Silica-supported silver nitrate as a highly active dearomatising spirocyclisation catalyst: synergistic alkyne activation by silver nanoparticles and silica

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**Abstract:** Silica-supported AgNO3 (AgNO3-SiO2) catalyses the dearomatising spirocyclisation of alkyne-tethered aromatics far more effectively than the analogous unsupported reagent; in many cases, reactions which fail using unsupported AgNO3 proceed effectively with AgNO3-SiO2. 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.

Pioneered 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 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 Marshall2a and Knight.2b-c As part of a wider program on dearomatising spirocyclisation 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 dearomatising spirocyclisation reactions3 of alkyne-tethered heteroaromatics of the type shown inFigure 1.4



**Figure 1.** AgNO3-SiO2 mediated dearomatising spirocyclisation.

Of much significance, several dearomatisation reactions that previously failed with unsupported AgNO3 can now be carried out in high yield with the AgNO3-SiO2 catalyst. These unexpected findings prompted a mechanistic investigation which ultimately, *via* the combined use of *in situ* infrared spectroscopy (via ReactIRTM) 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 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 dearomatising spirocyclisations (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 functionalisation.

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 optimisation (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 CH2Cl2 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



**Scheme 1.** Supported and unsupported Ag(I)-catalysed spirocyclisation.

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 ReactIRTM), 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), fully consistent with the synthetic reaction. In contrast, as expected from the synthetic work, the unsupported AgNO3 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.

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

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 spirocyclisation 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 spirocyclisation 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 pre-catalyst 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 colourless solution became yellow during the ageing process, which is indicative of AgNP formation,17 and the aged catalyst did indeed perform differently (grey 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 (~5 μL) was removed and dropped onto a copper TEM grid. The deposit that remained after the CH2Cl2 had evaporated was then analysed using TEM, and Ag-NPs were found to be present (Figure 3).

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**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

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**Figure 4.** TEM images for AgNO3-SiO2.

Thus, it appears that in both the supported and unsupported systems, Ag-NPs rather than AgNO3 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.

Next, to more fully evaluate the synthetic utility of our AgNO3-SiO2 catalyst, the optimised spirocyclisation conditions were applied to other alkyne tethered-aromatics, and compared to unsupported AgNO3 in each case (Scheme 2).

**Scheme 2.** Supported and unsupported Ag(I)-catalysed spirocyclisation. 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.



Indolyl spirocyclic products **2a**–**2e** were all obtained in excellent yields (94–100%), with the supported catalyst out-performing unsupported AgNO3 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 AgNO3, but using AgNO3-SiO2 spirocyclic dienones **4a**–**4f** 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 AgNO3-SiO2 superior to unsupported AgNO3 in all examples. The quantitative formation of spirocycles **6e**–**g** is especially noteworthy, given the rarity of dearomatised 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 AgNO3-SiO2 catalyst in a continuous flow reaction22 has been demonstrated. Thus, a 0.1 M 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 mL/min, concentrated *in vacuo*, and analysed 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.



**Scheme 3.** Flow spirocyclisation of ynone **1a**.

In summary, 1 wt. % AgNO3-SiO2 is a very effective catalyst for the dearomatising spirocyclisation of alkyne-tethered heteroaromatics, with its efficacy believed to stem from a synergistic relationship between the silica support and Ag-NPs formed during its preparation. Itis 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 Ag-NPs,6a,8b our catalyst is easy to prepare with full silver incorporation into the supported catalystand 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 analysed 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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[11] Ynone **1a** (0.1 mmol) was stirred with 10 mol % of AgNO3-SiO2 (10 wt. %, Sigma Aldrich, 248762) in CH2Cl2 for 10 min, resulting in full conversion into spirocycle **2a**.

[12] 1 wt. % AgNO3-SiO2 was prepared by adding AgNO3 (100 mg) to a slurry of Fluka silica gel (9.90 g, pore size 60 Å, 220–440 mesh particle size) in deionised water (27 mL). The mixture was stirred for 15 min, concentrated *in vacuo* at 60 °C to form a free-flowing powder and dried by heating to 140 °C under high vacuum for 4–5 h.

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[24] See Supporting Information for details. Very consistent (high) yields were achieved in these recycling studies, highlighting the reliability and reproducibility of these reactions.

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