Supported Catalysts

Silica-Supported Silver Nitrate as a Highly Active Dearomatizing Spirocyclization Catalyst: Synergistic Alkyne Activation by Silver Nanoparticles and Silica

Aimee K. Clarke, Michael J. James, Peter O'Brien, Richard J. K. Taylor,* and William P. Unsworth*

Abstract: Silica-supported $AgNO_3$ ($AgNO_3$ -SiO_2) catalyzes the dearomatizing spirocyclization of alkyne-tethered aromatics far more effectively than the analogous unsupported reagent; in many cases, reactions which fail using unsupported $AgNO_3$ proceed effectively with $AgNO_3$ -SiO_2. Mechanistic studies indicate that this is a consequence of silver nanoparticle formation on the silica surface combined with a synergistic effect caused by the silica support itself. The remarkable ease with which the reagent can be prepared and used is likely to be of much synthetic importance, in particular, by making nanoparticle catalysis more accessible to non-specialists.

 \mathbf{P} ioneered in the 1960s, silica-supported AgNO₃ (AgNO₃-SiO₂) is well-known for its use as a support in the separation of *E*- and *Z*-alkenes by column chromatography.^[1] However, the synthetic potential of AgNO₃-SiO₂ as a catalyst has been mostly over-looked, with just a handful of reports on its use as a reagent in organic synthesis.^[2] To the best of our knowledge, examples are limited to syntheses of 5-membered heterocycles from alkynes and allenes, reported by Marshall^[2a] and Knight.^[2b,c] As part of a wider program on dearomatizing spirocyclization reactions,^[3,4] we decided to investigate the catalytic potential of AgNO3-SiO2 due to its limited previous use in synthesis and with the intention of exploiting the practical benefits of using a solid-supported reagent.^[5] To our surprise, we found that AgNO₃-SiO₂ offers vastly superior reactivity compared with unsupported AgNO₃ in dearomatizing spirocyclization reactions^[3] of alkyne-tethered heteroaromatics of the type shown in Figure 1.^[4]

Of much significance, several dearomatization reactions that previously failed with unsupported $AgNO_3$ can now be carried out in high yield with the $AgNO_3$ –SiO₂ catalyst. These unexpected findings prompted a mechanistic investigation which ultimately, via the combined use of in situ infrared spectroscopy (via ReactIR) and TEM, implicated a key role for silver nanoparticles (Ag-NPs)^[6] formed during the preparation of AgNO₃–SiO₂ together with a synergistic effect from the silica support itself. Pre-prepared Ag-NPs have been used

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Figure 1. AgNO₃-SiO₂ mediated dearomatizing spirocyclization.

as catalysts previously,^[7-9] but to the best of our knowledge, the catalytic role of Ag-NPs formed while supporting silver salts on silica has not been documented. In this paper, we highlight AgNO₃–SiO₂ as an easily prepared and highly active catalyst for dearomatizing spirocyclizations (Figure 1), showcasing the methodology with the AgNO₃–SiO₂-mediated synthesis of 23.6 g of a spirocycle in a simple continuous flow set-up. Furthermore, our mechanistic finding of the synergistic alkyne activation by Ag-NPs and silica provides a new alkyne activation pathway that could have much synthetic scope for alkyne functionalization.

To start, we examined the conversion of ynone 1a into spirocyclic indolenine 2a.^[10] Commercial AgNO₃-SiO₂ (10 wt % AgNO₃ on silica) was found to effect this transformation with reasonable efficiency,^[11] and following additional optimization (see Supporting Information) it was discovered that "home-made"^[12] AgNO₃-SiO₂ with a reduced AgNO₃ loading of 1 wt% was an even more effective catalyst; stirring ynone 1a at RT in CH_2Cl_2 with catalytic (1 mol%) 1 wt% AgNO₃-SiO₂ led to the formation of spirocycle 2a in 98% isolated yield in 30 minutes (Scheme 1, conditions A). Interestingly, this is significantly faster than the same reaction with unsupported AgNO3 (6 h, conditions B).^[4a] Even more dramatic differences were seen in the reactions of ynones tethered to other aromatics; phenol 3a, pyrrole 5a and benzofuran 7 were reacted with both catalyst systems, and while spirocyclic products 4a, 6a, and 8 were isolated in high yields when 1 wt % AgNO₃-SiO₂ was used, AgNO₃ alone led to no reaction in all three cases (Scheme 1).^[13,14]

In view of these marked differences, a mechanistic study was initiated. We first monitored the conversion of ynone **1a** into spirocycle **2a** with in situ infrared spectroscopy (via ReactIR), using the decrease in intensity of the C=C stretch of ynone **1a** (2208 cm⁻¹) to monitor reaction progress. Using 1 mol% of the 1 wt% AgNO₃-SiO₂ catalyst, ynone **1a** was converted into spirocycle **2a** in 30 min (blue line, **A**, Figure 2),





Scheme 1. Supported and unsupported Ag¹-catalyzed spirocyclization.



Figure 2. 2D ReactIR plots of the conversion of 1a into 2a using catalysts A–D (1 mol%) in CH₂Cl₂ at RT.

fully consistent with the synthetic reaction. In contrast, as expected from the synthetic work, the unsupported $AgNO_3$ reaction was much slower, requiring > 6 h to reach completion (purple line, **B**); interestingly, there was a clear induction period of around 2 h, and even after this time the reaction was slower.

To explore the role of silica, AgNO₃ and silica were both added to a solution of **1a** in CH₂Cl₂ (i.e. the AgNO₃ was not supported on the silica in advance). In this experiment (pink line, **C**), an induction period was still observed (around 90 min), but once this period had passed, the reaction proceeded at a similar rate to the standard AgNO₃–SiO₂ reaction (blue line, **A**). Silica is not able to promote spirocyclization on its own (stirring ynone **1a** in silica in CH₂Cl₂ led to no reaction after several days) but clearly its presence significantly increases the rate of the Ag-mediated spirocyclization reaction. We suggest that this may be due to accelerated protodemetallation;^[15] silanol groups on the silica surface might be expected to facilitate this step, thus releasing the silver for further catalysis and increasing the turnover rate.

Our results also indicate a clear difference between the supported AgNO₃-SiO₂ catalyst and unsupported AgNO₃ in the presence of silica (which should have the same elemental composition). This led us to propose that AgNO₃ is a precatalyst in the unsupported reaction and that the induction period is connected to the time taken for Ag-NPs to form in situ. To test this, unsupported AgNO₃ was "aged" by stirring the standard reaction dose in CH₂Cl₂ for 24 h before adding ynone 1a; the expectation was that by ageing the catalyst, Ag-NPs would form in advance and alter the reaction profile.^[16] The initially colorless solution became yellow during the ageing process, which is indicative of Ag-NP formation,^[17] and the aged catalyst did indeed perform differently (gray line, **D**). The reaction proceeded at a similar rate to the standard AgNO₃ reaction (purple line, **B**), but crucially there was no induction period. A mercury drop test was also performed which led to the complete cessation of the reaction,^[18] adding additional support to the idea that Ag-NPs are the true catalyst. Further supporting evidence was obtained using transmission electron microscopy (TEM); AgNO₃ was stirred for 24 h at RT in CH₂Cl₂ and an aliquot of the solution ($\approx 5 \,\mu$ L) was removed and dropped onto a copper TEM grid. The deposit that remained after the CH₂Cl₂ had evaporated was then analyzed using TEM, and Ag-NPs were found to be present (Figure 3).



Figure 3. TEM images for AgNO₃ "aged" in CH₂Cl₂.

In view of the above results, we considered it likely that Ag-NPs were also present in our standard supported AgNO₃–SiO₂ (1 wt%) catalyst system, as they could potentially form during the preparation of the supported reagent. This was confirmed by TEM imaging of the supported catalyst; crystalline Ag-NPs were observed (Figure 4) and the electron diffraction pattern enabled the identification of a cubic silver crystal phase (space group *Fm3m*) and showed that the particles had a spacing of around 0.205 nm, which is representative of cubic silver.^[19]

Thus, it appears that in both the supported and unsupported systems, Ag-NPs rather than $AgNO_3$ are predominantly responsible for the conversion of **1a** into **2a**. Silica was also shown to be important, leading to an increased reaction rate, even when added separately to the silver. This may be due to faster protodemetallation, and hence more effective catalyst turnover and/or its role may also be to adsorb the Ag-NPs and control their growth/aggregation.

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Figure 4. TEM images for AgNO₃-SiO₂.

Next, to more fully evaluate the synthetic utility of our $AgNO_3$ -SiO₂ catalyst, the optimized spirocyclization conditions were applied to other alkyne-tethered aromatics, and compared to unsupported $AgNO_3$ in each case (Scheme 2).

Indolyl spirocyclic products **2a–e** were all obtained in excellent yields (94–100%), with $AgNO_3$ -SiO₂ promoting a faster transformation than with unsupported $AgNO_3$ in all cases. More pronounced differences in reactivity were observed for 2- and 4-phenol derivatives **3a–f**; these substrates did not react at all using unsupported $AgNO_3$, but using $AgNO_3$ -SiO₂ spirocyclic dienones **4a–f** were all formed in high yield, notably including compound **4f**, an advanced intermediate in a published route to spirobacillene A.^[14a] Pyrrole derivatives **5a–g** are also well tolerated, with $AgNO_3$ -SiO₂ superior to unsupported $AgNO_3$ in all examples. The quantitative formation of spirocycles 6e-g is especially noteworthy, given the rarity of dearomatized products derived from 3-pyrroles.^[20] Thus a wide range of substituted aromatics are compatible with this simple, mild method, and furthermore, even broader functional group tolerance was demonstrated by an extensive robustness screen, detailed in the Supporting Information.^[21]

Finally, the use of our $AgNO_3$ -SiO₂ catalyst in a continuous flow reaction^[22] has been demonstrated. A 0.1M solution of ynone **1a** in toluene was simply passed through a 1 cm diameter column packed with 1.93 g of our standard 1 wt% catalyst (19.3 mg of AgNO₃) at a flow rate of 0.3 mLmin⁻¹, concentrated in vacuo, and analyzed using ¹H NMR spectroscopy. This reaction proceeded very efficiently, converting a total of 23.6 g of ynone **1a** into spirocycle **2a** in quantitative yield over a 51 h period (Scheme 3). This corresponds to a total catalyst loading of 0.12 mol% and an NMR aliquot measured after 51 h showed that the product was still being formed cleanly, indicating that the catalyst remained active.

In summary, 1 wt% AgNO₃–SiO₂ is a very effective catalyst for the dearomatizing spirocyclization of alkynetethered heteroaromatics, with its efficacy believed to stem from a synergistic relationship between the silica support and Ag-NPs formed during its preparation. It is much more reactive than unsupported AgNO₃, and in our hands, it is also more reactive than silica-supported Ag-NPs made by literature methods in which the Ag-NPs were prepared separately.^[23] In contrast to existing methods to prepare supported



Scheme 2. Supported and unsupported Ag¹-catalyzed spirocyclization. Isolated yields (following catalyst removal) are quoted, or for incomplete reactions, conversion (conv.) was calculated based on analysis of the ¹H NMR spectrum on the unpurified product mixture.

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Scheme 3. Flow spirocyclization of ynone 1a.

Ag-NPs,^[6a,8b] our catalyst is easy to prepare with full silver incorporation into the supported catalyst and it can be stored in the dark at RT for several months with no loss of activity.^[12] The reactions are easy to perform and are purified simply by removing the supported catalyst by filtration, which can then be reused five times with no apparent loss of activity.^[24] ICP-MS analysis confirmed that spirocycle 2a formed under the standard conditions contains ca. 60 ppm silver (which is pleasing given that no aqueous work-up or chromatography was performed on the analyzed samples), and by performing the same reaction in toluene rather than CH₂Cl₂, silver contamination in the product could be reduced to just 5 ppm, which is significantly below the 17 ppm limit set by the FDA for the permissible amount in a drug.^[25] All of these findings have potential implications in both previous and future work; it may now be considered that the processes previously described by Marshall and Knight using AgNO₃-SiO₂ also benefitted from the presence of Ag-NPs, while moving forwards, AgNO₃-SiO₂ may also represent a more convenient source of Ag-NPs than those prepared by conventional methods.

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Silica-Supported Silver Nitrate as a Highly Active Dearomatizing Spirocyclization Catalyst: Synergistic Alkyne Activation by Silver Nanoparticles and Silica



Nanoparticle catalysis: Silica-supported AgNO₃ catalyzes the dearomatizing spirocyclization of alkyne-tethered aromatics far more effectively than the analogous unsupported reagent. Mechanistic studies indicate that this is a consequence of silver nanoparticle formation on the silica surface combined with a synergistic effect caused by the silica support itself.

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