

Silver(I)-catalyzed C-X, C-C, C-N and C-O cross couplings using aminoquinoline directing group via elusive aryl-Ag(III) species

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ABSTRACT: Cross-coupling transformations are a powerful tool in organic synthesis. It is known that this kind of transformations undergoes 2-electron redox processes and, for this reason, silver has been nearly forgotten as catalyst for cross-couplings since silver is mainly considered as a 1-electron redox metal. Herein, we disclose effective Ag(I)-catalyzed cross-coupling transformations using bidentate aminoquinoline as a directing group towards different nucleophiles to form C-C, C-N and C-O bonds. DFT calculations indicate the feasible oxidative addition of **L_r-I** substrate via Ag(I)/Ag(III) catalytic cycle. Furthermore, ion spectroscopy experiments suggest a highly reactive aryl-Ag(III) that in absence of nucleophiles reacts to form an intermolecular cyclic product [**5d-Ag(I)-CH₃CN**], which in solution forms **5a**. This work proves that silver can undergo 2-electron redox processes in cross-coupling reactions like Pd and Cu.

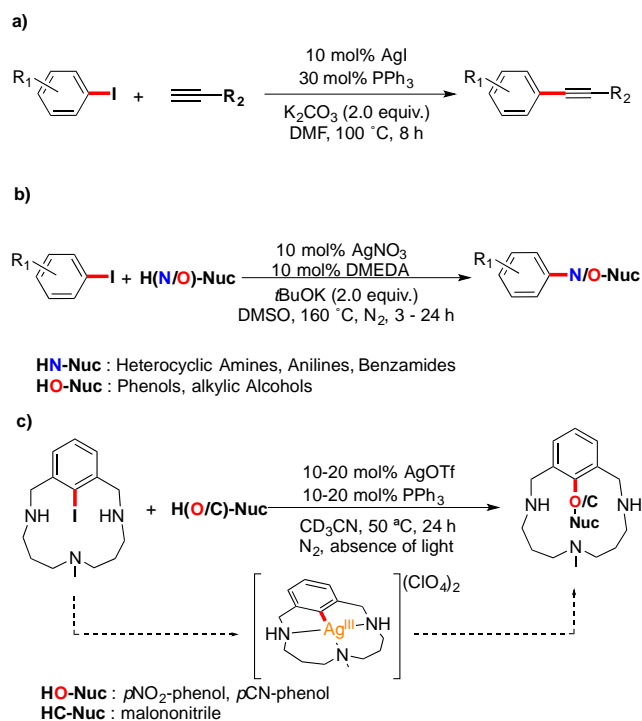
KEYWORDS. Silver, Cross-Coupling, Two-Electron Redox Catalysis, Mass Spectrometry, Infrared Photodissociation Spectroscopy.

INTRODUCTION

The vast majority of C-heteroatom cross-coupling processes are governed by palladium (C-N, Buchwald-Hartwig) and copper (Ullmann-type) catalysis, constructing a myriad of scaffolds useful as pharmaceuticals, materials, etc.¹⁻⁵ However, there is continuous need to discover new synthetic tools in order to have in hand versatile solutions for a given cross-coupling transformation. Silver has been completely forgotten in its use as catalyst for cross-coupling,⁶⁻⁷ which typically undergoes 2-electron redox processes, since it is generally believed that Ag only shows 1-electron redox chemistry.⁸⁻⁹ Nevertheless, albeit scarce, there are reports showing that silver catalyzes Sonogashira-type couplings¹⁰ and Ullmann-type C-N and C-O couplings,¹¹ although with complete lack of mechanistic understanding. In that respect, our group reported the unprecedented experimental evidence that 2-electron redox Ag(I)/Ag(III) catalysis can take place if the right coordination environment is provided to stabilize the key aryl-Ag(III) intermediate species (Scheme 1a,b,c).⁹ It was shown that triazamacrocyclic aryl-Br substrates enforced an ideal square-planar environment to stabilize aryl-Ag(III) species formed through facile oxidative addition at Ag(I). Strikingly, the aryl-Ag(III) species reacted with O- and C-nucleophiles under mild conditions via 2-electron

reductive elimination, and the whole cross-coupling process could be engaged in a catalytic mode.

In the present work, we aim at transferring the Ag-catalyzed cross-coupling reactions into non-cyclic aryl-halide substrates by using bidentate aminoquinoline (AQ) directing group, thus exploring the limits of the transient stabilization of the putative aryl-Ag(III) in a non-constrained system. To that end, we used **L_r-I** as model substrate (see Figure 1) and investigated the silver catalysis for halide exchange reactions, Ullmann-type C-N and C-O couplings, and Hurtley-type C-C couplings with active methylene nucleophiles.¹²⁻¹⁴ The implication of putative aryl-Ag(III) species has been analyzed by helium and D₂ tagging infrared photodissociation (IRPD) spectroscopy¹⁵⁻¹⁹ and will be discussed in detail.



Scheme 1. a) Ag-catalyzed Sonogashira-type coupling. b) Ag-catalyzed Ullmann-type C-N and C-O reaction. c) Ag-catalyzed C-O and C-C bond forming cross-coupling reaction.⁹

RESULTS AND DISCUSSION

We had previously shown that well-defined aryl-Ag(III) could undergo reductive elimination with different halides to effectively afford the halide exchange reaction within aryl-halide triazamacrocycles.⁹ More importantly, the system was catalytic in Ag(I) for the aryl-iodide to aryl-Br exchange. In this work we started by analyzing the ability of Ag(I) to catalyze the halide exchange reactions using non-cyclic aryl-halide substrates bearing an amino-quinoline bidentate Directing Group (DG), ligands L₁-X, L₂-X (X = I, Br, Cl, F; Figure 1). This non-cyclic model substrate enforces a square-planar coordination upon oxidative addition at Ag(I), reduces from three to two the number of N-coordination sites compared to the triazamacrocyclic substrates, and loses the macrocyclic effect.

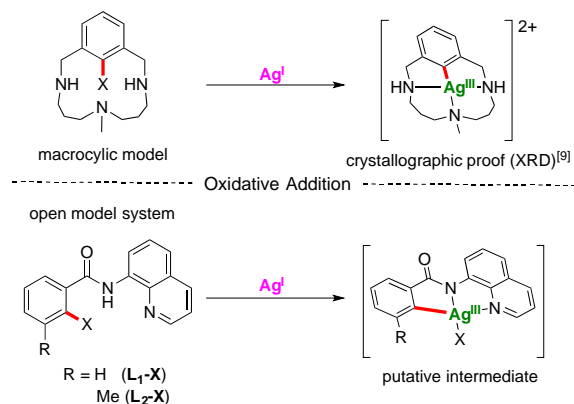
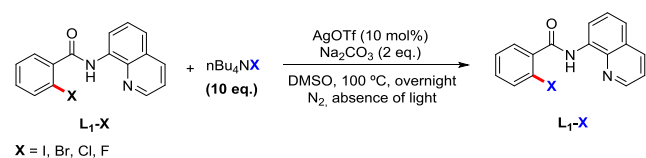


Figure 1. Macrocyclic model⁹ and open model system were compared in oxidative addition step.

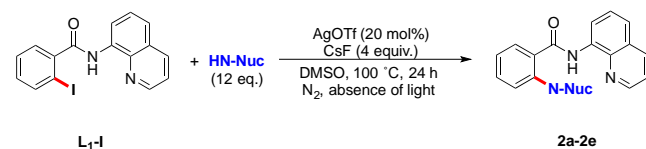
Thus, we analyzed first the viability of this halide exchange catalysis using L₁-I with nBu₄NX salts (X = Cl, Br). After optimization, we found that the catalysis was effective at 100 °C for the coupling with Cl and Br using 10 mol % of Ag(I)OTf (see Table 1). The catalysis can be performed in CH₃CN or DMSO solvents, affording good-to-excellent yields. The high reaction temperatures needed to achieve the halide exchange suggested a significantly higher energy barrier for the oxidative addition step in L₁-I than in the triazamacrocyclic aryl-I model substrate, where the reaction was conducted at room temperature (in agreement with DFT study, see below). When L₁-Br was used as substrate with nBu₄NX salts (X = Cl, I), the Br-to-Cl exchange was optimized in DMSO affording up to 78% yield. On the other hand, the Br-to-I exchange could only be optimized to afford a 38% yield in CH₃CN when 20 mol% of AgOTf was used as catalyst. This could be increased up to 50% when 20 mol% of PPh₃ was used as an additive (we also observed the beneficial use of PPh₃ as additive in cross-coupling catalysis using the triazamacrocyclic aryl-I substrate).⁹ When L₁-Cl was used as substrate, no halide exchange reaction occurred and L₁-Cl was fully recovered, presumably due to the unsurmountable energetic barrier for the oxidative addition under these conditions.

Given that the halide-exchange catalysis proved that the activation of aryl-I and aryl-Br was feasible via silver-catalysis, we aimed at exploring the ability of generating C-N heteroatom bonds, using aliphatic amines as nucleophiles, as well as imidazole and anilines (Table 2). Under optimized conditions (DMSO as solvent and CsF as base), couplings with cyclohexanamine and cyclopentanamine afforded moderate yields of the coupling products (37-53% yield), as depicted in Table 2. Similarly, when imidazole was used, the coupling product **2c** was obtained in 59% yield. We then tested *para*-substituted anilines (NO₂- or MeO-), and they afforded a 79% yield of **2d** (NO₂) and a moderate 33% yield of **2f** (OMe). The beneficial electron-withdrawing effect of the NO₂ group suggested that the underlying mechanism for C-N couplings might be related to a facile deprotonation of the N-nucleophile.

Table 1. Ag-catalyzed halide exchange reactions

Entry	L ₁ -X	nBu ₄ NX	Yield (%) ^a (Yield in CH ₃ CN)
1	L ₁ -I	nBu ₄ NCl	82 % (95 %) L ₁ -Cl
2 ^b			20 % L ₁ -Cl
3		nBu ₄ NBr	74 % (46 %) L ₁ -Br
4 ^b			0 % L ₁ -Br
5 ^c		nBu ₄ NF·3H ₂ O	0 % L ₁ -F
6	L ₁ -Br	nBu ₄ NCl	78 % L ₁ -Cl
7 ^b			0 % L ₁ -Cl
8		nBu ₄ NI	0 % (38 %, ^d 50 % ^e) L ₁ -I
9	L ₁ -Cl	NaI	0 % L ₁ -I

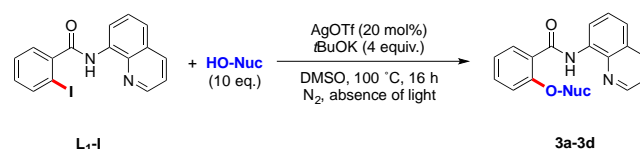
^a Yield calculated from ¹H-NMR of crude using trimethoxybenzene as internal standard. ^b The reaction was carried out without AgOTf. ^c Using 10 mol% of AgF. Side reaction was observed (34 % yield of L₁-DMSO). ^d Using 20 mol% of AgOTf. ^e Using 20 mol% of AgOTf and 20 mol% of PPh₃.

Table 2. Ag-catalyzed C-N bond forming reactions

Entry	Nuc.	Yield (%) ^a	Conv. (%)
1 ^b		53 % (51 %) 2a	>99 %
2 ^c		0 % 2a	5 %
3 ^b		37 % (31 %) 2b	>99%
4		59 % (54 %) 2c	71 %
5		79 % (61 %) 2d	>99%
6 ^d		85 % (59 %) 2e	>99 %
7 ^b		33 % (30 %) 2f	86 %

^a Yield calculated from ¹H-NMR of crude using trimethoxybenzene as internal standard (isolated yield in parenthesis). ^b Side reactions were observed: 18 % of L₁-H and 19 % of L₁-L₁ homocoupling (entry 1), 10 % of L₁-H and 18 % of L₁-L₁ homocoupling (entry 3), traces of L₁-H and 10 % of L₁-L₁ homocoupling (entry 7). ^c The reaction was carried out without AgOTf. ^d Using L₂-I as a substrate.

We then explored the silver-catalyzed aryl-O cross-couplings with phenols bearing different *para*-substituents (R = H, Cl, OMe, NO₂) (Table 3). In this case, reactions were optimized in DMSO and *t*BuOK as a base. Good yields were obtained for phenol (73%, **3a**) and *p*-Cl-phenol (74%, **3b**), whereas low yield was obtained when electron donating *p*-MeO-phenol was used (38%, **3c**). Surprisingly, the reaction was completely ineffective when *p*-NO₂-phenol was used as nucleophile. These results suggest that deprotonation is not a key step in the C-O coupling reaction and that a correct electronic balance is needed to achieve the desired coupling products. We also attempted the cross-coupling catalysis with CH₃OH as nucleophile, but only stoichiometric amounts of the desired **3e** coupling product were obtained when 10 and 20 mol% of AgOTf were used (CH₃OH as solvent and *t*BuOK as a base).

Table 3. Ag-catalyzed C-O bond forming reactions

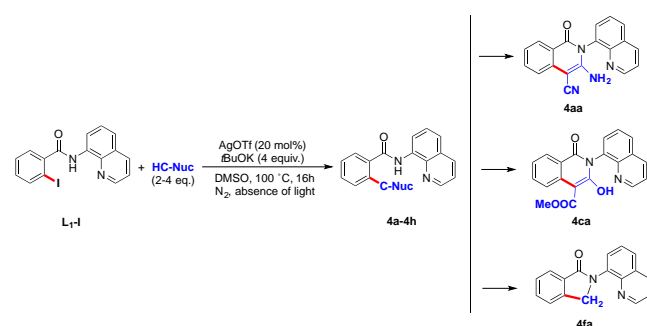
Entry	Nuc.	Yield (%) ^a	Conv. (%)
1		74 % (73 %) 3a	73 %
2 ^b		12 % 3a	19 %
3		73 % (60 %) 3b	94 %
4 ^c		38 % (22 %) 3c	71 %
5		0 % 3d	12 %
6 ^d		12 % 3e	66 %
7 ^d		21 % (13 %) 3e	73 %

^a Yield calculated from ¹H-NMR of crude using trimethoxybenzene as internal standard (isolated yield in parenthesis). ^b The reaction was carried out without AgOTf. ^c 32 % of L₁-H. ^d Using 2.5 mL of MeOH instead of DMSO, 10 mol% of AgOTf was used (entry 6).

Finally, C-C cross-couplings were explored using activated methylene-type substrates (Hurtley-type couplings), nitromethane and *p*-MeO-phenylboronic acid (Table 4). Under the optimized conditions (DMSO as solvent, *t*BuOK as a base and 20 mol% AgOTf), malononitrile afforded a 74% yield of the coupling product **4aa**, which consists of an initial C-C coupling and a subsequent cyclization by nucleophilic attack of the amide to one of the -CN groups (entry 1). The blank experiment did not afford **4aa** (entry 2). The same product **4aa** was obtained in 90% yield in CH₃CN, but some degree of decomposition of acetonitrile to form trimeric triazine-coupled product was

observed,²⁰ thus the solvent of choice was DMSO for the other C-nucleophiles. When ethyl 2-cyanoacetate was used, 48% yield of **4b** was obtained (entry 3), which is the C-C coupling product without further intramolecular reorganization. In this case, only 9% yield of **4ba**, the intramolecular cyclization product analogous to **4aa**, was obtained. On the other hand, dimethyl malonate afforded 62% yield of **4ca** which corresponds to the cyclic product formed by a nucleophilic attack of the amide to one of the carbonyl groups (with loss of MeOH). In the case of acetylacetone and ethyl 2-nitroacetate, the catalysis was completely ineffective. Surprisingly, nitromethane worked well as nucleophile yielding a 59% yield of **4fa**, which bears an isoindolin-1-one formed after the loss of the nitro group. Also, 16 % of **L₁-DMSO** is obtained (coupling of a deprotonated DMSO solvent molecule).

Table 4. Ag-catalyzed C-C bond forming reactions



Entry	Nuc.	Yield (%) ^a	Conv.(%)
1		74 % (71 %) 4aa ^b	99 %
2 ^c		0 % 4aa	16 %
3		48 % (41 %) 4b 9 % 4ba	99 %
4 ^d		62 % 4ca	63 %
5 ^e		0 % 4d	64 %
6		0 % 4e	19 %
7 ^e	H ₃ C-NO ₂	59 % (47 %) 4fa	99 %
8 ^f		20 % (15 %) 4g	57 %
9 ^f		0 % 4h	71 %

^aYield calculated from ¹H-NMR of crude using trimethoxybenzene as internal standard (isolated yield in parenthesis). ^b90 % of **4aa** was obtained using CH₃CN as solvent. ^cThe reaction was carried out without AgOTf. ^dThe reaction was carried out using DMSO-d₆. ^eSide reactions were observed 15 % of **L₁-H** (entry 5) and 16 % of **L₁-DMSO** (entry 7). ^fThe reaction was carried out using 10 equiv. of arylboronic acid at 120 °C.

Finally, arylboronic acids were also tested due to the effective reductive elimination observed using the triazamacrocyclic aryl-Ag(III) species.⁹ In the non-cyclized substrate, only 20% yield of the biaryl C-C coupling product **4g** was obtained, suggesting that transmetalation and reductive elimination occurred but the system could not enter into catalytic turnover. When *p*-NO₂-phenylboronic acid was used no coupling product was obtained, presumably because of the destabilizing effect of the electronwithdrawing group over the Ag(III) center.

Discarding contamination of other metals. Given the unusual two-electron redox Ag(I)/Ag(III) reactivity, we analyzed two AgOTf commercial samples by ICP-MS searching the content of traces of other possibly active metals in cross-coupling reactions, specifically Pd and Cu. No traces of Pd were found, and 0.01% content of Cu was determined in two batches of AgOTf. We then reproduced three of the above coupling reactions using [Cu(CH₃CN)₄]OTf as catalyst at 0.002 mol% (the content of Cu traces when using a 20 mol% AgOTf). No significant product yields were found (Table 5). In addition, the coupling reactions were also tested in the presence of Cu(OTf)₂, which might have a role if Ag(0) was formed in situ and was reoxidized to Ag(I). Again, no significant yields were obtained. Therefore, yields obtained using 0.002 mol% [Cu(CH₃CN)₄]OTf or Cu(OTf)₂ in the coupling catalysis tested clearly discard any significant role of Cu, and underline silver as the main catalyst (Table 5).

Table 5. Comparison of coupling reactions catalyzed by Ag or Cu impurities.

Entry	Nuc.	Yield (Conv.)		
		Ag(OTf) (20 mol%)	Cu(OTf) ^a (0.002%)	Cu(OTf) ₂ (0.002%)
1		53 % of 2a (99%)	6 % of 2a (6%)	9 % of 2a (24%)
2		79 % of 2d (99 %)	24 % of 2d (24 %)	-
3		74 % of 4aa (99 %)	0 % of 4a/4aa (36 %)	12% of 4aa (37 %)

^aUsing [Cu(CH₃CN)₄]OTf.

To further discard the activity of other impurities, small contents of HOTf, a typical impurity in triflate salts, were added in a AgOTf-catalyzed halide exchange reactions. The reactions in Table 1, entries 3 and 6 were repeated using 10 mol% AgOTf and HOTf (5% with respect to AgOTf), and smaller yields were obtained in both cases (55% of **L₁-Br** and 68% of **L₁-Cl**, respectively), discarding any beneficial role of triflic acid impurities.

Computational insight into the mechanism of the Ag-catalyzed cross-couplings. In order to gain insight

into the role of silver in the catalysis mechanism, DFT studies (see SI for details) were performed focusing on the I-to-Cl halide exchange reaction (Figure 2). We determined that the aryl-I oxidative addition step (TS1) lies at 24.7 kcal·mol⁻¹, rendering the key [L₁-Ag(III)-Cl](I) species. The latter shows a square-pyramidal geometry with I at the apical position (d_{Ag-I} = 3.7 Å), conforming to a d⁸ electronic configuration for Ag(III) in an analogous manner as well-defined aryl-Ag(III) species isolated in triazamacrocyclic scaffolds.⁹ [L₁-Ag(III)-Cl](I) undergoes subsequent aryl-Cl reductive elimination (TS2 = 28.1 kcal·mol⁻¹) to obtain the final (L₁-Cl)AgI compound. The barrier of 28.1 kcal·mol⁻¹ agrees with the high temperature (100 °C) needed for the reaction to take place. It is noteworthy that the reverse reaction, formally the aryl-Cl oxidative addition, has a larger barrier (up to 32.5 kcal·mol⁻¹) and conforms to the unobserved halide exchange when L₁-Cl is used as substrate.

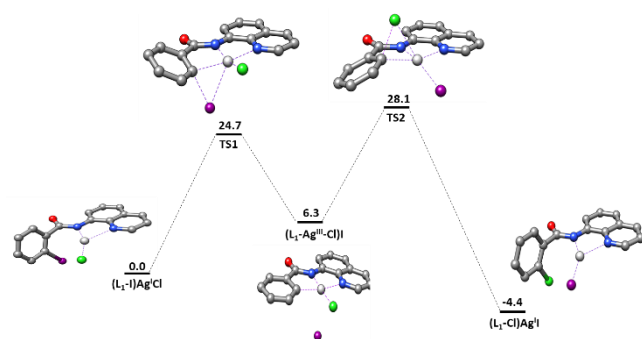


Figure 2. Gibbs energy profile of the oxidative addition and reductive elimination steps in the L₁-I-to-L₁-Cl halide exchange reaction.

Experimental IRPD-MS analysis of operando catalysis. Aiming for direct experimental proof of aryl-Ag(III) active species, we applied high resolution mass spectrometry (HRMS) and helium tagging infrared photodissociation (IRPD) spectroscopy to our system.¹⁶⁻¹⁹ Initial HRMS

analysis at short reaction times of the reactions using L₁-I and stoichiometric amounts of silver salt in CH₃CN (suitable solvent for the HRMS analysis) showed significant amounts of C-N homocoupling products. This result was a good indication of aryl-I activation but complicated the analysis. To simplify the reaction and the ulterior analysis, we designed the oMe-L₁-I (L₂-I) substrate to minimize the formation of homocoupling products by steric hindrance. For instance, using L₂-I as a substrate and pNO₂-aniline as a nucleophile for the silver-catalyzed C-N coupling affords 85 % of **2e**. Focusing in the MS study, no nucleophile was added to the reaction in order to analyze only the putative [L₂-Ag(III)]⁺ species formed by aryl-I oxidative addition at Ag(I). The main peak observed at *m/z* 494.9088 presumably corresponded to [(L₂-I)Ag]⁺ (Figure S1). Noteworthy, small peak at *m/z* 366.9987 was detected, tentatively assigned to [L₂-Ag(III)]⁺.

In order to identify the structure of the detected silver complexes, we have recorded their IRPD spectra. It turned out that the theoretically predicted IR spectrum of [(L₂-I)Ag]⁺ nicely reproduced the IRPD spectrum of the ions with *m/z* 495 (Figure 3).²¹⁻²⁶ It clearly confirmed that the detected *m/z* 495 ions peak correspond to the Ag(I) complexation to L₂-I. The putative silver(III) intermediate (*m/z* 367) was detected as a complex with acetonitrile at softer ionization condition (*m/z* 408). We assumed that acetonitrile fills in the fourth coordination site of the silver(III) complex and therefore stabilizes this intermediate. However, the experimental IRPD spectrum of the ions with *m/z* 408 and the theoretical spectrum of the proposed [L₂-Ag(III)-(CH₃CN)]⁺ intermediate did not agree. In particular, the theoretical spectrum of this Ag(III) complex did not contain any bands that could be attributed to the experimental peaks at 1110 and 2770 cm⁻¹. The search for alternative structures resulted in finding a series of more stable complexes with the same mass (see Figure S4). The theoretical IR spectrum for the complex [5d-Ag(I)-CH₃CN]⁺ resulting from an intramolecular cyclization conformed to the experimental spectrum (Figure 4).

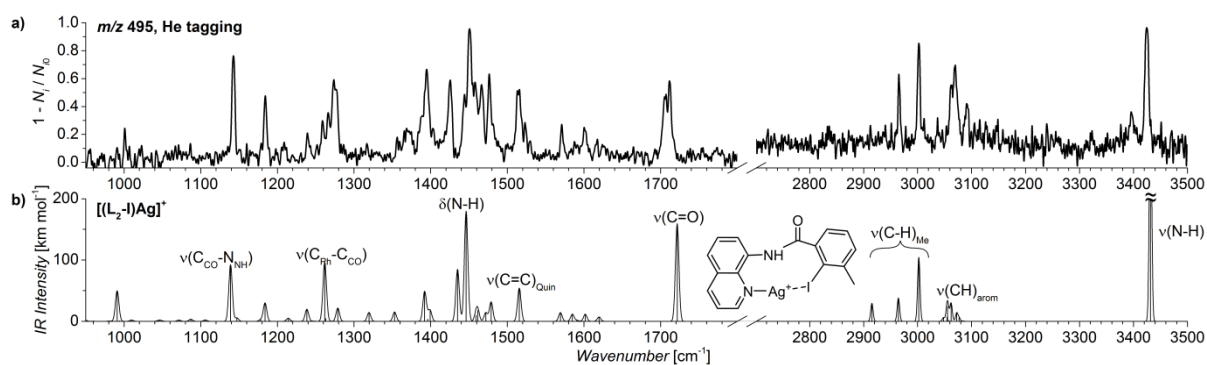


Figure 3. a) Helium tagging IRPD spectra of ions with *m/z* 495. b) Theoretical IR spectrum (B₃LYP²¹⁻²⁴-D₃BJ²⁵⁻²⁶/6-311+g(2d,p):SDD-(Ag,I)) of [(L₂-I)-Ag(I)]⁺. The scaling factor was 0.98 (below 2000 cm⁻¹) and 0.96 (above 2000 cm⁻¹). Predicted IR intensities above 2700 cm⁻¹ were multiplied by 10.

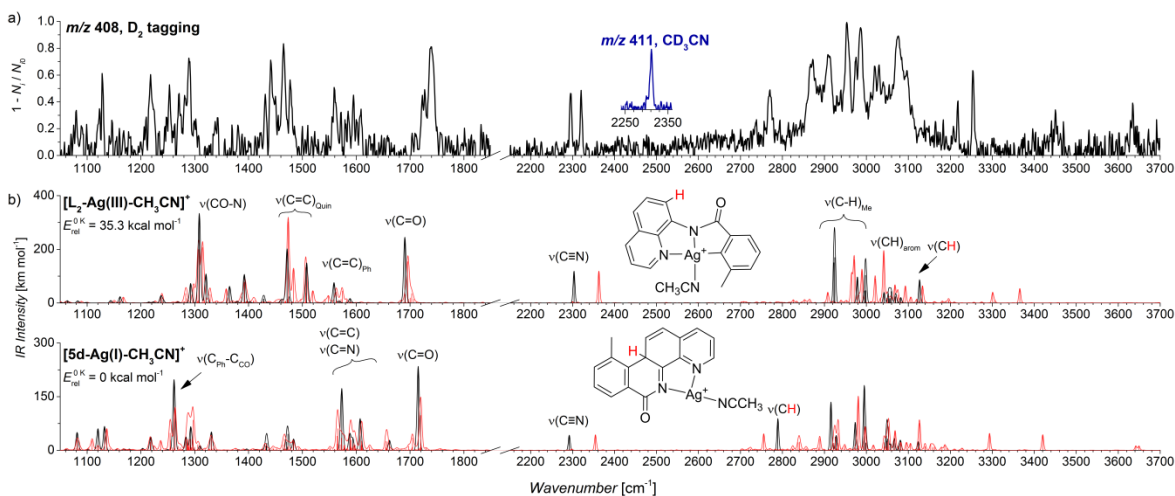
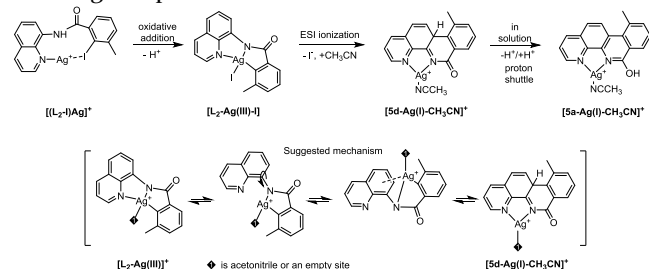


Figure 4. a) D₂ tagging IRPD spectra of ions with *m/z* 408. b) Theoretical IR spectra (B₃LYP-D₃BJ/6-311+g(2d,p):SDD-Ag) of [L₂-Ag(III)-CH₃CN]⁺ and [5d-Ag(I)-CH₃CN]⁺. The harmonic IR spectra are in black; the scaling factor was 0.98 (below 2000 cm⁻¹) and 0.96 (above 2000 cm⁻¹). The anharmonic IR spectra (B₃LYP-D₃BJ/6-311+g(2d,p):SDD-Ag) are in red and were not scaled. Predicted IR intensities above 2700 cm⁻¹ were multiplied by 10.

The formation of [5d-Ag(I)-CH₃CN]⁺ was rationalized as depicted in Scheme 2. The first species formed is the coordination of Ag(I) to the substrate (*m/z* 495), which undergoes oxidative addition, formal loss of HI and coordination of one CH₃CN molecule to transiently form the sought [L₂-Ag(III)-(CH₃CN)]⁺. Since IRPD analysis discarded that *m/z* 408 corresponded to the latter species, [5d-Ag(I)-CH₃CN]⁺ was formed in the gas phase as an intramolecular cyclization of the transient aryl-Ag(III) via formation of a Ag(I) complex bearing a cationic benzenylium moiety (a theoretical energy of 17 kcal·mol⁻¹ was calculated for this intermediate), which rapidly collapses to produce [5d-Ag(I)-CH₃CN]⁺. In solution, further proton-shuttle affords [5a-Ag(I)-CH₃CN]⁺, isolating 10-methylbenzo[*c*][1,10]phenanthrolin-6(5H)-one (**5a**) as the final organic product.

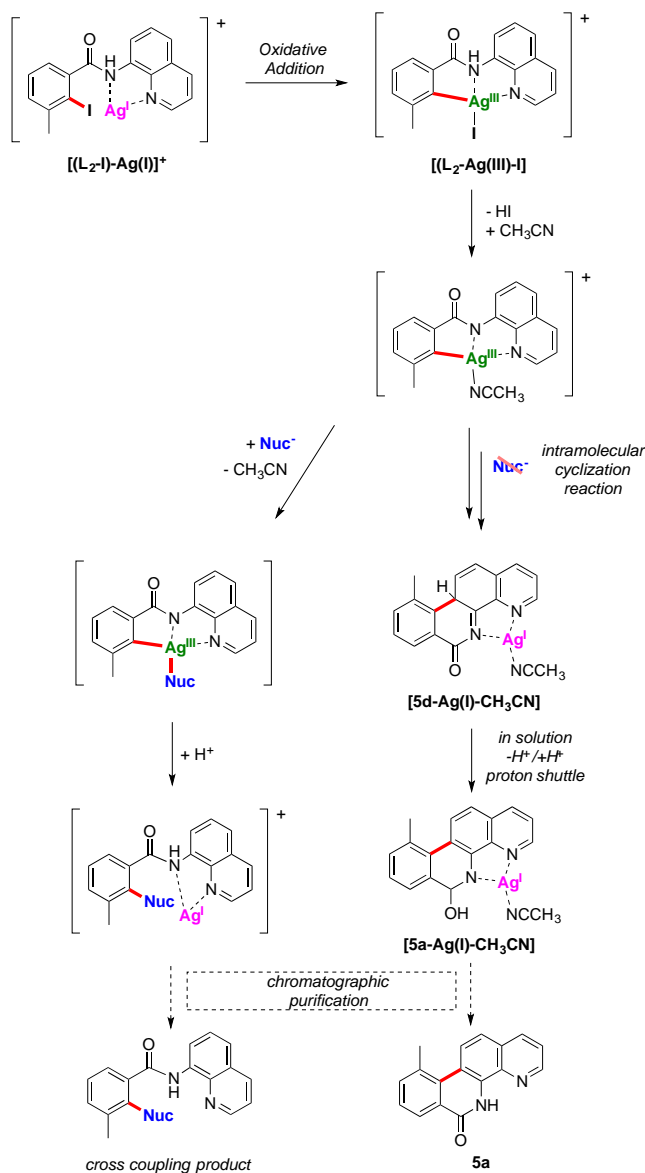


Scheme 2. Suggested mechanism of the formation of [5a-Ag(I)-CH₃CN], the experimentally observed intermediate.

To clarify whether [5d-Ag(I)-CH₃CN]⁺ was only formed in the gas phase or it was also formed in the reaction mixture, we repeated the reaction at ~0.1 g scale in order to isolate the products of the reaction of L₂-I and AgClO₄ in the presence of Na₂CO₃. Upon optimization (100 °C, 24 h),

analysis by HRMS of the reaction crude indicated that a compound at *m/z* 261 appeared mixed with starting L₂-I and byproducts. After chromatographic purification of the 261 peak, NMR and HRMS characterization confirmed the formation of the intramolecular cyclization organic product (**5a**) (Scheme 3), which results from a tautomerization of tautomer of **5d**.

Global mechanism. The mechanistic proposal depicted in Scheme 3 is derived from all the experimental and theoretical results disclosed in this work. The initial step of the reaction conforms to an aryl-halide oxidative addition that converges into the key aryl-Ag(III) species. This species is at a crossroads depending on whether the nucleophile is present in the reaction mixture. If present, nucleophile coordination and reductive elimination affords the desired coupling product following a 2-electron Ag(I)/Ag(III) catalysis. If absent, the highly reactive aryl-Ag(III) species undergoes an intramolecular cyclization reaction to form the experimentally characterized 10-methylbenzo[*c*][1,10]phenanthrolin-6(5H)-one (**5a**) species.



Scheme 3. Global mechanistic proposal in solution.

CONCLUSIONS

The ability of silver to undergo non-canonical 2-electron redox Ag(I)/Ag(III) cross-coupling catalysis for C-heteroatom and C-C bond formation has been successfully proven for a non-cyclic substrate bearing an amino-quinoline bidentate DG (L_1-I). Contrary to the rigid triazamacrocyclic model firstly used to isolate a well-defined aryl-Ag(III) complex, the non-cyclic L_1-I supports the same kind of intermediate species but much more reactive. Despite our attempts to directly detect organometallic aryl-Ag(III) species, those remained elusive although their existence is clearly inferred experimentally and theoretically in the four kinds of cross-coupling catalysis studied (halide exchange, C-N, C-O and C-C couplings), and also in the IRPD-MS studies without nucleophile. The sharply enhanced reactivity of this species in non-cyclic substrates compared to macrocyclic substrates

was also observed when studying Cu(III) intermediate species.¹⁸ We envision that this work might trigger more research efforts on Ag-catalyzed cross-couplings, to further evaluate its use as an actual synthetic tool in organic synthesis, complementary to the well-known Pd(o)/Pd(II) and Cu(I)/Cu(III).

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ASSOCIATED CONTENT

Supporting Information. Detailed spectroscopic characterization of all compounds is included. Also, computational DFT data and technical details of the IRPD experiments are included. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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