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Article

Silver−N-Heterocyclic Carbenes in π−Activation: Synergistic Effects between the Ligand Ring Size and the Anion

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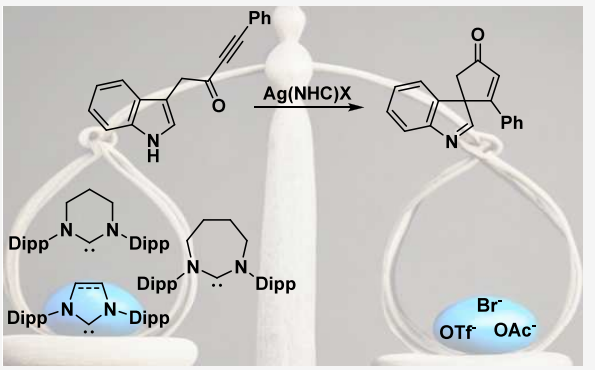
ABSTRACT: A series of 12 silver(I)−N-heterocyclic carbene (NHC) complexes were prepared featuring five- (both saturated and unsaturated backbone), six-, and seven-membered ring ligand scaffolds. The N-substituents of the NHCs were diisopropylphenyl in all cases, while the anion was varied between bromide, acetate, and triflate. The complexes were evaluated as catalysts in the spirocyclization of 1-(1*H*-indol-3-yl)-4-phenylbut-3-yn-2-one to give a spirocyclic indolenine product. To our knowledge, it is the first time that a systematic study has been conducted to examine the effects of both NHC ring size and anion in this type of silver-catalyzed reaction. While the acetate and triflate complexes catalyzed the reaction to 100% conversion, the bromide complexes exhibited a significant ligand/anion effect. Reactions catalyzed by both complexes bearing the five-membered ring NHC ligands and the complex bearing the seven-membered ring NHC ligand stalled after approximately two turnovers. However, the bromide complex bearing the six-membered ring NHC ligand catalyzes the reaction to almost full conversion, similarly to the acetate and triflate complexes. This demonstrates that the NHC ligand ring size can have a dramatic effect in these types of reactions and does not necessarily display a linear correlation.



INTRODUCTION

Since the first report on the facile preparation of silver−N-heterocyclic carbene (Ag−NHC) complexes using Ag_2O as a convenient basic metal precursor,[1] Ag−NHCs have been prepared and deployed in a variety of systems.[2] The major use for Ag−NHCs has been as transmetalating agents owing to the labile nature of the Ag-carbene bond, which allows the ligand to be readily transferred to another center. Wang and Lin observed the fluxional behavior of Ag(NHC)X species, which can also exist as $[Ag(NHC)_2][AgX_2]$ in solution,[1] with several further reports documenting the effects of ligand, anion, and solvent on ligand exchange rates.[3] Ag−NHCs have also been explored for their biological properties as antimicrobial[4] and anticancer[5] compounds, with the NHC ligand delivering the therapeutic silver at a slower rate when compared to simple silver salts.

Ag−NHCs have interesting properties that can be exploited in catalysis. The first report of Ag−NHCs being used in catalysis was in 2005,[6] when Fernandez and co-workers explored their use in the diboration of internal and terminal alkenes. More recently, the π-activation of alkynes by Ag−NHCs has been developed, with a variety of NHC structures examined with representative examples shown in Scheme 1.[7] These include the commonly used five-membered NHCs with bulky N-substituents (e.g., diisopropylphenyl, diisopentylphenyl),[8] triazole NHCs with bulky N-substituents,[9] and thiazole NHCs.[10] While an expanded nine-membered ring NHC has been reported for the carboxylative cyclization of propargylic alcohols and amines,[11] the effect of expanding the NHC ring in general has not previously been reported for the Ag−NHC-catalyzed π-activation of alkynes. This work describes a systematic study in which the NHC ring size is modified along with the anion and the effect on a π-activation reaction, with the aim of understanding the environment at the silver center and how this translates to catalysis. This will aid in the development of silver catalysts that necessitate the use of ligands, e.g., to induce selectivity in a given transformation.[12]

RESULTS AND DISCUSSION

A series of ligand precursors and their corresponding Ag−NHC complexes were prepared using modified literature procedures (Figure 1), and fully characterized using a suite of NMR spectroscopy and mass spectrometry methods (Support-

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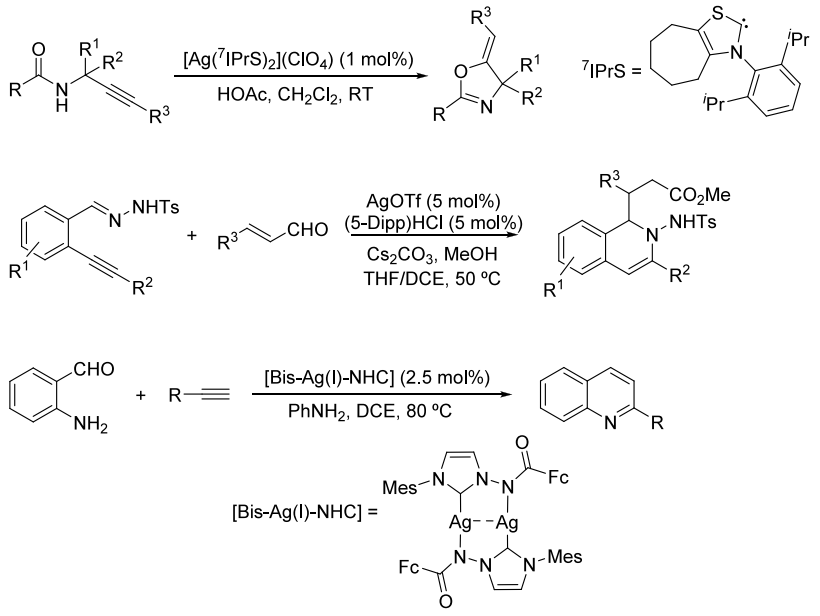
Scheme 1. Representative Examples of the π-Activation of Alkynes Using Ag–NHCs.[7]



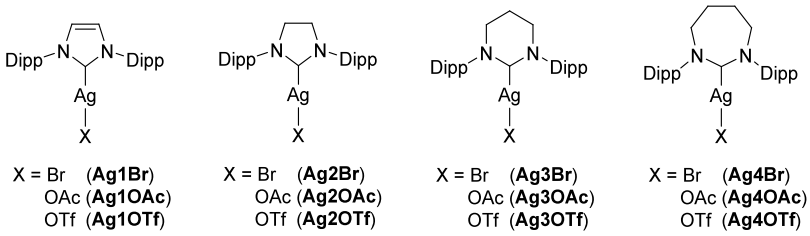
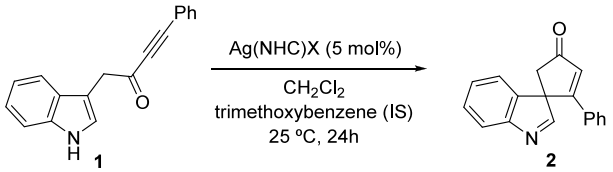


Figure 1. Series of Ag–NHC complexes prepared for catalytic study. Dipp = diisopropylphenyl.

ing Information). To our knowledge, complexes **Ag3OAc**, **Ag4OAc**, **Ag1OTf**, and **Ag4OTf** are novel.

To study the catalytic activity of the complexes, we sought to test them on a reaction system that had never been explored by using Ag–NHCs prior to this study. Indolyl ynones have been used as precursors to pharmaceutically relevant heterocycles and spirocycles through the π-activation of the alkyne and subsequent spirocyclization.[13] For example, 1-(1*H*-indol-3-yl)-4-phenylbut-3-yn-2-one (**1**) is known to cyclize in the presence of silver triflate to give the spirocyclic indolenine **2** (Scheme 2),[14] with various other Ag(I)-catalyzed protocols of related

Scheme 2. Spirocyclization of 1-(1*H*-Indol-3-yl)-4-phenylbut-3-yn-2-one 1[a]



[a]Conditions shown are those used in this study.

indole-ynone scaffolds also known.[12] The mild nature of the reaction to convert ynone **1** into spirocycle **2**, in addition to the simple workup and analysis through NMR spectroscopy, renders it a useful benchmark to examine the effect of adding NHC ligands to the silver (pre)catalyst. Although silver salts will catalyze this particular reaction effectively, understanding how different ligands and anions affect the outcome will aid in the development of efficient catalysts for reactions that require ligand enhancement, e.g., to direct stereo- or regioselectivity.[14] Following the development of a robust catalytic protocol (see the Supporting Information for full details), a screen was carried out in which all 12 Ag–NHCs were tested. Reactions were run for 24 h, and the conversion from starting material **1** into product **2** and NMR yield were recorded (Table 1). Reactions were carried out in duplicate to ensure reproducibility, and an internal standard (trimethoxybenzene) was used to measure the NMR yield, with an average of the two runs being reported.

From the data shown in Table 1, the anion has a clear effect on the catalytic activity. Using complexes with acetate (entries 5–8) or triflate (entries 9–12) anions results in conversions of 100%, albeit with lower NMR yields (~60% for acetate and ~30% for triflate complexes). In order to rule out hidden Bronsted acid catalysis, control reactions using AcOH and TfOH were performed, both of which resulted in no conversion of ynone **1** (Table 1, entries 13 and 14). The data for the bromide complexes are intriguing, with only the complex bearing the six-membered NHC ligand (**Ag3Br**, entry 3) showing good conversion in line with the acetate and triflate complexes, and the highest NMR yield of all complexes tested (68%). The remaining three bromide complexes with five-membered NHCs (entries 1–2) and seven-membered NHC (entry 4) reach conversions and NMR yields of about 10%, which equates to only two turnovers.

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Table 1. Conversion and Yield of Spirocyclized Product 2 following Ag−NHC-Promoted Spriocylization of Ynone 1[a]

entry	catalyst		conversion (%)	NMR yield (%)
1	**Ag1Br**	[Ag(5-Dipp)Br]	15	13
2	**Ag2Br**	[Ag(5-SDipp)Br]	9	8
3	**Ag3Br**	[Ag(6-Dipp)Br]	98	68
4	**Ag4Br**	[Ag(7-Dipp)Br]	9	9
5	**Ag1OAc**	[Ag(5-Dipp)OAc]	100	62
6	**Ag2OAc**	[Ag(5-SDipp)OAc]	100	55
7	**Ag3OAc**	[Ag(6-Dipp)OAc]	100	58
8	**Ag4OAc**	[Ag(7-Dipp)OAc]	100	60
9	**Ag1OTf**	[Ag(5-Dipp)OTf]	100	32
10	**Ag2OTf**	[Ag(5-SDipp)OTf]	100	31
11	**Ag3OTf**	[Ag(6-Dipp)OTf]	100	31
12	**Ag4OTf**	[Ag(7-Dipp)OTf]	100	31
13	AcOH (0.005 mmol)		0	0
14	TfOH (0.005 mmol)		0	0

[a] **1** (0.1 mmol), Ag(NHC)X (0.005 mmol), trimethoxybenzene (0.03 mmol), CH_2Cl_2 (1 mL). Conversion measured from starting material **1** to product **2** using ^{1}H NMR spectroscopy. The NMR yield is product **2** measured against internal standard trimethoxybenzene following filtration through silica.

We first turned our attention to the anion effect, with all acetate and triflate complexes giving 100% conversion regardless of the structure of the NHC. **Ag3Br** showed a similar result. In the case of the acetate complexes, only ∼60% yield was recovered following the silica filtration, with this lowering to ∼30% when the complexes bearing the more weakly coordinating triflate anion were used. As no further products were observed in the NMR data, the remaining organic material must be removed on the silica filter during workup, with the likelihood being that some of this is coordinated to silver species. A reaction catalyzed by **Ag3OTf** was characterized by ^{1}H NMR spectroscopy prior to silica filtration (Supporting Information Figure S15). A product yield of 26% was observed when resonances attributable to **2** were compared with the internal standard. Several additional resonances were observed that were not attributable to ynone **1**, product **2**, or other known compounds such as carbazoles or quinolines previously observed in the spirocyclization of **1**.[14] This indicates that there is a side reaction that is most prominent in reactions catalyzed by triflate complexes, with the side product being removed during filtration.

Stoichiometric Studies with Ag(NHC)OAc Complexes. In an attempt to understand the nature of the active species in these reactions, stoichiometric studies between ynone **1** and Ag(NHC)OAc complexes were carried out in an NMR tube with reactions being followed using ^{1}H NMR spectroscopy. Initially the Ag−NHC complexes were dissolved in CD_2Cl_2 in an NMR tube at the same concentration as the catalytic reactions (5 mM) and assessed for stability over 24 h, with no change observed for any of the complexes. Subsequently, 1 equiv of ynone **1** was added to each NMR sample and the reactions monitored over time by ^{1}H NMR spectroscopy. Using complexes **Ag3OAc** and **Ag4OAc** with expanded six- and seven-membered ring NHCs, full conversion into **2** was achieved by the time the first sample was taken at 50 min, whereas using complexes **Ag1OAc** and **Ag2OAc** with the unsaturated and saturated five-membered ring NHCs, reactions reached full conversion by 5 and 3 h, respectively. The ^{1}H NMR spectra following full conversion in each case exhibit resonances for Ag(NHC)OAc and product **2** (example in Figure 2), indicating that the Ag−NHCs stay intact during catalysis and that there is no interaction between the final product and the silver center. Upon leaving the samples, minor resonances grow in at 5.99, 7.57, 8.09, and 8.98 ppm. While the resonances could not be identified, the product(s) growing in are likely responsible for the lower yield in the catalytic reactions.

Equilibria between 2Ag(NHC)X and $[Ag(NHC)_2][AgX_2]$ are well documented,[15,16] with the equilibrium position being dependent upon many factors such as ligand substituents, ring size, anions, solvent, and other additives. The silver center in the cationic bis-NHC structure $[Ag(NHC)_2]^+$ is likely to be

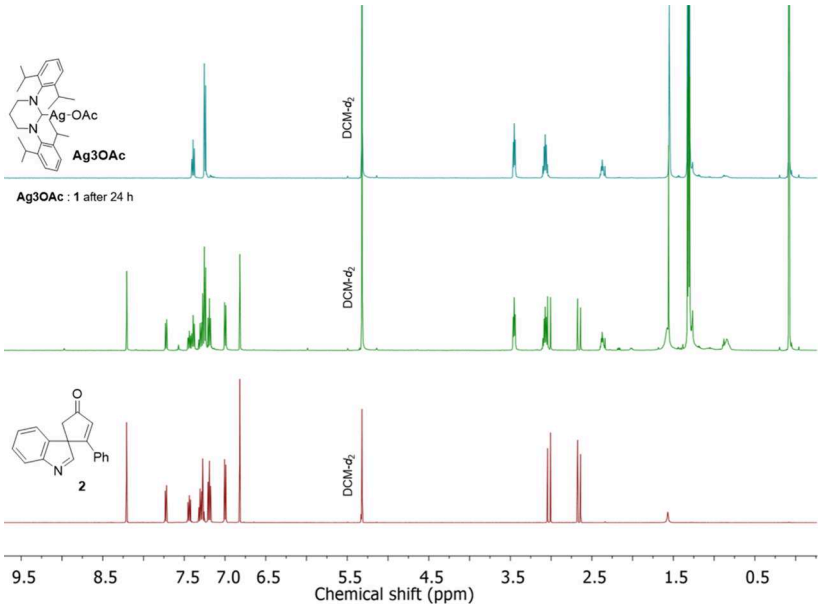

Figure 2. ^{1}H NMR spectra (DCM-d_2, 500 MHz) of **Ag3OAc** (top), spirocyclized product **2** (bottom), and 1:1 **Ag3OAc**:**1** (middle) after 24 h showing intact **Ag3OAc** and product **2**.

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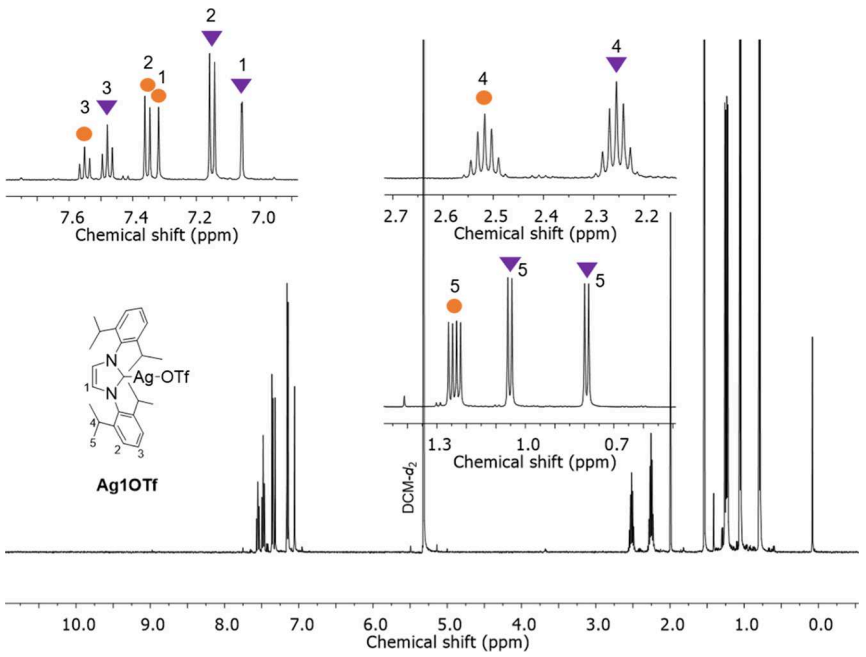

Figure 3. ^{1}H NMR spectrum (DCM-d_2, 500 MHz) of **Ag1OTf**. Two forms of the complex can be seen, highlighted by orange circles and purple triangles.

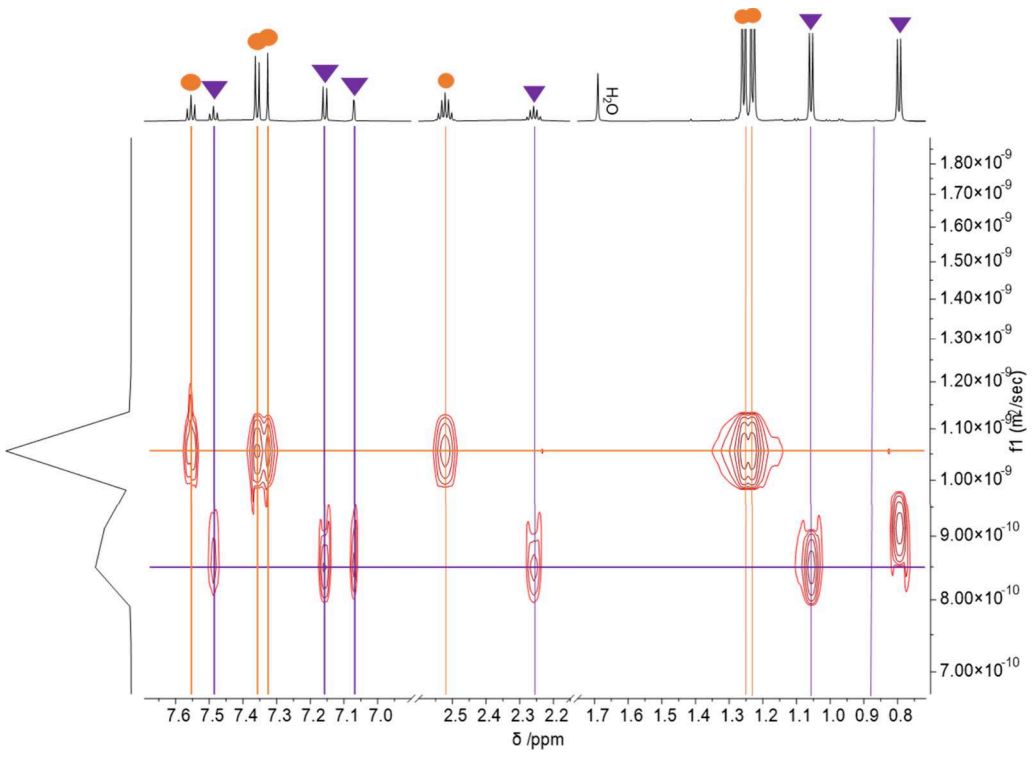

Figure 4. DOSY NMR spectra (DCM-d_2, 700 MHz) of **Ag1OTf** in solution showing two sets of resonances with diffusion coefficients 8.49×10^{-10} and 1.06×10^{-9} m^2/s. The bis-NHC complex is thought to be that highlighted in purple, while the mono-NHC complex is highlighted in orange.

inactive in catalysis due to the steric shielding of the silver center by the N-substituents of the ligands. This leaves Ag(NHC)X (or $[Ag(NHC)]^+$ when X is a weakly coordinating anion) and/or the halogeno counterion $[AgX_2]^-$ as potential active species, although $[AgX_2]^-$ can be involved in further coordination through bridging-, sandwich-, and staircase-type structures, which may render the silver less available.[16] In the case of the Ag(NHC)OAc complexes, it appears that they remain in the neutral form in DCM, with acetate likely coordinating to the silver center. It is therefore surprising that the complexes with the expanded six- and seven-membered ring NHCs are more active in stoichiometric studies than the five-membered NHCs, as they will impart a greater degree of steric shielding on the silver and their greater basicity will make the silver less cationic.

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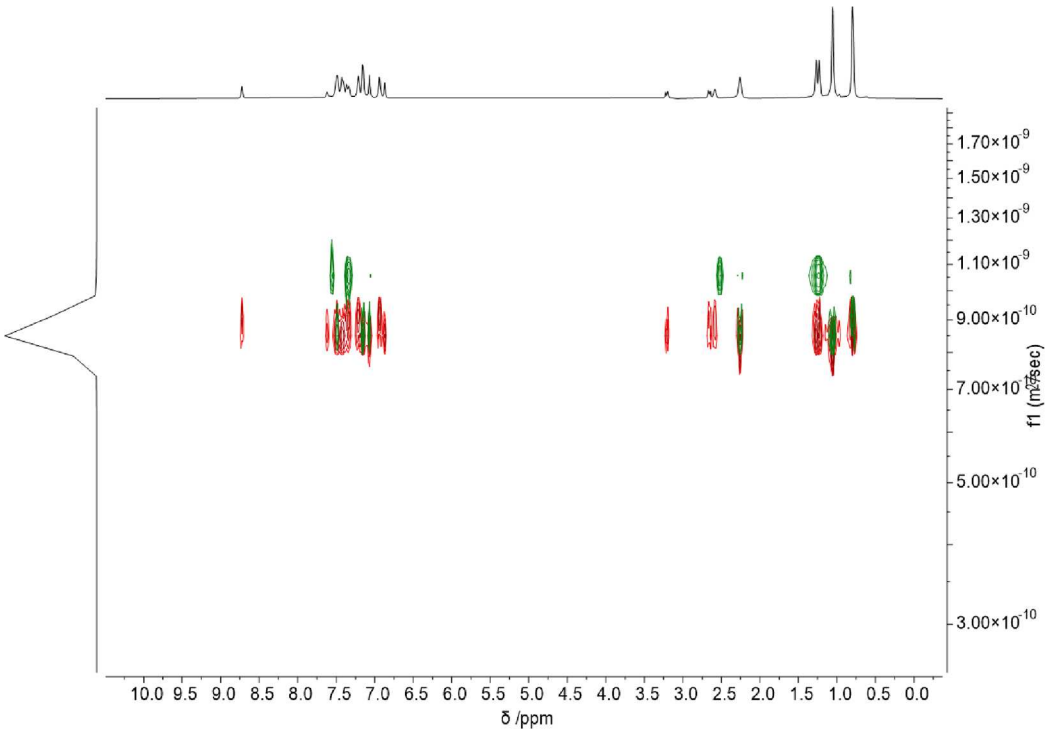

Figure 5. Stacked DOSY NMR spectra (DCM-d_2, 700 MHz) of **Ag1OTf** (green) and 1:1 **Ag1OTf:2** (red).

Stoichiometric Studies with Ag(NHC)OTf Complexes. The same stoichiometric study was conducted using Ag(NHC)OTf complexes. While **Ag2OTf** and **Ag3OTf** remained stable in DCM-d_2 over 24 h (recorded using ^{1}H NMR spectroscopy), **Ag1OTf** immediately showed two different species in solution (Figure 3). A combination of the small, unsaturated NHC with the weakly coordinating triflate anion is likely to drive the aforementioned equilibrium, with the likelihood that both Ag(NHC)OTf and $[Ag(NHC)_2]^+$ are observed on the NMR time scale.[17] Upon addition of ynone **1** to **Ag1OTf**, full conversion to spirocyclic indolenine **2** was observed within 20 min. **Ag2OTf** provided full conversion into **2** within 1 h and **Ag3OTf** within 1.5 h. The reduced steric shielding and basicity of the NHC in **Ag1OTf** when compared to **Ag2OTf** and **Ag3OTf** is potentially why this complex is more active, although the presence of a second species in solution may account for the faster rate and hence was studied further.

To characterize the two species, DOSY experiments were employed to separate the NMR signals of the two complexes based on their diffusion coefficients. A neutral mono-NHC complex was used as a reference sample to provide a benchmark of a known diffusion coefficient, in this case **Ag1Br**. A solution of **Ag1Br** in DCM-d_2 showed one set of signals with a diffusion coefficient of 1.15×10^{-9} m^2/s. In comparison, the solution of **Ag1OTf** in DCM-d_2 showed two sets of resonances with differing coefficients of 8.49×10^{-10} and 1.06×10^{-9} m^2/s (Figure 4). As larger molecules are expected to diffuse more slowly, it can be assumed that the resonances with coefficients at 8.49×10^{-10} m^2/s correspond to the cationic $[Ag(NHC)_2]^+$ form of **Ag1OTf** while the coefficient at 1.06×10^{-9} m^2/s can be assigned to the Ag(NHC)OTf complex.

Upon addition of ynone **1** to the DCM-d_2 solution of **Ag1OTf**, spirocyclic indolenine **2** formed immediately, with one of the sets of resonances in the ^{1}H NMR spectrum shifting, while the other set remains stationary. The stationary resonances correspond to $[Ag(NHC)_2]^+$; hence, it appears that the neutral Ag(NHC)OTf is the active species. Interestingly, the resonances attributable to spirocyclic indolenine **2** also shift when compared to those of isolated **2** in solution, which may indicate that the product coordinates to silver in this case. The resonance for the proton on the imine carbon shifts downfield from 8.21 ppm (**2** in DCM-d_2) to 8.26 ppm following spirocylization by **Ag1OTf** (Supporting Information Figure S16). Analogous shifts are seen in the ^{1}H NMR spectra for both the Ag(NHC)OTf complexes and product **2** following the spirocylization of **1** by **Ag2OTf** and **Ag3OTf**, suggesting the same active species and coordination of the product to the silver.

Next, preformed spirocyclic indolenine **2** was added to a solution of **Ag1OTf** in a 1:1 ratio. The ^{1}H NMR spectrum shows the same shift in resonances for both Ag(NHC)OTf and **2**, as those observed following the **Ag1OTf** promoted spirocylization reaction, with $[Ag(NHC)_2]^+$ resonances remaining unchanged. This indicates that the coordination of **2** to silver occurs even in the absence of catalysis. DOSY experiments conducted on the **Ag1OTf:2** mixture in DCM-d_2 shows resonances with diffusion coefficients around 9×10^{-10} m^2/s only, which is similar to the diffusion coefficient for $[Ag(NHC)_2]^+$ (Figure 5). This supports the theory that product **2** coordinates to the Ag(NHC)OTf complex in solution, forming $[Ag(NHC)(\mathbf{2})]^+$ and decreasing the diffusion coefficient. The difference in molecular weight between $[Ag(NHC)(\mathbf{2})]^+$ and $[Ag(NHC)_2]^+$ is around 130 Da, so similar diffusion coefficients would be expected, with $[Ag(NHC)_2]^+$ having a slightly lower coefficient due to being the heavier molecule. The coordination of **2** to silver is the likely cause of reduced yield compared to conversion following catalysis and workup, with the greatest loss being with the

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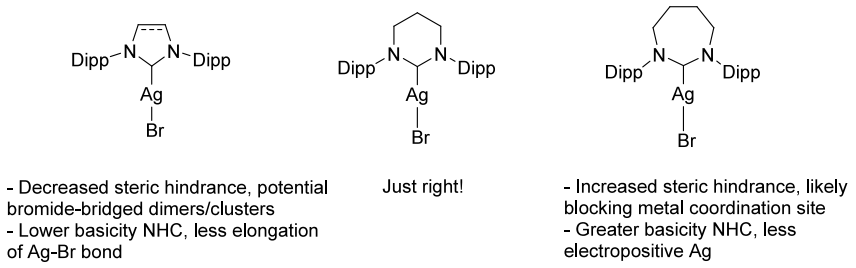

Figure 6. Potential factors contributing to the Goldilocks effect in **Ag3Br**.

triflate complexes due to the weakly coordinating anion and the greater likelihood for product coordination.

The acetate and triflate complexes all appear to follow the same route to catalysis, with the reaction rate being dependent upon the ligand and loss of product through workup being dependent upon the anion. As Ag(NHC)X appears to be the active species, the Ag(NHC)Br complexes might be expected to follow the same pathway, albeit with lower activity due to the more strongly coordinating nature of the bromide anion. **Ag1Br**, **Ag2Br**, and **Ag4Br** all show significantly reduced activity; however, the observed yields are much closer to conversions when compared to those of acetate and triflate complexes. This implies a lack of available coordination space at the silver centers for either starting ynone **1** or final product **2**. The 1:1 studies using these complexes and ynone **1** showed negligible conversion into product **2**, indicating that excess ynone is required to drive the reaction.

Stoichiometric Studies with Ag(NHC)Br Complexes. **Ag3Br** gave 98% conversion and the highest yield of 68% in the initial screen. In the 1:1 study using **Ag3Br**, full conversion was observed after 16 h; hence, the reaction is slower than those using AgOAc and AgOTf complexes but appears to be more selective. The ^{1}H NMR spectrum following the 1:1 study shows only **Ag3Br** and spirocyclic indolenine **2**, with no evidence of any other material in solution. This complex appears to have the optimal profile for catalysis out of those tested (Figure 6), whereby the strongly coordinating nature of bromide is most likely to retain the active Ag(NHC)Br form of the complex. This also reduces the product coordination to silver and its loss during the workup. The six-membered ring NHC appears to have the ideal stereoelectronic profile for catalysis to take place, a phenomenon that has also previously been observed in a different catalytic system.[18] Catalysis is almost shut down upon decreasing the steric bulk and NHC basicity by moving to the five-membered ring NHCs, or by increasing steric bulk and NHC basicity in the seven-membered ring NHC.

CONCLUSIONS

Twelve silver(I)−N-heterocyclic carbene complexes have been prepared and fully characterized. AgOAc and AgOTf complexes catalyze the spirocyclization of 1-(1*H*-indol-3-yl)-4-phenylbut-3-yn-2-one to give the spirocyclic indolenine product with 100% conversion, although product recovery is low, indicating low selectivity and/or loss of product during the workup due to silver coordination. Three of the AgBr complexes (**Ag1Br**, **Ag2Br**, and **Ag4Br**) perform poorly in catalysis, while **Ag3Br** performs similarly to the AgOAc and AgOTf complexes. Catalysis by this complex also gives the highest NMR yield of 68% following workup. This systematic study demonstrates that the stereoelectronic effects of the ligand, and the anion should not be considered independently of each other when designing a catalyst for a particular π-activation reaction and that the effect of the NHC ring size may not necessarily be linear.

EXPERIMENTAL SECTION

General Procedure for Catalytic Reactions. 1-(1*H*-Indol-3-yl)-4-phenylbut-3-yn-2-one (182 mg) and trimethoxybenzene (39 mg) were dissolved in DCM (3.5 mL) and the solution added via a syringe into six catalysis reaction vials (0.5 mL per vial). Three silver complexes were dissolved separately in DCM (1.5 mL each), and 0.5 mL (5 mol %) of each catalyst solution was added via syringe into two vials so that each reaction was run in duplicate. The reactions were stirred at 25 °C for 24 h, after which Et_2O (4 mL per vial) was added and the reaction mixtures filtered through silica (eluted with Et_2O). The resulting mixture was concentrated and analyzed by ^{1}H NMR spectroscopy.

Spirocyclic Indolenine. ^{1}H NMR (501 MHz, Chloroform-d): δ 8.20 (s, 1H, HN = CH), 7.76 (d, J = 7.8 Hz, 1H, H−Ar), 7.44 (td, J = 7.6, 1.4 Hz, 1H, H−Ar), 7.33−7.23 (m, 3H, H−Ar), 7.18 (t, J = 7.6 Hz, 2H, H−Ar), 6.99−6.95 (m, 2H, H−Ar), 6.84 (s, 1H, PhC = CH), 3.04 (d, J = 18.7 Hz, 1H, CH_2), 2.70 (d, J = 18.7 Hz, 1H, CH_2).

General Procedure for Stoichiometric Studies. The Ag complex was dissolved in DCM-d_2 (3 mL) and divided into three vials to give 1 equiv per vial. From the first vial, 0.6 mL was added via syringe into an NMR tube with a Young's tap. The remaining vials were kept sealed in the dark. The reaction mixture in the tube was monitored every hour over 24 h by ^{1}H NMR spectroscopy. After this time, 1-(1*H*-indol-3-yl)-4-phenylbut-3-yn-2-one (1 equiv) was added to the second vial. This was added via syringe into an NMR tube with a Young's tap (0.6 mL). The reaction mixture in the tube was monitored every hour over 24 h by ^{1}H NMR spectroscopy.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.organomet.3c00476.

General considerations; synthesis of imidazolium ligand precursors; synthesis of silver(I)−N-heterocyclic carbene complexes; synthesis of an organic precursor; catalytic protocol; and NMR spectra (PDF)

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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Notes

The authors declare no competing financial interest.

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