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Indole Synthesis Using Silver Catalysis

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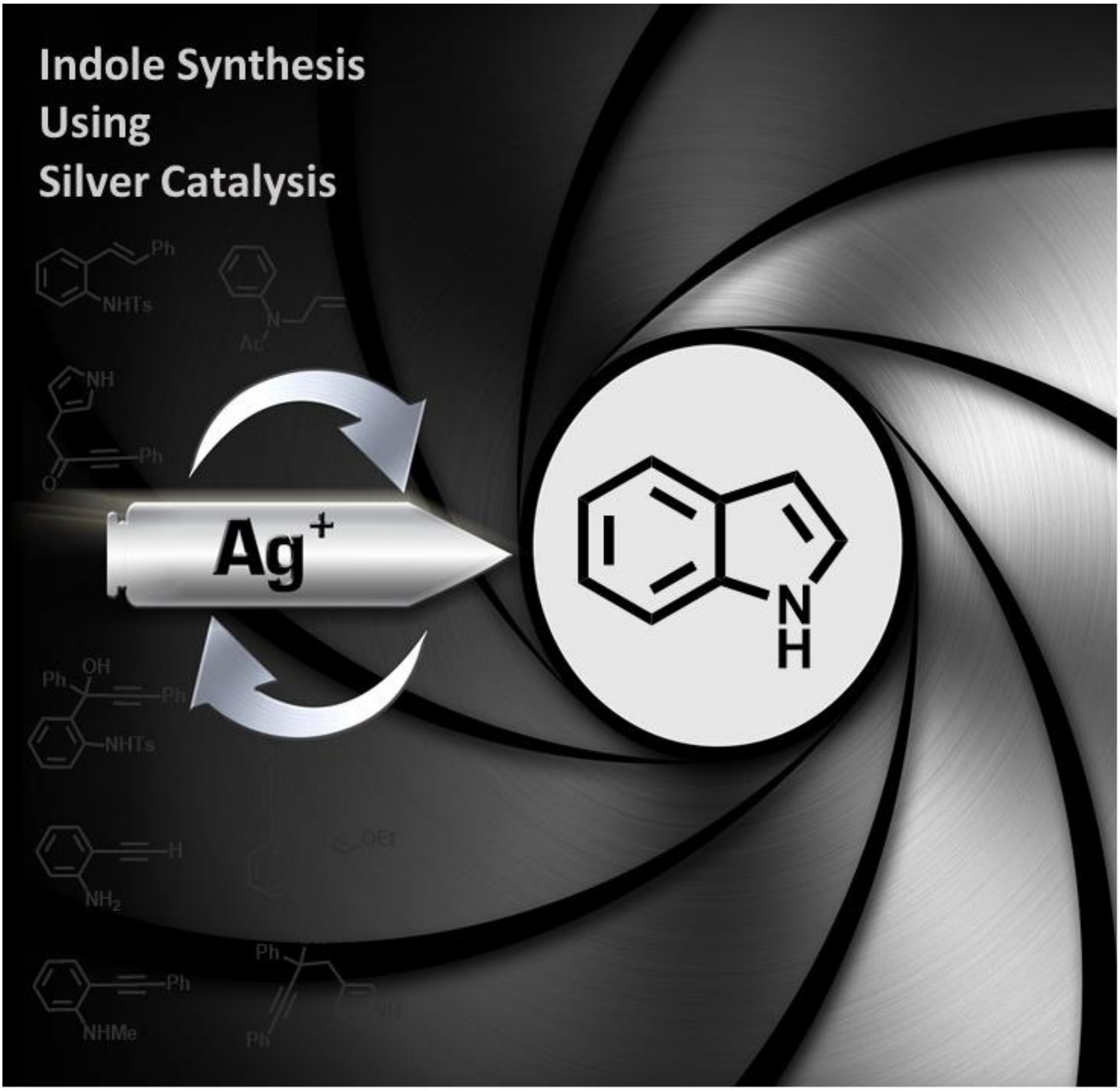


Abstract: Indoles are amongst the most important class of heteroaromatics in organic chemistry, being commonly found in biologically active natural products and therapeutically useful compounds. The synthesis of indoles is therefore important and several methods for their synthesis that make use of silver(I) catalysts and reagents have been developed in recent years. This Focus Review contains, to the best of our knowledge, a comprehensive coverage of silver-mediated indole forming reactions since the first reaction of this type was reported in 2004.

1. Introduction

The indole core is a key structural component in many natural products and pharmaceuticals and serves as a fundamental building block in organic synthesis.[1] The synthesis of indole scaffolds has therefore been the focus of much research and a myriad of methods to construct indole rings have been developed over the years.[2] Classical methods include the Fischer indole[3] and Bartoli syntheses which are widely and routinely used by the synthetic community.[4] Nonetheless, limitations associated with these classical procedures mean that establishing novel strategies to prepare indoles are still important and continue to be actively pursued.

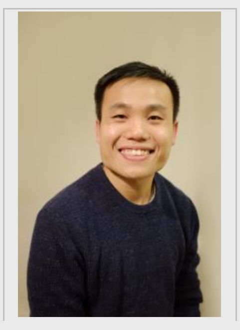
Many indole syntheses make use of alkyne activation approaches, typically involving coordination of a metal catalyst to the alkyne to activate it towards cyclization.[5] Silver, a member of the 'coinage metal' family, can be readily obtained in the form of silver(I) salts with a variety of different counterions. These salts, which have a d^{10} electronic configuration at silver, are well-established as being good σ-/π-Lewis acids and are recognized as being powerful catalysts in alkyne activation.[6] In addition to their ability to interact with π-systems to promote useful reactivity, the use of silver in organic transformations has important economic benefits relative to other more expensive transition metals such as gold, palladium and platinum.[5,6]

Indole synthesis has been extensively reviewed previously,[2] however, a comprehensive review focusing specifically on silver-catalyzed approaches has not been reported before. As the use of silver catalysis in heterocycle synthesis is becoming more prevalent,[5] a review of this topic in the context of indole synthesis is timely. To the best of our knowledge, this Focus Review summarizes all silver-catalyzed indole syntheses to date, with a cut-off period of papers published before January 2019. Note that whilst we believe that all publications that feature examples within the remit of this review are discussed, we have not reproduced all of the individual examples from these studies.

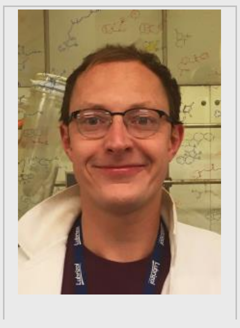
Many indole syntheses utilize silver in mixed catalytic systems (*e.g.* mixed gold/silver systems),[5] but this Focus Review is limited to examples in which the silver species have been shown to be competent at catalyzing the reaction without the influence of another metal species. The review is organized in chronological order and is divided based on the type of reaction used to construct the indole core, starting with the most commonly used hydroamination pathway, before moving on to other methods. Mechanisms are included and described in more detail whenever they deviate from the typical hydroamination mechanism.

Dr. Aimee K. Clarke completed both her undergraduate degree and Ph.D. studies at the University of York working on the synthesis of spirocyclic scaffolds. Aimee is currently an EPSRC funded postdoctoral research associate at the University of York working with Dr William P. Unsworth and Prof. Richard J. K. Taylor. Her current research focuses on the development of novel methodologies to access natural product scaffolds.

Dr. Hon E. Ho completed his Masters and Ph.D. degree at the Tohoku University in Japan under the supervision of Prof. Tienan Jin and Prof. Yoshinori Yamamoto. Ho then joined Prof. Richard J. K. Taylor and Dr. William P. Unsworth at the University of York as an EPSRC funded post-doctoral researcher. His current research is focused on the development of new methodologies to access spirocycles, heterocycles, and natural products.



James A. Rossi-Ashton completed his Masters degree at the University of Bristol. He then joined Prof. Richard. J. K. Taylor and Dr. William P. Unsworth at the University of York where he is currently undertaking his Ph.D. studies. During his Ph.D. James spent three months working under the supervision of Prof. Shuli You at the Shanghai Institute of Organic Chemistry. His current research interests focus on the asymmetric functionalization of heterocycles.



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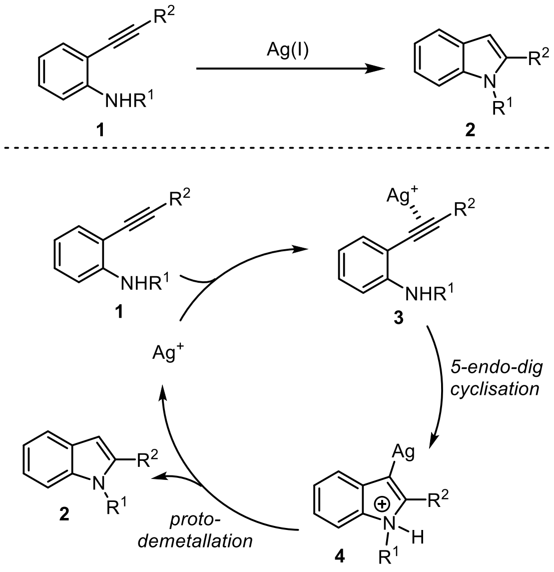
Dr William P. Unsworth obtained his Mchem. and Ph.D. from the University of Oxford, where he worked with Prof. Jeremy Robertson. He is now an independent research fellow (Leverhulme Trust funded) at the University of York. His two main research interests are the synthesis of spirocycles using catalytic dearomative approaches and macrocycle synthesis using iterative ring expansion reactions. His work in both of these areas has been recognized by several prizes and awards, most notably the 2018 RSC Hickinbottom Award.

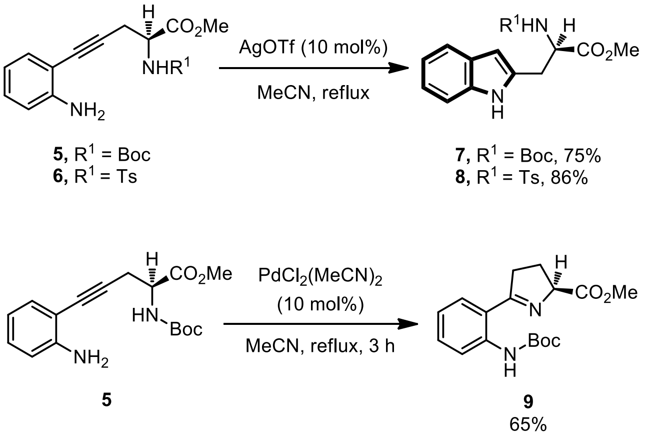
2. Hydroamination Strategies

Alkyne hydroamination[7] is by far the most common synthetic strategy used for silver-catalyzed indole syntheses. In such reactions, anilines **1** substituted with an alkyne at their 2-position are treated with a silver(I) species which acts as a π-acid to activate the alkyne towards attack from a pendant aniline nitrogen via a *5-endo-dig* cyclization mode (**3** → **4**). Protodemetallation then liberates the silver(I) species (meaning that the reactions can be catalytic in the silver species) and deprotonation completes the synthesis of the indole product **2** (Scheme 1).



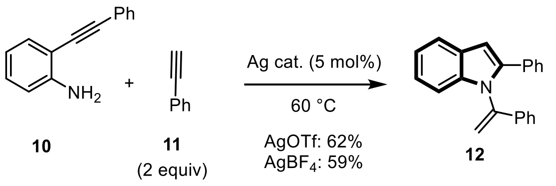
Scheme 1. General silver(I)-catalyzed hydroamination sequence.

To the best of our knowledge, the earliest example of the silver-catalyzed hydroamination strategy being used to prepare indole derivatives was reported by Rutjes and co-workers in 2004.[8] This group described the transition metal-catalyzed cyclization of *o*-alkynylanilines to access indole 2-propargylglycine (isotryptophan) derivatives. *o*-Alkynylpropargylglycine anilines **5** and **6** were prepared using Sonogashira cross-coupling between *o*-iodoanilines and enantiopure propargylic glycine precursors. The use of 10 mol% AgOTf in MeCN at reflux for 20 h furnished the isotryptophan products **7** and **8** in good yields. By comparison, the use of a Pd(II) catalytic system resulted in formation of the undesired cyclization product **9**, which was not observed when AgOTf was employed (Scheme 2).



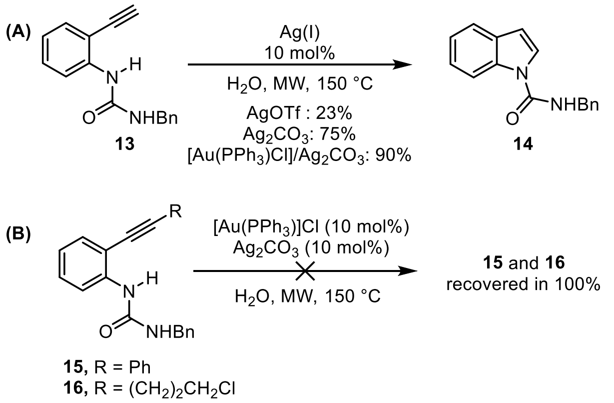
Scheme 2. Ag(I)-catalyzed hydroamination to prepare isotryptophans **7** and **8** and an alternative Pd(II)-mediated reaction pathway leading to **9**.

In 2007, Li *et al.* reported a gold and silver co-catalyzed double hydroamination of *o*-alkynylanilines with terminal alkynes to access *N*-vinyl indole derivatives.[9] During the catalyst screening process, the separate use of both 5 mol% AgOTf and 5 mol% $AgBF_4$ at 60 °C for 2 h under neat conditions gave the *N*-vinyl indole product **12** in 62% and 59% yields, respectively (Scheme 3). Although a silver(I) species can facilitate the cascade hydroamination process alone, it was later revealed that the combination of 5 mol% of $AuCl_3$/AgOTf at RT was more efficient and hence was the main focus of the study.



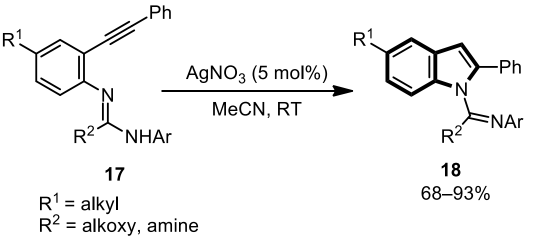
Scheme 3. Ag(I)-catalyzed hydroamination to prepare *N*-vinyl indole **12**.

In 2009, Liu *et al.* reported a gold and silver co-catalyzed microwave-assisted intramolecular hydroamination of *o*-alkynylamides to construct *N*1-carbamide indole derivatives.[10] Although the combination of Au(I)/Ag(I) in aqueous media using microwave irradiation at 150 °C was chosen as the optimal reaction conditions, using 10 mol% AgOTf or Ag_2CO_3 alone displayed catalytic activity to afford the cyclized indole product **14** in 23% and 75% yields, respectively (Scheme 4A). It was also found that the reaction conditions were exclusive to *o*-terminal alkynes as no reaction was observed when 2-substituted *o*-alkynylcarbamides **15** and **16** were used as substrates (Scheme 4B).



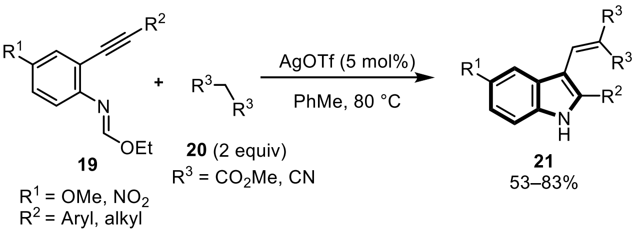
Scheme 4. Ag(I)-catalyzed hydroamination to prepare indole **14**.

In 2009, Ding *et al.* reported a silver-catalyzed hydroamination process using (*o*-alkynylphenyl)guanidines **17** to access *N*-carboximidamide or *N*-carboximidoate indole derivatives **18** (Scheme 5).[11] By using 5 mol% $AgNO_3$ at RT and MeCN as the solvent, guanidines **17** were found to selectively undergo 5-*endo-dig* cyclization to afford a range of indole derivatives **18** in good yields. The authors also conducted a comparison study between Ag(I) and other commonly used π-acids such as Pd(II) and Cu(I) salts. It was reported that the reaction using a $AgNO_3$ catalyst was the most effective, proceeding efficiently and in high yield; meanwhile, the analogous reactions using both Pd(II) and Cu(I) catalytic systems were incomplete, even after extended reaction times. Overall, this silver(I)-catalyzed cyclization provides access to *N*-carboximidamide or *N*-carboximidoate indole-2-phenyl derivatives under simple and mild reaction conditions.



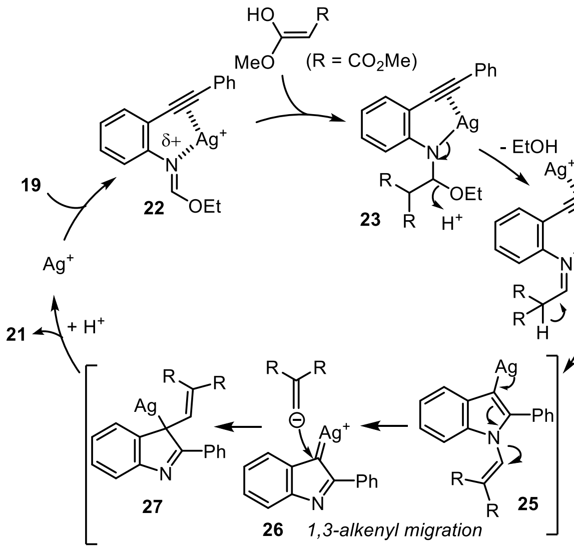
Scheme 5. Ag(I)-catalyzed hydroamination to prepare indoles **18**.

In 2010, Chang *et al.* reported a silver(I)-catalyzed cascade process based on the reaction of *o*-alkynylformidates **19** and activated methylene compounds **20** to synthesize 3-vinyl indole derivatives **21** (Scheme 6).[12] Typically, these reactions were performed using 5 mol% AgOTf in toluene at 80 °C for 12 h, enabling a range of 3-vinyl indoles **21** to be prepared in moderate to good yields.



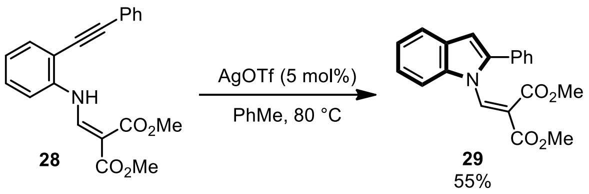
Scheme 6. Ag(I)-catalyzed hydroamination to prepare 3-vinyl indoles **21**.

The authors suggested a plausible mechanism for the transformation this, involving an interesting 3-alkenyl migration process (Scheme 7). First, coordination of silver(I) to the alkyne facilitates enolate addition into imine **22** to form **23**. This is followed by π-acid activation of the alkyne by silver(I) to induce a 5-*endo-dig* cyclization to form the indole core. 1,3-Alkenyl migration is then proposed to occur via a silver-carbene intermediate **26**, which is followed by rapid protodemetallation under acidic conditions to furnish the 3-vinyl indole product **21**. Note that similar migration patterns have also been reported by using other transition metals such as Pd(II), Pt(II), and Au(III).[5,13]



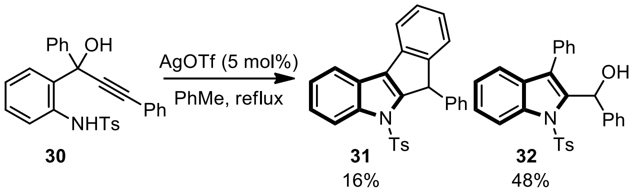
Scheme 7. Proposed mechanism for synthesis of indole **22**.

The 1,3-alkenyl migration mechanism shown in Scheme 7 was supported by a series of control experiments. For example, when *o*-alkynylenamine **28** was subjected to the standard reaction conditions, only the hydroamination product **29** was isolated in 55% yield (Scheme 8). This suggested that fast protodemetallation was competing with the 1,3-alkenyl migration pathway in some instances.



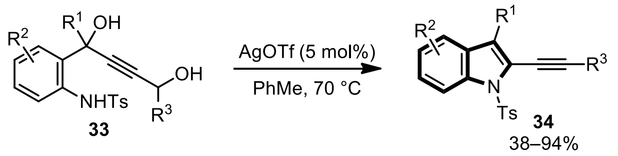
Scheme 8. Ag(I)-catalyzed hydroamination to prepare *N*-vinyl indole **29**.

In 2010 Chan *et al*. described a system for the synthesis of indoles via gold-catalyzed cycloisomerization reactions.[14] During this investigation, as a control experiment, 1,3-diphenyl-1-(2-(tosylamino)phenyl)prop-2-yn-1-ol **30** was treated with 5 mol% AgOTf, which yielded the corresponding indenyl-fused indole **31** in 16% yield, alongside the alcohol-tethered indole **32** in 48% yield (Scheme 9). Although it was proven that AgOTf could facilitate indole formation, a gold-catalyzed method was shown to be more efficient and was the main focus of this investigation.



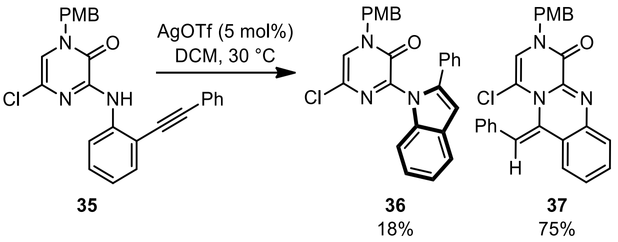
Scheme 9. Ag(I)-catalyzed hydroamination to prepare indoles **31** and **32**.

Two years later, Chan *et al*. developed a silver-catalyzed tandem heterocyclization/alkynylation process using propargylic 1,4-diols **33** to generate *o*-alkynyl indoles **34**, liberating two molecules of water as the sole by-products (Scheme 10).[15] This was the first reported indole synthesis which introduced alkyne moieties at the 2-position of the indole ring without relying on traditional cross-coupling methods. A variety of tosyl-protected *o*-alkynyl indoles **34**, bearing additional substituents in the 3-, 5- and 6-positions, were generated in good to excellent yields employing AgOTf as the catalyst. Interestingly, the reaction proceeds well in the absence of a group in the R^1 position, which leads to the formation of 3*H*-indole products; this is particularly noteworthy as these products cannot be formed using traditional cross-coupling approaches. The authors suggested that the silver catalyst activates the C-OH bonds in the diol substrates, rather than the alkyne moiety directly, and that this subsequently triggers cyclization/hydroamination.



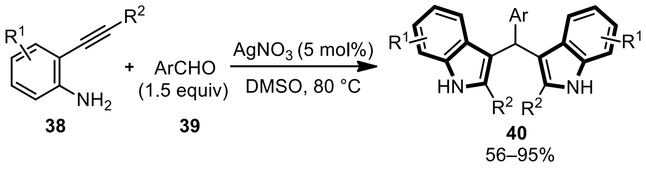
Scheme 10. Ag(I)-catalyzed hydroamination to prepare alkynyl indoles **34**.

In 2012, Van der Eycken *et al.* reported the microwave-assisted syntheses of pyrazino-quinazolines and indolyl-pyrazinones from alkyne-tethered pyrazinones using either silver or gold catalysis.[16] Treatment of alkyne-tethered pyrazinone **35** with AgOTf, using conventional heating, resulted in the synthesis of indole **36** in 18% yield, alongside quinazoline product **37** in 75% yield (Scheme 11). Silver was found to be the superior catalyst for the formation of the quinazoline products, but AuCl was in fact identified as the optimum catalyst for formation of the indole products.



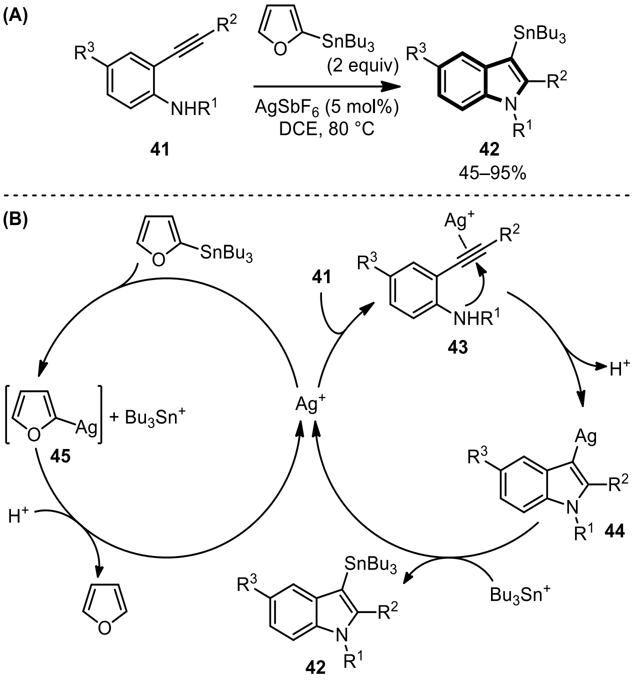
Scheme 11. Ag(I)-catalyzed hydroamination to prepare indole **36**.

In 2012, Tang *et al.* reported a silver-catalyzed process for the synthesis of bis(indolyl)methanes **40** from *o*-alkynylanilines **38** and aryl aldehydes **39** (Scheme 12).[17] Their simple one-pot procedure was performed in the presence of 5 mol% $AgNO_3$ in DMSO at 80 °C for 12 h. A wide range of *o*-alkynylanilines **38** and aryl aldehydes **39** were tolerated in this process, providing access to the corresponding bis(indolyl)methanes **40** in moderate to excellent yields. Based on previously reported mechanisms, the authors suggested that these reactions proceed via a hydroamination pathway in which the silver catalyst activates both alkyne and aldehyde starting materials.



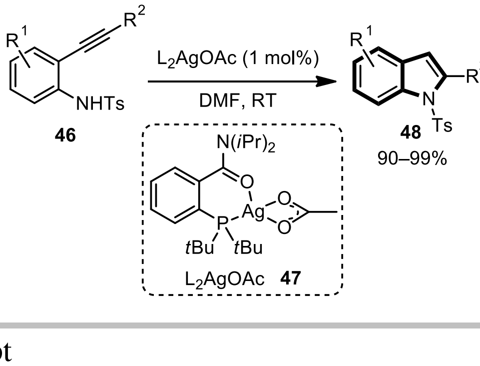
Scheme 12. Ag(I)-catalyzed synthesis of bis(indolyl)methanes **40**.

In 2013, Liu *et al.* reported the synthesis of (3-indolyl)stannanes **42** via a silver-catalyzed cyclization/stannylation cascade process.[18] Starting from a series of *o*-alkynylanilines **41** and reacting with 5 mol% $AgSbF_6$ and two equivalents of 2-tributylstannylfuran, a wide range of N1-protected-(3-indolyl)stannanes **42** were synthesized (Scheme 13A). The procedure was shown to tolerate both electron-donating and electron-withdrawing groups on the alkyne phenyl ring and substituents at the 4-position of the parent aniline ring. It was found that the presence of an electron-withdrawing protecting group is essential to the success of the reaction, as the non-stannylated 3*H*-indole product was isolated when a *N*-methyl aniline starting material was tested. It was also found that indoles bearing electron-withdrawing protecting groups other than sulfonyl were unstable during purification via column chromatography. The authors showcased the utility of the 3-stannylated indole products **42** by performing a series of elaboration reactions. To probe the reaction mechanism, 3*H*-indole was subjected to the optimized reaction conditions and no stannylated product was observed, which indicated that the stannylation did not occur via C-H functionalization of the indole product but instead through a silver-tin transmetallation process as shown in Scheme 13B. In this mechanism, the silver is proposed to have a dual role; activating the alkyne towards attack from the amino group via the silver-coordinated alkyne **43** whilst also catalyzing the destannylation of 2-tributylstannylfuran through a transmetallation protodemetallation pathway, thus liberating Bu_3Sn^+ which goes on to react with the 3-indolyl silver(I) intermediate **44**.



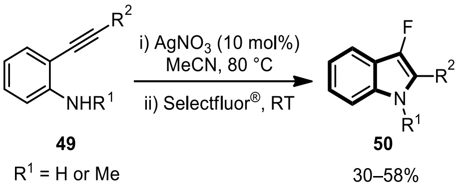
Scheme 13. Proposed mechanism for an amino stannylation cascade process to prepare indoles **42**.

In 2014, McNulty *et al.* reported the synthesis and application of a series of homogenous silver(I) acetate complexes as catalysts in intramolecular hydroamination reactions using *N*-protected *o*-alkynylanilines **46**.[19] A range of *N*-protected indoles **48** were formed in high yields with the process performed at room temperature in the absence of base or other additives (Scheme 14). The authors conducted a catalyst screen of heterogeneous silver(I) salts at 100 °C, which furnished indole products from their corresponding *o*-alkynylanilines. It was found that those salts with weakly coordinating anions were ineffective in the intramolecular hydroamination. Next, they screened a series of homogeneous ligated silver species and found catalyst **47** to be the most efficient at catalyzing indole formation. Further investigations revealed that the reactions could be performed at room temperature and that polar solvents were required, with DMF being optimal. A wide range of *N*-tosylindoles **48** were then accessed in high yields and the procedure was shown to tolerate sensitive functionalities such as a TMS-functionalized alkyne.



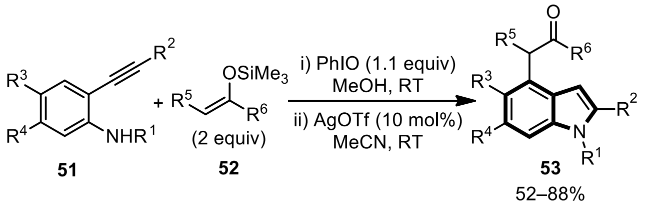
Scheme 14. Ag(I)-catalyzed synthesis of *N*-protected indoles **48.**

In 2014, Song and You *et al.* reported a one-pot silver-catalyzed cyclization/fluorination cascade to deliver structurally diverse fluorinated indole derivatives **50** from *o*-alkynylanilines **49** (Scheme 15).[20] Overall, four different indolenine, indoline and indole derivatives were accessed in good yields by alteration of the reaction conditions. A limited range of 3-fluorinated indoles **50** were synthesized as it was found that an electron-withdrawing group on the alkynyl phenyl ring was required for a successful reaction. The reaction was shown to tolerate both unprotected and *N*-methyl protected aniline starting materials. A tentative general mechanism was proposed, whereby silver(I) activates the alkynyl aniline triple bond towards attack by the nitrogen, forming the corresponding 3*H*-indole upon protodemetallation, at which point the mechanism for each derivative varies according to the reaction conditions. In the case of the 3-fluorinated indole products **50**, the 3*H*-indole is simply monofluorinated by the electrophilic Selectfluor® reagent, forming the corresponding 3-fluorinated indole.



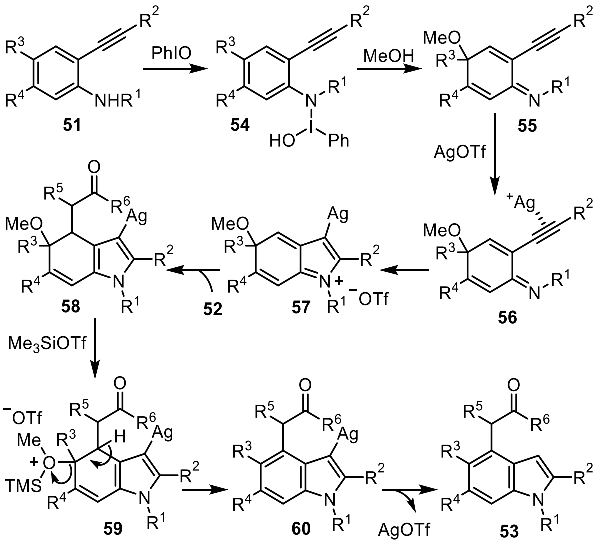
Scheme 15. Ag(I)-catalyzed synthesis of 3-*F* indoles **50**.

In 2014, Rang and Fan *et al.* reported the synthesis of *N*-protected 4-acetonylindoles **53** from *o*-alkynylanilines **51** and silyl enol ethers **52** (Scheme 16).[21] Their two-step, one-pot procedure involved a hypervalent iodide mediated oxidative dearomatisation and silver-catalyzed cyclization mechanism which includes an interesting conjugate addition step of a silyl enol ether (*mechanism discussed later*, see Scheme 17). Iodosylbenzene was identified as the optimum oxidant due to the absence of acidic contaminants which were produced when using other hypervalent iodine sources. Although the acidic species did not impede the oxidation step, they were found to be harmful to the subsequent silyl enol ether reaction. To avoid decomposition of the silyl enol ether, methanol from the iodosylbenzene step was removed under reduced pressure prior to addition of the silyl enol ethers. The catalytic activity of a variety of metal salts was investigated, and AgOTf was found to be the optimum salt for catalyzing the process. Gold(I) salts gave reduced yields of the 4-acetonylindole products **53** relative to that of AgOTf, whereas other metal salts, such as Bi(III), In(III), Zn(II), Cu(II), Au(III), Pd(II), or Pt(II) gave rise to the 4-methoxyindole product.



Scheme 16. Iodosylbenzene and Ag(I)-mediated synthesis of indoles **53**.

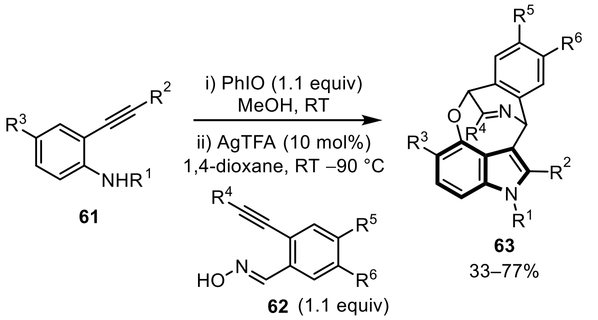
A range of substituted *o*-alkynylanilines were shown to undergo the one-pot procedure in good yields with groups at the *para*-position required for a successful reaction. The *N*-protecting group was also shown to play a crucial role. The reaction proceeded smoothly in the presence of an extensive series of silyl enol ethers furnishing the corresponding 4-acetonylindole products **53**. The authors proposed an iodosylbenzene-mediated oxidative dearomatization of *para*-substituted *o*-alkynylanilines **51** (Scheme 17), forming *o*-alkynylcyclohexadienimines **55**. AgOTf is then proposed to activate the triple bond to induce heterocyclization, to form intermediate **57,** which then undergoes a Mukaiyama−Michael-type addition with the silyl enol ether to generate intermediate **58**. Me_3SiOTf generated *in situ* then promotes rearomatization to give indole **60**. Subsequent protodemetallation by TfOH produces 4-acetonylindole **53** and regenerates the AgOTf catalyst.



Scheme 17. Proposed mechanism for iodosylbenzene and Ag(I)-mediated synthesis of indoles **53**.

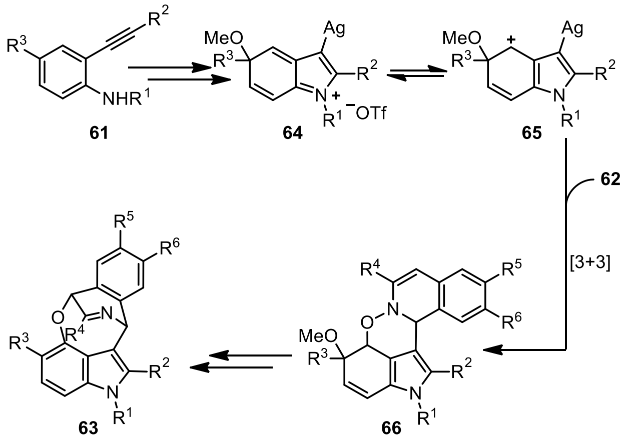
In an extension to their previous work (shown in Scheme 16), Fan and co-workers went on to report another oxidative dearomatization/silver-catalyzed cyclization domino process, this time involving an interesting [3+3]-dipolar cycloaddition reaction.[22] This procedure afforded 3,4-fused indoles **63** directly in a one-pot process from *o*-alkynylanilines **61** and *o*-

alkynylbenzaldoximes **62** (Scheme 18). The reaction was shown to tolerate an extensive range of *N*-protecting groups, aniline ring substituents, alkynyl phenyl ring substituents and a variety of *o*-alkynylbenzaldoximes **62**.



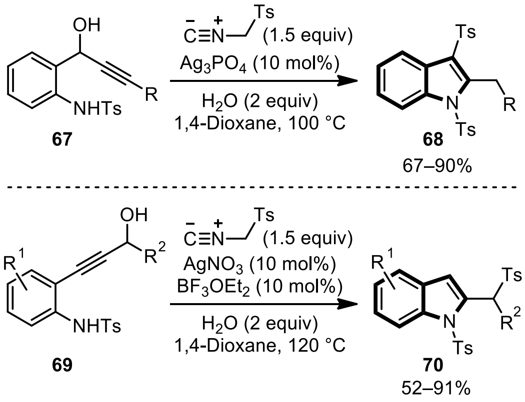
Scheme 18. Iodosylbenzene and Ag(I)-mediated synthesis of polycyclic indoles **63**.

The mechanism of this process (shown in Scheme 19) is thought to proceed via an oxidative dearomatization of *para*-substituted *o*-alkynylaniline **61**, which furnishes intermediate **64** following a silver-catalyzed cyclization (see Scheme 17 for details of these steps). This species is then proposed to undergo a [3+3]-dipolar cycloaddition (this step is best thought of as operating on resonance form **65**) to form an unstable cycloadduct product **66**. The authors then suggest two possible radical pathways (not shown) for the thermal rearrangement of cycloadduct **66** resulting in the formation of 3,4-fused indole **63**.



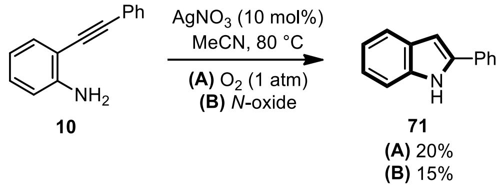
Scheme 19. Proposed mechanism for iodosylbenzene and Ag(I)-mediated synthesis of polycyclic indoles **63**.

In 2014, Bi *et al.* reported silver-catalyzed heteroaromatization of propargylic alcohols to form a range of 3-tosyl benzofurans, benzothiophenes and indoles.[23] Key to this work is the dual role of *p*-toluenesulfonylmethyl isocyanide, which serves as both the sulfonyl source and the ligand for the silver catalyst. An extensive mechanistic study was conducted on the silver-catalyzed benzofuran forming part of this work, resulting in the proposal of a deoxysulfonylation/hydration/condensation reaction pathway, which was extended to the analogous indole formation. While the main focus of this investigation was on benzofuran synthesis, a smaller series of indoles **68** were synthesized from propargylic alcohols **67** with a variety of aryl and heteroaryl functionality on the C2 indole tether (Scheme 20). The scope of the investigation was expanded to isomeric propargylic alcohols **69** which resulted in the formation of 3*H*-indoles **70** with tosyl functionality on the C2 indole tether. A similar reaction pathway was proposed to operate when isomeric propargylic alcohols **69** were reacted under broadly the same reactions conditions.



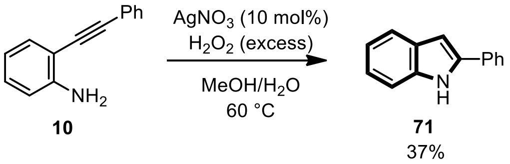
Scheme 20. Isocyanide and Ag(I)-mediated synthesis of indoles **68** and **70**.

In 2016, Michelet and co-workers described the synthesis of benzoxazinone and benzisoxazole derivatives using silver or gold catalysts in the presence of oxone.[24] During optimization studies, the formation of an indole side product **71** was observed when reacting *o*-alkynylaniline **10** with catalytic quantities of $AgNO_3$ under an oxygen atmosphere (**A**) or in the presence of 2,6-lutidine *N*-oxide (**B**). There were just two examples of the 2-phenylindole side product **71** being formed in low yield (15% and 20%, Scheme 21). These were the only reported examples of silver-catalyzed indole formation in the publication but note that this was not the main focus of the study. The oxidants themselves are not involved in the formation of the indole product **71**, but they were added in an attempt to promote subsequent oxidation reactions.



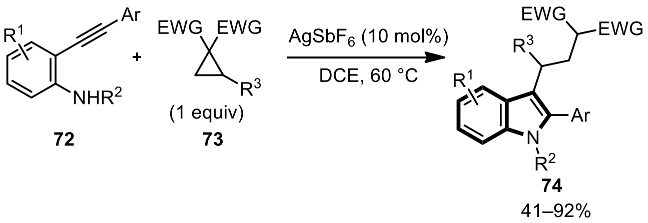
Scheme 21. Ag(I)-catalyzed hydroamination to prepare indole **71**.

The authors also observed the same silver-catalyzed intramolecular hydroamination reaction in a follow-up paper; this time indole **71** was isolated in a 37% yield when aniline **10** was heated in the presence of $AgNO_3$ and a large excess of H_2O_2 in a methanol/water solvent system (Scheme 22).[25] Again, the oxidant appears not to be involved in this reaction.



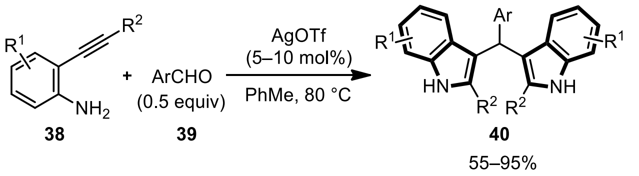
Scheme 22. Ag(I)-catalyzed hydroamination to prepare indole **71**.

A silver-catalyzed indolization of *o*-alkynylanilines **72** followed by ring-opening of donor-acceptor cyclopropanes (DACs) **73** in one-pot was reported by Singh *et al.* in 2016 (Scheme 23).[26] This cascade process features an initial intramolecular hydroamination reaction catalyzed by $AgSbF_6$ and is followed by an unprecedented Ag(I)-mediated ring-opening/trapping of DAC **73**, which functionalizes the resulting indole at the C3 position. When unprotected anilines were used, most DACs tested underwent ring-opening prior to cyclization leading to a diminished indole product yield, therefore protection of the free amine is necessary for these reactions to proceed successfully. This methodology tolerates a wide range of DACs incorporating aryl, heteroaryl and vinyl functionalities as well as a variety of substituted *o*-alkynylaniline partners, furnishing 2,3-disubstituted indole derivatives **74** in good to excellent yields. The authors also described the elaboration of their cascade products into useful intermediates, further showcasing their synthetic utility.



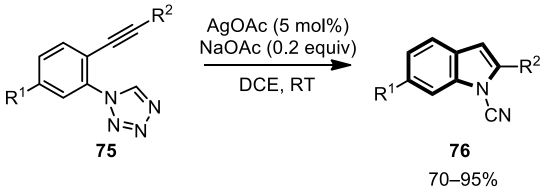
Scheme 23. DAC and Ag(I)-mediated synthesis of indoles **74**.

Following on from the work reported by Tang *et al.* in 2012 on the preparation of bis(indolyl)methanes **40** (see Scheme 12), a similar procedure was reported by Chattopadhyay *et al.* in 2016.[27] An efficient one-pot domino process for the formation of symmetrical bis(indolyl)methanes **40** from *o*-alkynylanilines **38** and aldehydes **39** using silver catalysis was described (Scheme 24). Although conceptually similar to Tang's work, this paper did significantly extend the scope of this reaction; in particular, this study focused on exploring substituents on the pyrrole ring to include aryl, heteroaryl and alkyl groups, which were limited to aryl moieties in Tang's earlier work. Interestingly, substrates featuring a *n*-butyl or an ester group on their alkyne unit proceeded particularly well in this transformation, which is surprising given that a hexyl substituted alkyne in Tang's work did not generate any of the desired bis(indolyl)methane.



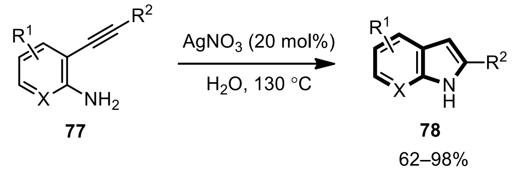
Scheme 24. Ag(I)-catalyzed synthesis of bis(indolyl)methanes **40**.

In view of the importance of 2-substituted indoles in medicinal applications, a facile silver-catalyzed route towards *N*-cyano-2-substituted indole derivatives was developed by Trivedi *et al.* and reported in 2017.[28] Hydroamination reactions commonly use *o*-alkynylanilines as starting substrates for indole formation but, in contrast, Trivedi and co-workers utilized a unique intramolecular cyclization of alkynyl tetrazoles **75** instead, which was catalyzed by AgOAc under ambient conditions (Scheme 25). Linear alkyl, cycloalkyl and aryl substituted alkynes are tolerated in the starting tetrazoles **75**, with this method used to prepare a range of 2/7-substituted *N*-cyanoindoles **76** in high yields. The authors propose that the mechanism proceeds via a typical Ag(I)-alkyne activation pathway followed by nucleophilic intramolecular cyclization, whereby the nucleophilic nitrogen is generated from deprotonation of the acidic tetrazole proton and subsequent loss of N_2 produces an *N*-phenylcyanamide species.



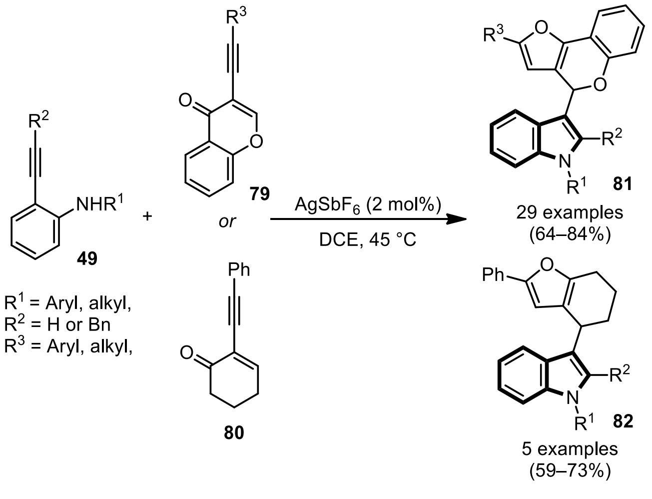
Scheme 25. Ag(I)-catalyzed synthesis of 2-substituted indoles **76**.

A "greener" $AgNO_3$-catalyzed approach to indole and 7-aza-indole derivatives **78** using water as the reaction solvent has been reported by Shao *et al* (Scheme 26).[29] The majority of the indoles and aza-indoles **78** obtained using this method were isolated in excellent yields following a simple filtration and drying process. The authors also explored recycling the aqueous $AgNO_3$ medium, whereby the product from each cycle was obtained by filtration and the resulting aqueous filtrate (containing $AgNO_3$) could be used in the next reaction immediately; three reaction cycles were successfully achieved in yields of 93% and above, although a prolonged reaction time of 36 h compared to 10 h was required for the third cycle. Interestingly, none of the desired indole products were formed when the reactions were carried out in organic solvents such as DMF, toluene or ethanol. The authors suggested that this was because their process belonged to the ‘on-water’ reaction class, which requires a water-oil phase boundary for the chemical transformation to take place. They proposed that a cooperative hydrogen bond network forms at the water-oil interface between the substrate and solvent which helps to lower the energy of the cyclization transition state and hence promote hydroamination.



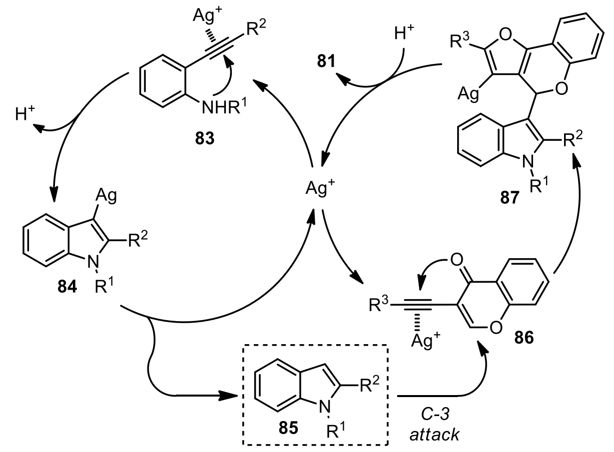
Scheme 26. Ag(I)-catalyzed synthesis of 2-substituted indoles **78** in water.

In 2018, Samanta and co-workers reported a one-pot silver-catalyzed intramolecular hydroamination of *o*-alkynylanilines **49** to construct complex 2,3-substituted indole derivatives **81** and **82** (Scheme 27).[30] Various acids including Au(III), Cu(I), Zn(II), Fe(III), TfOH, and HBF_4 were screened in the optimization studies; 2 mol% $AgSbF_6$ in DCE at 45 °C was found to be optimal for the synthesis of indoles **81** and **82**. A wide range of substituents were tolerated on *o*-alkynylanilines **49**, as well as the *o*-alkynyl cyclic enynones **79** and **80**, to afford the 2,3-disubstituted indoles **81** and **82** in moderate to excellent yields.



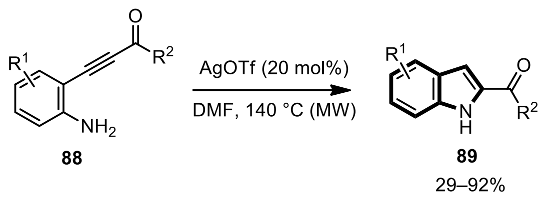
Scheme 27. Ag(I)-catalyzed synthesis of 2,3-disubstituted indoles **81** and **82**.

A mechanism involving a silver(I)-catalyzed intramolecular hydroamination and Friedel-Crafts alkylation/oxacyclization cascade was proposed, as depicted in Scheme 28. First electrophilic activation of the alkynylaniline by Ag(I) occurs to form species **83** which then undergoes hydroamination (**83** → **84**) followed by fast protodemetallation to furnish indole intermediate **85** whilst regenerating the silver catalyst. Then, indole **85**, generated *in situ*, undergoes a C3 Friedel-Crafts type alkylation at the β-position of enynone-Ag complex **86**, followed by a 5-*endo-dig* oxacyclization in a concerted fashion to form the vinyl-Ag species **87**. Finally, fast protodemetallation of **87** produces the 2,3-disubstituted indole **81**.



Scheme 28. Proposed mechanism for synthesis of 2,3-disubstituted indoles **81**.

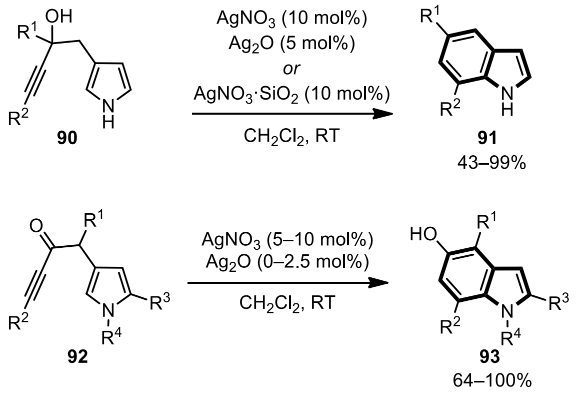
In 2018, a silver-catalyzed ‘anti-Michael’ hydroamination procedure to access 2-acylindoles **89** was developed by Marinelli and co-workers (Scheme 29).[31] This method complements existing procedures for the synthesis of 2-acylindoles and the fact that it is fully atom-economical and does not require any additional protection/deprotection strategies is particularly advantageous. Other coinage metals were explored in this procedure; CuOTf also promoted the desired transformation, albeit with lower efficiency and interestingly, Au(I) salts were completely ineffective. Silver(I) salts, in particular AgOTf, were the best catalysts for this transformation. A variety of 2-acylindoles **89** bearing aryl, heteroaryl, vinyl and alkyl groups were prepared in good to excellent yields. Thienyl and cyclohexyl substituted products unfortunately led to lower isolated yields and propargyl alcohols and alkynoate esters were not suitable substrates for this cyclization.



Scheme 29. Ag(I)-catalyzed synthesis of 2-acylindoles **89.**

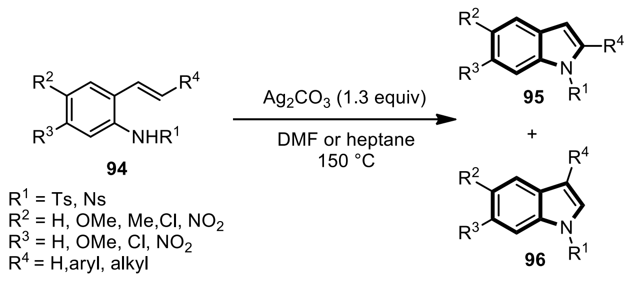
3. Other Examples

While most of the procedures featured in this Focus Review involve hydroamination of alkynes, this section includes rare examples of silver(I)-catalyzed indole synthesis via other methods. One of these methods was developed in our laboratory,[32] as part of a wider programme of research into silver-catalyzed alkyne activation[33] and indole dearomatization reactions.[34] This work is based on the use of pyrrole-tethered alkyne precursors (Scheme 30). A variety of substituted indole derivatives were prepared via an unusual “back-to-front” approach, whereby pyrrole-based starting materials (**90** and **92**) were used instead of anilines or related benzene derivatives, which are more typically employed in indole synthesis. Both $AgNO_3$ (sometimes with a Ag_2O additive) and a silica-supported silver catalyst (1 weight% $AgNO_3{\cdot}SiO_2$)[35] were shown to catalyze the formation of a variety of substituted indole products under mild conditions. Both propargyl alcohols **90** and ynones **92** were suitable substrates generating indoles **91** and 5-hydroxy indoles **93** respectively in good to excellent yields. The range of substitution patterns achieved on the benzene ring portion of the indole products is noteworthy; a range of starting materials can be employed in this procedure, allowing a variety of substitution patterns to be obtained that are difficult to access using traditional indole syntheses. DFT studies were also performed as part of this study, and these revealed that the reactions are likely to proceed via initial nucleophilic attack through the pyrrole C3 position before migrating, which goes against the generally accepted view that pyrroles are more nucleophilic through their C2 position in such systems.



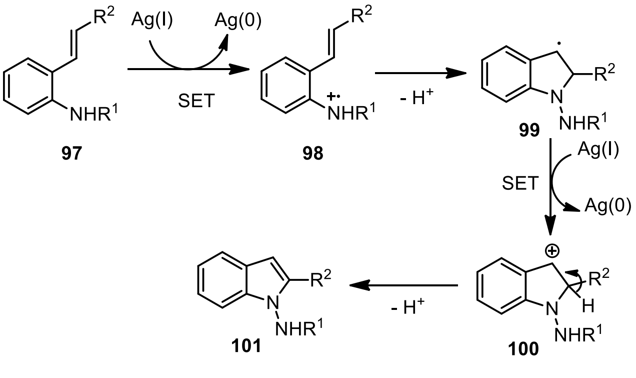
Scheme 30. “Back-to-front” indole synthesis from pyrroles **90** and **92**.

Another non-hydroamination method, published in 2015 by Youn and co-workers, concerns the silver(I)-mediated C-H amination of *o*-alkenyl anilines **94** to access 2,3-substituted indole derivatives **95** and **96** (Scheme 31).[36] The authors report the use of 1.3 equivalents of Ag_2CO_3 as an oxidant and heating to 120 °C in DMF for 0.5 h as being optimal reaction conditions for this transformation. It was noted that relatively high dilution (0.025*M*) was needed to achieve good yields and short reaction times. Interestingly, changing the solvent from DMF to heptane (0.05*M*) promoted 2,3-migration of the aryl/alkyl substituents, which suggests that a rearrangement process is involved in the mechanism. The use of *N*-nosyl *o*-alkenyl anilines and heptane as the solvent gave a mixture of 2- or 3-substituted indole products, with a ratio of up to 4.5:1 in favour of the 3-substituted indole.



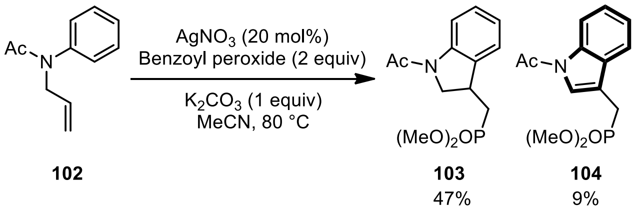
Scheme 31. Silver(I)-mediated C-H amination of o-alkenyl anilines **94** to make 2- and 3-substituted indoles **95** and **96**.

Reducing the loading of Ag_2CO_3 resulted in lower yields, hence a catalytic protocol was not pursued further. Despite the process requiring a stoichiometric loading of silver, the authors demonstrated that the Ag_2CO_3 can be partially recovered after the completion of the reaction and reused in up to 4 cycles without any significant loss in activity. A mechanism as depicted in Scheme 32 was proposed. A nitrogen-centered radical cation **98** is believed to be generated from the Ag(I) reagent via a single-electron transfer (SET) mechanism. This is followed by electrophilic radical addition to the tethered alkene coupled with deprotonation to afford a benzylic radical species **99**. Subsequent oxidation of **99** to form benzylic carbocation intermediate **100**, followed by rearomatization via deprotonation, then affords the 2-substituted indole **101**.



Scheme 32. Proposed mechanism for the silver(I)-mediated C-H amination of *o*-alkenyl anilines **97**.

In 2018, Liang *et al.* reported the isolation of phosphonoalkyl indole **104** from allylphenylacetamide **102** in 9% yield as a minor side-product from a silver-catalyzed radical phosphorylation/cyclization cascade (Scheme 33).[37] This is the only example of indole formation in this report, with the focus of the paper being the formation of 3-phosphonoalkyl indolines **103**. The authors hypothesized that the indole product was formed via oxidation of the initial indoline product **103** under the reaction conditions.



Scheme 33. Silver(I)-mediated synthesis of indoline **103** and indole **104**.

4. Summary

In view of the variety and number of silver-mediated indole forming reactions described in this review, it should be clear that silver chemistry has an important role to play in the synthesis of indole derivatives. Most of these procedures involve silver(I) catalysis and alkyne hydroamination, starting from an aniline precursor. Silver(I) species are well suited to promote this chemistry in view of their usually high π-acidity, which enables the alkyne to be activated under relatively mild conditions in many cases. The resulting vinyl silver species typically undergo fast protodemetallation, which is also important as this can facilitate faster catalyst turnover. Another important feature of silver(I) species in general is that these reagents are typically easy to handle, readily available and moderately priced in most cases (at least compared with other precious metal reagents). They are also compatible with a range of reaction conditions, solvents and other reagents, which is crucial in terms of them being applied in the wide range of silver-mediated processes described herein, particularly in the cascade processes that go beyond simple hydroamination/protodemetallation. The fact that suitable alkyne substituted aniline starting materials are usually relatively easy to prepare (*e.g.* via Sonogashira reactions or other cross coupling processes) is also likely to be have contributed to the utility and popularity of these methods.

By bringing all this science together in a Focus Review, we hope to facilitate the development of more efficient and ambitious silver(I)-mediated methods for the synthesis of important indole derivatives.

Acknowledgements

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Keywords: Indole • silver • catalysis • hydroamination • alkyne

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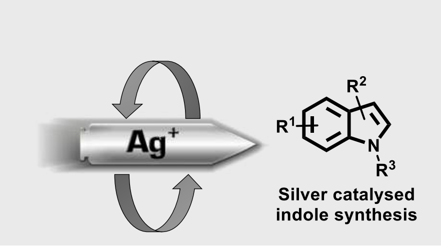

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