing groups such as $–CF_3$ and $–NO_2$, the yields dramatically decreased. A possible reaction mechanism was proposed, involving a 1,3-dipolar cycloaddition with silver−carbene intermediates **410-1** and cyclopropanation steps.



Scheme 121

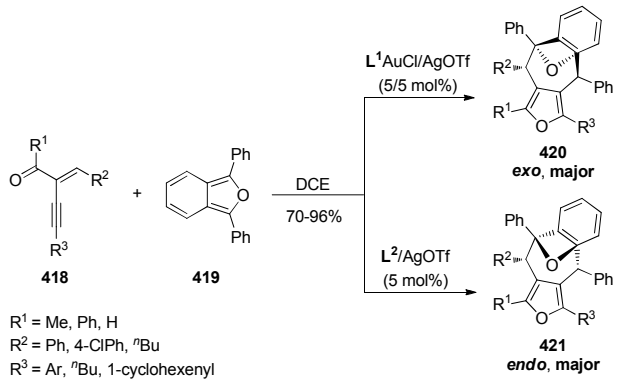
Rather than aryl-substituted monoalkenes, the same group

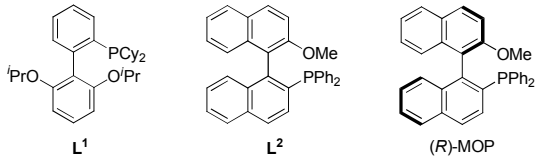
applied aryl 1,3-butadienes **414** to the silver-catalysed cycloisomerisation reaction with enynals **413**, resulting in benzocycloheptene skeletons **415** *via* a tandem Diels–Alder/Friedel–Crafts reaction (Scheme 122).[299] Control reactions revealed that only *cis*-isomers of 1,3-butadienes **414** were applicable, as *cis*-dienes could generate the required *cis*-pyrylium intermediates **413-1**. The presence of an alkyl group on the alkyne moeity induced a competitive β-H elimination of **413-1**, thus affording 1,2-dihydronaphthalenes **416**. With [AuCl(SIMes)]/Selectfluor system, however, highly-strained benzotricyclo[3.2.1.$0^{2,7}$]octanes **417** were produced through a two-fold Diels–Alder reaction. The *cis*/*trans* ratio of 1,3-dienes **414** showed a slight impact on the resulting product structures, which suggested a mechanism that the vinyl-substituted cyclic-*o*-QDM (*o*-Quinodimethane) **417-2** generated *in situ* from pyrylium intermediate **417-1** subsequently proceeded an intramolecular [4 + 2] annulation to produce the final product **417**.



Scheme 122

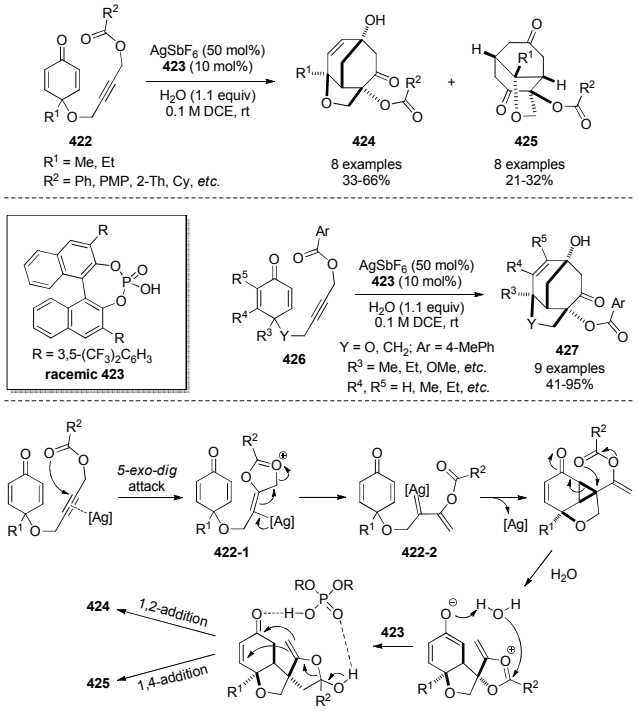
Besides *ortho*-alkynylarylaldehydes, other enynal or enyone substrates could also play a similar role to generate a carbonyl ylide intermediate. In 2010, Zhang and co-workers reported an *exo*/*endo* stereo-controlled tandem carbonyl cycloisomerization/[4+3] cycloaddition of 2-(1-alkynyl)-2-alken-1-ones **418** and 1,3-diphenylisobenzofuran **419**, affording highly fused polycyclic skeletons **420** and **421** under gold or silver catalysis (Scheme 123).[300] In the case of $\mathbf{L^1}$AuCl-catalyzed reaction, *exo*-isomers **420** were obtained as major products, whereas use of silver/$\mathbf{L^2}$ as a catalyst mainly afforded *endo*-isomers **421**, albeit with a longer reaction time. Control experiments demonstrated that the phosphine ligands ($\mathbf{L^1}$ and $\mathbf{L^2}$) played a crucial role in determining the diastereoselectivity, although the exact reasons remianed unclear. Aided by a gold(I) catalyst coordinated with a ligand (*R*)-MOP, an enantioselective version was realized, albeit with moderate *ee* values.





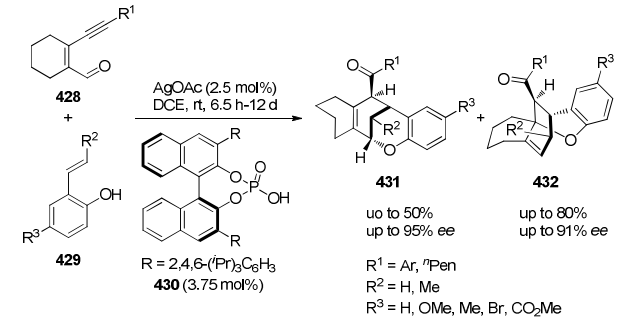
Scheme 123

In the presence of racemic phosphoric acid **423**, a silver-mediated conversion of propargylic ester-tethered to cyclohexadienones **422** into bicyclo[3.3.1]nonane isomers **424** and **425** was described by Wang *et al*., in which the propargylic ester moiety played a role as the precursor to produce the carbonyl ylide intermediate **422-1** (Scheme 124).[301] Mechanistically, this tandem reaction proceeded through a unique sequence involving silver carbenoid species **422-2** generated *in situ via* the 5-*exo*-*dig*-mode, subsequent enone cyclopropanation initiation, cyclopropyl vinyl ester hydrolytic fragmentation, and competitive carbonyl addition *vs* 1,4-conjugative addition events. Interestingly, if the substrates **426**, with asymmetrically substituted cyclohexadienones (Y = O or CH_2), were subjected to the same conditions, 1,2-addition products **427** were exclusively formed, with complete stereochemical control. Importantly, this discovery shed further light on the expanding potential of Ag(I) catalysts as robust and elusive metallo-carbenoid intermediates.



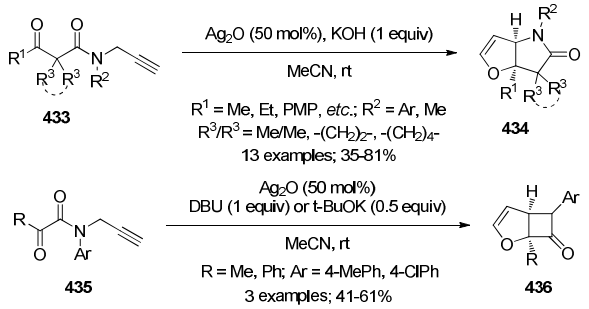
Scheme 124

Following success in the $Pd(OAc)_2$-catalysed asymmetric tandem cyclization reaction between 2-hydroxystyrenes and 2-alkynylbenaldehyes or 1-(2-alkynylphenyl)ketones,[302] the Yao group further described an asymmetric annulation of 3-alkynylacrylaldehydes **428** with 2-hydroxystyrenes **429** *via* the synergetic catalysis of AgOAc and the chiral phosphoric acid, *e.g.*, (*S*)-TRIP **430**, to yield novel benzofused polycyclic products **431** and **432** (Scheme 125).[303] This reaction proceeded through the initial alkyne−carbonyl cycloisomerization to form pyrylium intermediate, and following counter anion-directed asymmetric oxa [4 + 2]-cycloaddition, and intramolecular S_N2 or S_N2' substitution.



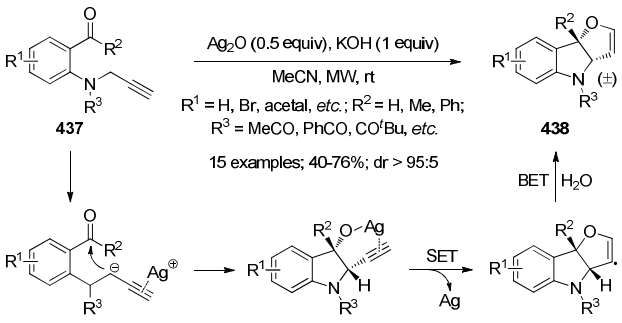
Scheme 125

Intramolecular 1,3-dipolar cycloaddition reactions provide an efficient and direct route for the synthesis of cyclic compounds. Although a number of C_3 1,3-dipolar reagents or their synthetic equivalents have been developed, the generation of all-carbon 1,3-dipoles in an efficient pathway has been more challenging.[304] In 2010, Zhang and Liu *et al*. reported Ag_2O-mediated, a diastereoselective 1,3-dipolar cycloaddition reaction of diverse oxo-*N*-propargylamides **433** and **435**, affording furo[3,2-*b*]-β-lactams **434** and furo[3,2-*b*]-γ-lactams **436** (Scheme 126).[305] The propargyl moiety served as a potential 1,3-dipole.



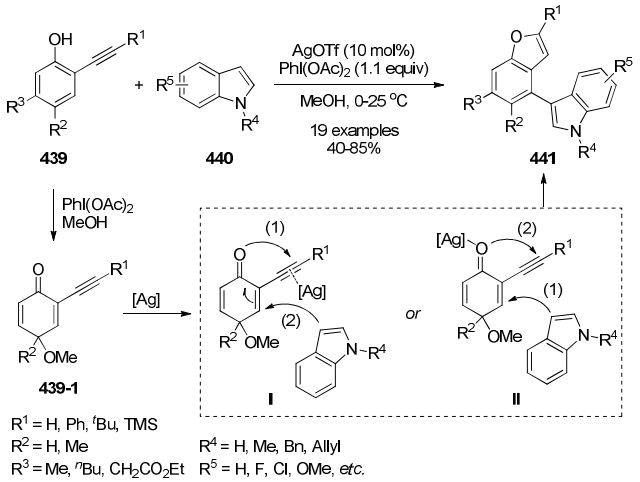
Scheme 126

Further, the same group developed a microwave-assisted, Ag_2O-mediated one-pot methodology for the facile synthesis of dihydrofuro[3,2-*b*]indoles **438** from *o*-propargylamino-acetophenones/-benzaldehydes **437** in a regiospecific and diastereoselective manner, which involved an intramolecular [3 + 2] cycloaddition pathway (Scheme 127).[306] Mechanistic studies identified the formation of elemental silver instead of Ag_2O. Therefore, they hypothesized that Ag_2O played dual roles as a base and an oxidant and thus proposed a single electron-transfer (SET) mechanism to account for the formation of heterocyclic frameworks.



Scheme 127

The oxidative dearomatization of *ortho*- and *para*-substituted phenols to cyclohex-2-enones could be triggered by means of appropriate internal or external nucleophiles, thus leading to a variety of synthetically useful multi-functionalized aromatic compounds that are difficult to prepare through electrophilic substitution reactions.[307] Based on this strategy, in 2011, Ye and Fan *et al*. described a AgOTf-catalysed, $PhI(OAc)_2$-mediated one-pot method for the synthesis of 4-(3-indole)-benzofuran derivatives **441** from the reaction of 4-alkyl-2-ynylphenols **439** with indoles **440** (Scheme 128).[308] The reaction proceeded through the initial hypervalent iodine-induced oxidative dearomatization to form **439-1** and the following silver(I)-catalysed tandem Michael addition-cyclization (pathway I or II), and rearomatization. Compared with $Cu(OTf)_2$ and $AuCl_3$, AgOTf showed superior catalytic activity.

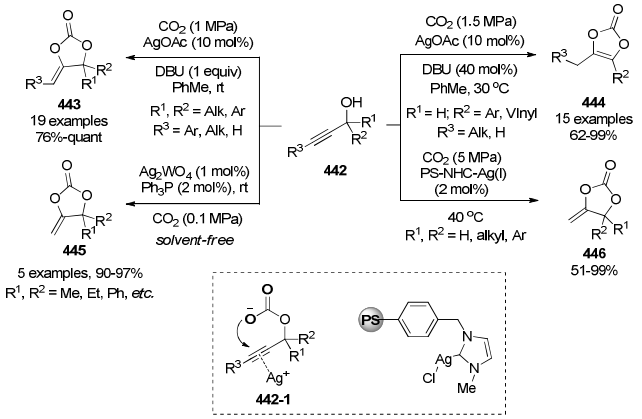


Scheme 128

4.3 CO_2 Incorporation

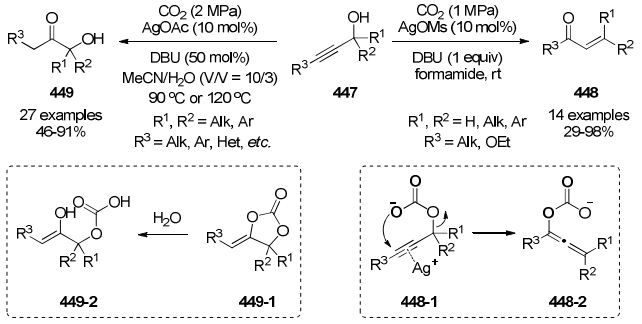
Carbon dioxide (CO_2) is an attractive C1 feedstock for organic syntheses due to its high abundance, ubiquity, and reduced toxicity compared with other C1 sources, such as carbon monoxide and phosgene. However, due to its lower reactivity, harsh reaction conditions (high pressure/energy) are generally required to activate and incorporate CO_2 molecules into organic compounds.[22b] Therefore, it is necessary to develop a mild catalyst system to efficiently capture CO_2 and convert it into a variety of chemicals. Since 2007, by starting from the readily available propargylic alcohols, propargylic amines and *ortho*-alkynylanilines, the Yamada group has developed a series of CO_2-incorporation reactions under mild conditions by combining silver catalysts and DBU, thereby producing the corresponding cyclic carbonates, oxazolidinones, and benzoxazine-2-one derivatives, respectively.[309] These achievements have been summarized in the latest review by Yamada *et al*. in 2014; however, some new advances have occurred in the last year. For example, rather than the previously reported 4-(aryl)alkylidene cyclic carbonates **443** produced from tertiary propargylic alcohols **442**, Yamada *et al*. found that the vinylene carbonates **444** could be obtained *via* the AgOAc-catalysed carboxylic cyclization of secondary propargylic alcohols (Scheme 129).[310] Mechanistically, the initial cyclic carbonate generated by intermediate **442-1** was converted to the more thermodynamically stable vinylene carbonate derivatives **444** by olefin isomerization. Meanwhile, Li and He *et al*. recommended a solvent-free protocol for the CO_2 incorporation of terminal propargylic alcohols **442** (R^3 = H) to α-methylene cyclic carbonates **445** by a cooperative Ag_2WO_4 (1 mol%) and Ph_3P (2 mol%) catalyst system under atmospheric CO_2.[311]

In 2013, the heterogeneous catalysts including PS-NHC-Ag(I) and PS-NHC-Cu(I) complexes were synthesized and applied to catalyze the reaction of propargylic alcohols **442** with CO_2 for producing α-methylene cyclic carbonates **446**. PS-NHC-Ag(I) as a recyclable catalyst exhibited excellent catalytic activity and afforded the corresponding products **446** in 51–99% yields under solvent-free conditions, whereas PS-NHC-Cu(I) was not effective.[312]



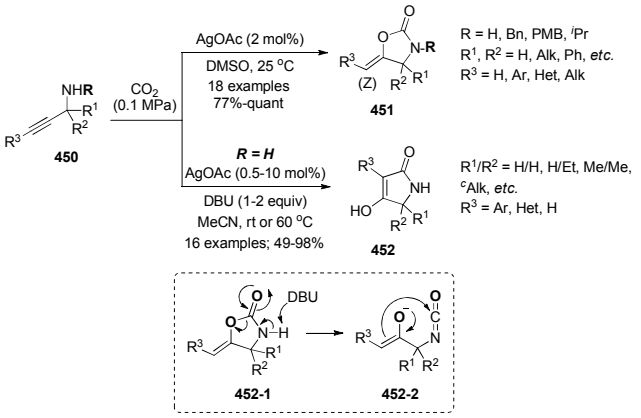
Scheme 129

In the presence of AgOMs (10 mol%) in a polar solvent (formamide), the Yamada group discovered a new transformation leading to the production of α,β-unsaturated ketones **448** from propargyl alcohols **447** (Scheme 130).[313] The mechanism involved the CO_2 incorporation of propargyl alcohols **447**, followed by a [3,3]-sigmatropic rearrangement of intermediate **448-1** into the allene-enolate **448-2**. Recently, Qi *et al*. reported a chemoselective transformation of propargyl alcohols **447** to α-hydroxy ketones **449** in an aqueous acetonitrile solution at elevated temperature. The reaction proceeded through a tandem carboxylic cyclization/regioselective hydration sequence by intermediates **449-1** and **449-2**.[314] Interestingly, Jiang and co-workers discovered a different catalytic performance of CuI/DBU catalyst system, which allowed for a three-component reaction of propargyl alcohols, nitriles and CO_2 to produce highly substituted 3(2*H*)-furanones; CuI was used to activate the propargylic alcohols and nitriles.[315]



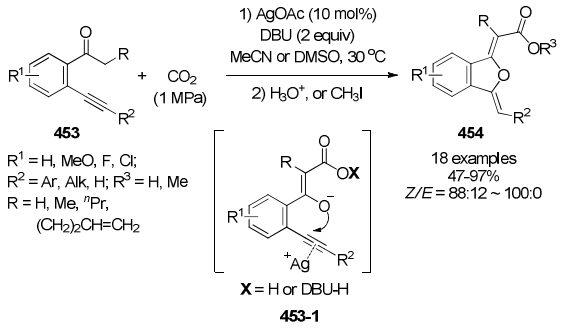
Scheme 130

Meanwhile, the Yamada group has studied the reactivity of propargylic amines **450** with CO_2 by the AgOAc-catalysed carboxylic cyclization, which afforded oxazolidinones **451** in high to excellent yields (Scheme 131).[316] Recently, they found a completely different reaction pattern in the presence of DBU that led to the formation of tetramic acids **452**.[317] A variety of propargylic amines were suitable for the reaction. Mechanistically, the reaction was assumed to proceed through the DBU-promoted rearrangement of the initially formed oxazolidinone ring **452-1** to yield the tetramic acid **452** by intermediate **452-2**.



Scheme 131

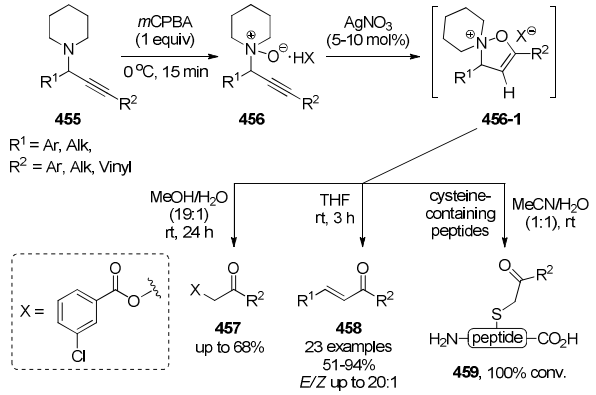
The *ortho*-alkynyl acetophenones were also shown to be suitable substrates in the silver-catalysed carboxylic cyclization with CO_2. In 2013, Yamada *et al*. reported that the AgOAc/DBU catalyst system effectively catalysed the tandem reaction of *ortho*-alkynyl acetophenones **453** and CO_2, resulting in dihydroisobenzofuran derivatives bearing a carboxyl group **454** in high to excellent yields (Scheme 132).[318] Among the examined Ag(I), Cu(I), Au(I), Pd(II) salts/complexes, silver salts displayed high catalytic activities, whereas other metals afforded trace amounts of desired products. Subsequently, Zhang and Lu revised this silver-catalysed reaction under atmospheric CO_2 using a $AgBF_4$/MTBD catalyst system. Moreover, the authors rationalized the exclusive selectivity of 5-*exo* oxygen cyclization through a computational study.[319]



Scheme 132

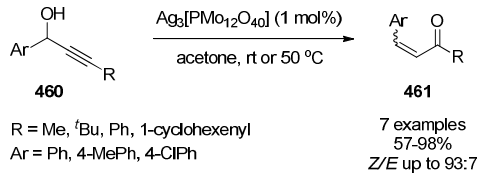
4.4 Miscellaneous Reactions

A one-pot oxygenation and rearrangement of tertiary propargylic amines **455** was reported by Wong *et al*., who prepared a reactive isoxazolinium intermediate **456-1** *via* the sequential treatment of propargylic amines with *m*CPBA and $AgNO_3$ *via* the isolatable *N*-oxides **456** (Scheme 133).[320] The product profiles from intermediate **456-1** can be controlled by the use of protic or aprotic solvents, thus chemoselectively producing 3-chlorobenzoxymethyl ketones **457** and enones **458**. Control experiments demonstrated the necessity of both $AgNO_3$ and *m*CPBA for the reaction, as no enone product was observed if other metal salts/complexes were used as a catalyst, such as copper(I, III), gold(I, III), zinc(II). Furthermore, the selective modification of the cysteine residue of peptides was realized using this *in situ*-generated isoxazolinium intermediate **456-1**, thereby establishing a propargylic amine-based bioconjugation reaction that was highly chemoselective for cysteine-containing peptides **459**.



Scheme 133

The Meyer–Schuster rearrangements have traditionally led to the more thermodynamically stable *E* isomers using transition metal catalysts such as Au, Re, and Ru, whereas the formation of the less stable *Z* isomers is rare.[321] In 2011, Akai *et al*. demonstrated the first example of stereoselective Meyer–Schuster rearrangement of propargyl alcohols **460**, affording thermodynamically unfavourable (*Z*)-α,β-unsaturated ketones **461** under the silver-based heteropolyoxometallate, $Ag_3[PMo_{12}O_{40}]\cdot nH_2O$ catalysis (Scheme 134).[322]



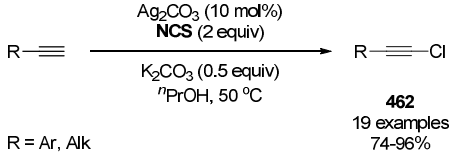
Scheme 134

5. Formation of Carbon–X Bonds

5.1 Formation of Carbon–Halogen Bonds

The dehydro-halogenation[323] of terminal alkynes or halogen addition[324] to alkynes with the aid of NXS has been an efficient and practical method for synthesizing halogen-substituted hydrocarbons, which are reactive intermediates in organic synthesis.

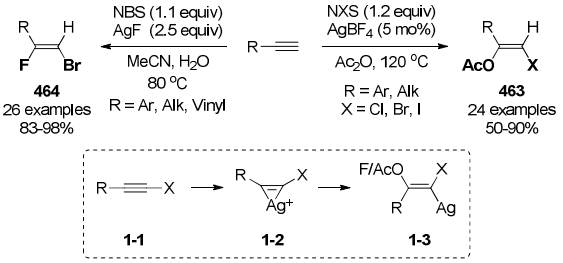
In contrast with the well-established methods for producing 1-iodoalkynes and 1-bromoalkynes, efficient synthetic methods for 1-chloroalkynes remain scarce. Recently, Shi and Chen *et al.* reported an efficient protocol for 1-chloroalkyne **462** synthesis by the silver-catalyzed reaction of terminal alkynes with NCS (Scheme 135).[325] By comparison, lower yields were obtained using copper(I) catalyst, due to the homocoupling diynes.



Scheme 135

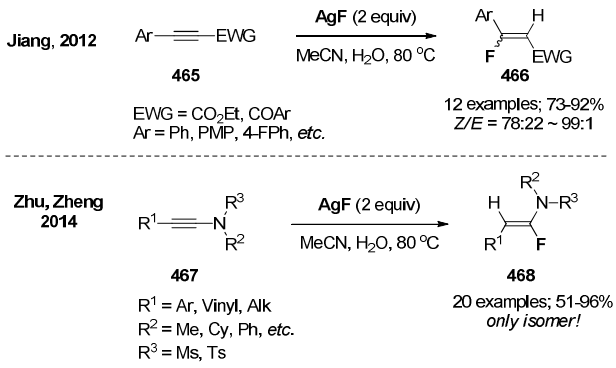
In 2010, Jiang and co-workers developed a convenient method

for synthesizing of β-haloenol acetates **463** through the $AgBF_4$-catalysed difunctionalization of terminal alkynes.[326] In most cases, the (*Z*)-β-haloenol acetates **463** were obtained regio- and stereospecifically in moderate to excellent yields. Then, the same group expanded this methodology to the synthesis of bromofluoroalkenes **464** using a stoichiometric amount of AgF rather than acetic anhydride.[327] AgF served as a fluorine source and promoted the reaction to proceed. Notably, 1,*n*-diynes also smoothly participated in such reaction. As shown in Scheme 136, a plausible reaction mechanism was proposed, involving the sequential formation of a haloalkyne intermediate **1-1**, a silver-π-complex **1-2**, and a silver-σ-complex **1-3**.



Scheme 136

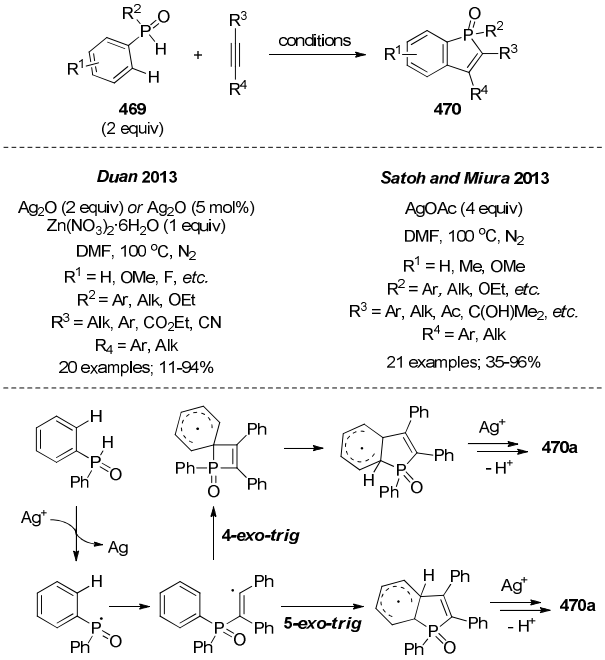
As an extension, the Jiang group treated the electron-deficient internal alkynes **465** such as 3-phenylpropiolate and aryl alkynyl ketones with AgF (2 equiv), resulting in the β-fluorination products **466** in 73–92% yields and with high *Z*/*E* selectivities (Scheme 137).[327] The electron-deficient functional groups were assumed to assist the β-fluorination reaction. However, in a recent report,[328] Zheng and Zhu *et al*. investigated the reaction of electron-rich *N*-sulfonyl ynamides **467** with AgF and regioselectively obtained (*Z*)-α-fluoroenamides **468** by a *trans*-hydrofluorination reaction, which tolerated a variety of functional groups.



Scheme 137

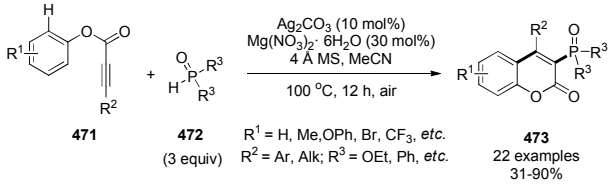
5.2 Formation of Carbon–Phosphorus Bonds

The addition of P-centred radicals to unsaturated systems has become a reliable procedure for constructing of highly complex organophosphorus compounds.[329] Recently, the groups of Duan,[330] Satoh and Miura[331] simultaneously demonstrated the silver-mediated dehydrogenative annulation of arylphosphine oxides **469** with internal alkynes affording benzo[*b*]phosphole oxides **470** (Scheme 138). The annulation proceeded smoothly either by AgOAc (4 equiv) or Ag_2O (2 equiv) in DMF at 100 °C under a N_2 atmosphere, providing a step-efficient route to produce benzo[*b*]phosphole oxides **470**. Notably, the asymmetrical alkynes with diphenylphosphine oxide regioselectively resulted in single regioisomers, whereas the diarylphosphine oxides with different aryl substituents or one aryl group with two annulated sites generally produced a mixture of regioisomers. Mechanistically, a radical process was proposed by both research groups involving two possible 4-*exo-trig* and 5-*exo-trig* annulation pathways. Very recently, Ackermann *et al*. described a similar silver-mediated annulation reaction, albeit using DMSO as the solvent at 120 °C.[332]



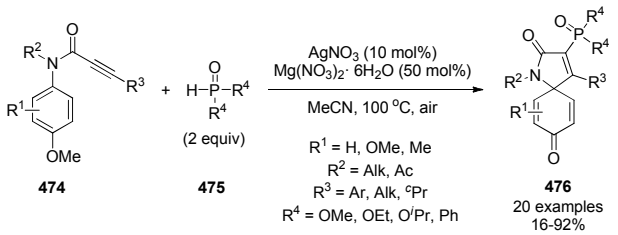
Scheme 138

The method of forming organophosphorus compounds by the addition of P-centred radicals to alkynes was further expanded by Wang and Wu *et al.* to the Ag_2CO_3-catalysed difunctionalization of aryl alkynoates **471** with *H*-phosphonates **472**, providing a convenient pathway for the regioselective synthesis of 3-phosphonated coumarin derivatives **473** in 31–90% yields *via* a tandem radical phosphonation and C–H functionalization process (Scheme 139).[333] Both C–P and C–C bonds were formed in one pot through the generation and cyclization of a highly reactive phosphonated vinyl radical intermediate. In the presence of $Mg(NO_3)_2$ and using molecular sieve (MS) as an additive, the silver and copper salts such as AgOAc, Ag_2O, AgOTf, $Cu(OAc)_2$, were effective, whereas Ag_2CO_3 gave the highest yield. The role of $Mg(NO_3)_2$ was assumed to form HNO_3 that participated in the redox of silver(0/I).



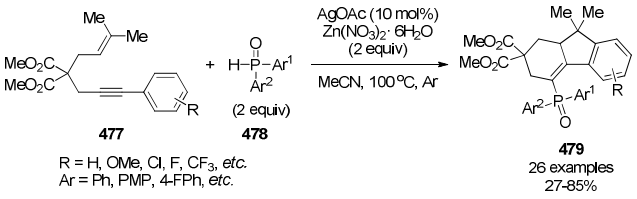
Scheme 139

Rather than aryl alkynoates, Liang *et al.* realized the tandem annulation of *N*-(*p*-methoxyaryl)propiolamides **474** with *H*-phosphonates **475**, which yielded phosphorylated aza-decenones **476** under mild conditions (Scheme 140).[334] In the presence of $Mg(NO_3)_2{\cdot}6H_2O$, various silver(I) salts, such as $AgNO_3$, AgOTf, Ag_2CO_3 resulted in the desired products with high yields. A reaction mechanism was involved in the initial phosphorus radical generation, the subsequent intermolecular phosphonation and intramolecular 5-*exo*-cyclization, and the final dearomatization steps.



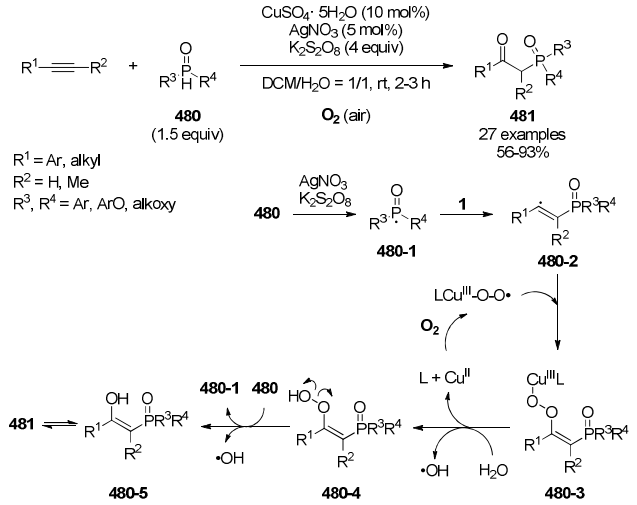
Scheme 140

Moreover, the Liang group developed a AgOAc-cayalysed cyclization of 1,6-enynes **477** with phosphine oxides **478** in the presence of 2 equiv of $Zn(NO_3)_2{\cdot}6H_2O$, leading to functionalized fluorene derivatives **479** (Scheme 141).[335] The reaction proceeded with high regioselectivity by constructing one C−P bond and two C−C bonds in one step. Notably, in the case of 1,6-enynes with an un-/mono-substituted olefin moiety, a stoichiometric amount of AgOAc (3 equiv) was required without $Zn(NO_3)_2$. However, this reaction was limited to diaryl-substituted phosphine oxides **478** because the –OEt/–Ph substituted phosphine oxide resulted in a mixture, whereas the –Alk/–Ph or –Alk/–Alk phosphine oxides yielded a trace amount of products.



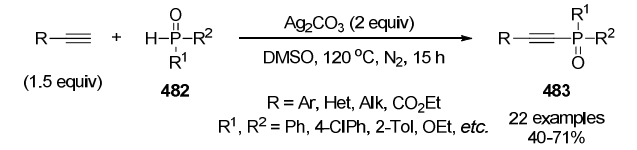
Scheme 141

Silver(I)/$K_2S_2O_8$ was capable of serving as P-centred radical initiator.[336] A direct, facile and novel strategy to acess diverse β-ketophosphonates **481** were reported by Chen, Qu and Zhao *et al.* through the silver/copper-cocatalyzed oxyphosphorylation of alkynes with organophosphorous reagents **480** under open-air conditions (Scheme 142).[337] Various available aryl/aliphatic alkynes and diphenyl/dialkoxyl/ethyoxyl phenyl substituted phosphine oxides **480** were applicable to this reaction and afforded the corresponding products **481** in good to excellent yields (56–93%). Radical trapping and control experiments confirmed a radical mechanism. As shown in Scheme 142, a plausible reaction mechanism was proposed that phosphite radical **480-1**, generated from **480** *via* $Ag^{I/II}$ circulation oxidized by $K_2S_2O_8$, inserted into the C–C triple bond to produce an alkenyl radical **480-2**, which was then trapped by the active-oxygen copper complex and afforded the complex **480-3**. Following the reaction with H_2O, hydroperoxide **480-4** was generated with the release of a Cu^{II} cation, and further underwent homolysis of the oxygen–oxygen bond and captured a hydrogen proton from **480** to afford an enol complex **480-5**, accompanied by the release of a hydroxyl radical and a phosphite radical **480-1**. Finally, β-ketophosphonates **481** were formed by the tautomerism of enolates **480-5**.



Scheme 142

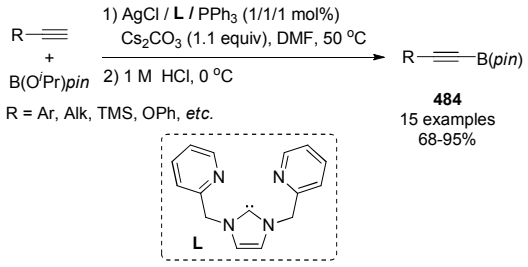
A silver-mediated oxidative C−H/P−H oxidative-coupling between terminal alkynes and phosphine oxides **482** was developed by Gao and Lei *et al*. (Scheme 143).[338] This approach provided an efficient and straightforward entry into the alkynyl-phosphine oxides **483** in one step, especially the alkynyl(diaryl)-phosphine oxides.[339] Although some preliminary mechanistic investigations have been conducted, the exact mechanism remains unclear.



Scheme 143

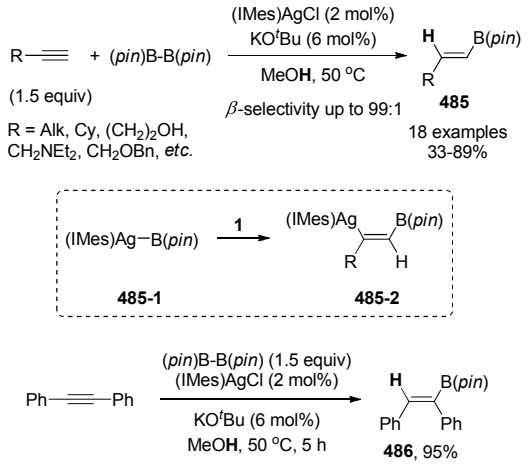
5.3 Formation of Carbon–Boron Bonds

Transition metal-catalysed Csp–H borylation is an ideal synthetic route for producing synthetically useful borylated alkynes; however, most borylated alkynes were synthesized using an equivalent amount of a strong base such as *n*BuLi.[340] Recently, Hu and co-workers described a mild Ag(I)-catalysed C–H borylation of various functionalized terminal alkynes with B(O^{i}Pr)*pin*, which afforded alkynyl boronates **484** on a gram scale (Scheme 144).[341] Notably, the Ag(I) catalyst could be recycled by a cooperative PPh_3 and BF_3 system.



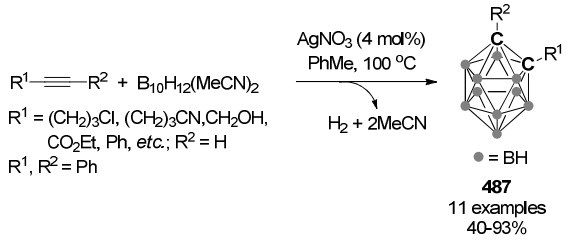
Scheme 144

In marked contrast to the considerable progress in the copper-catalysed hydroboration reactions of alkynes,[342] the catalytic use of silver salts in such reactions remain largely underdeveloped. In 2014, Yoshida and co-workers revealed the (IMes)AgCl-catalysed hydroboration of terminal alkynes with (*pin*)B-B(*pin*), affording β-borylalkenes **485** in high yields with good regio-/stereoselectivity (Scheme 145).[343] Symmetrical internal alkynes such as 1,2-diphenylethyne also underwent hydroboration to afford (*Z*)-borylalkene **486** in 95% yield. By comparison of different catalysts including (IMes)AgCl, (IPr)AgCl, (IMes)CuCl, and (Ph_3P)AuCl, (IMes)AgCl resulted in the highest *ee* value, and (IMes)CuCl afforded the best yields, whereas the gold complex was not effective. The proposed mechanism involved the formation of a boryl-silver(I) species (IMesAg-B(*pin*)) **485-1**, arising from σ-bond metathesis between a silver(I) alkoxide and diboron, the subsequent addition to alkynes to produce intermediate **485-2**, and the final protonation leading to borylalkenes. However, the factors responsible for the high β-selectivity with terminal alkynes presently remain unclear.



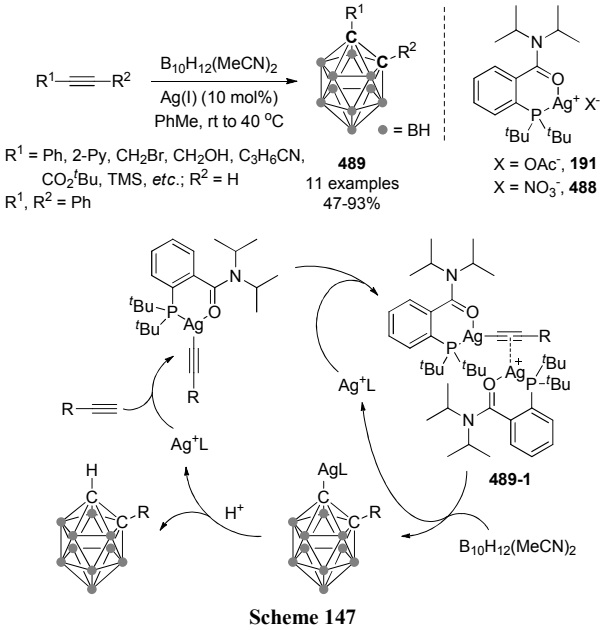
Scheme 145

1,2-Dicarba-closo-dodecaboranes (*ortho*-carboranes) have been increasingly used in material science and medicinal chemistry in recent years.[344] One of the most longstanding critical challenges associated with carborane chemistry is the low yields; thus the design and development of synthetic methods to offer high yields of corresponding carboranes are highly demanded. Recently, this issue was addressed the Valliant group through a $AgNO_3$-catalysed method for preparing dicarba-closo-dodecaboranes **487** using a dehydrogenative alkyne-insertion protocol (Scheme 146).[345] A catalytic amount of $AgNO_3$ could result in the efficient annulation of diverse alkynes and $B_{10}H_{12}(CH_3CN)_2$, with good functional group tolerance. Furthermore, the corresponding carboranes could be simply isolated by a chromatographic method.



Scheme 146

However, the dependence on a high temperature restricted the range of functionalized carboranes directly incorporated from alkyne precursors. Therefore, Valliant *et al*. further developed a mild protocol for the synthesis of carboranes **489** using the *P,O*-ligand-Ag(I) complex at 40 °C or even at room temperature. The silver(I) complexes with different anion **191** and **488** were superior to simple silver salts that were potentially utilized as an efficient homogeneous catalyst to promote the formation of carboranes **489** (Scheme 147).[346] Both internal and terminal alkynes were suitable for the reaction. The ability to perform reactions at significantly reduced temperatures created opportunities to prepare carboranes from thermally sensitive alkynes which would degrade or undergo unwanted side reactions. Mechanistic investigations by MS analysis and preliminary kinetic studies have been conducted, and proposed a key bimetallic species **489-1**.



Scheme 147

6. Conclusion

Gold, silver, and copper, known as "coinage metals", have exhibited interesting catalytic activities in organic synthesis, which have been compared critically by the groups of Yamamoto and Harmata.[11,13] Generally, compared with Ag(I), Au(I) exhibits stronger σ-and/or π-Lewis acidity, which render Au(I) catalyst

acceptable and feasible for diverse types of transformations, *e.g.*, the hydrofunctionalization of alkynes, and cycloisomerization of enynes/multiynes, and therefore silver(I) has been intensively exploited to activate gold catalysts through anion metathesis (counterion exchange). Whereas copper salts prefer to function as versatile catalysts for oxidative coupling reactions *via* a single electron transfer (SET) process. In addition, both silver and copper salts are extensively used as a outer-sphere oxidant.

As outlined in this review, over the past five years, the field of silver-catalysed reactions of alkynes has rapidly developed, as demonstrated by the numerous novel transformations allowing for the construction of diverse C–C and C–heteroatom bonds. Compared with the continuous and remarkable development of C–C, C–N and C–O bond-forming reactions, the formation of C–Halo, C–P and C–B bonds has become a new trend and has stimulated considerable research interest. Silver acetylide, which has evolved from the silver π-complex of terminal alkynes, has been widely exploited in A^3-coupling, C−H carboxylation, oxidative coupling, among others. The generation and reactivity of reactive intermediates such as arynes in the HDDA reaction, isoquinolinium intermediates in C–N bond formation, and isobenzopyrylium cations and their silver−carbene tautomers in C–O bond formation in silver-catalysed cascade reactions are impressive. In addition to simple alkynes, functionalized alkynes such as *ortho*-alkynylarylaldehydes/-arylaldimines, ynol ethers, siloxy alkynes, propargyl alcohols/esters/amines, enynes, and multiynes have accounted for a large proportion of the reports of silver-based alkyne chemistry; these alkynes will continue to be employed in synthetic practice. The superior catalytic activity exhibited by heterogeneous silver catalysts and silver complexes such as supported silver nanoparticles, NHC-Ag(I), Ag_2WO_4 and McNulty's hemilabile *P,O*-ligand-silver(I) complex are noteworthy. In contrast with the classical chiral ligands, use of the asymmetric counterion-directed catalysts (ACDC), such as chiral silver phosphate (the combination of silver(I) and chiral binaphthyl phosphoric acids) have attracted much attention and become a powerful tool in asymmetric synthesis, such as in AA^3 reaction and enantioselective cyclization of *ortho*-alkynylaryl ketones. In addition, $Au^{I/III}$ and $Cu^{I/III}$ redox cycles have been well established and extensively exploited in organic synthesis, but $Ag^{I/III}$ cycle is urgent to be developed.[347]

Despite all of these developments in the past years, ample work remains ahead, as follows: 1) achieving low loadings of silver catalytic systems, supported or not; 2) enhancing the catalytic activity of silver catalysts turned on by ligands and counter anions; 3) the expansion of silver-based ACDC in asymmetric synthesis; and 4) the synthesis and application of new alkynylation reagents, particularly in radical reactions. There is no doubt that alkyne chemistry will greatly benefit from the emerging "*Silver Rush*" and will continue to generate increasingly more synthetic possibilities in the near future.

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