Supported Catalysts

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

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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.*

Pioneered in the 1960s, silica-supported $AgNO_3$ ($AgNO_3$–SiO_2) 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 $AgNO_3$–SiO_2 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 $AgNO_3$–SiO_2 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 $AgNO_3$–SiO_2 offers vastly superior reactivity compared with unsupported $AgNO_3$ 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 $AgNO_3$–SiO_2 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 $AgNO_3$–SiO_2 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 $AgNO_3$–SiO_2 as an easily prepared and highly active catalyst for dearomatizing spirocyclizations (Figure 1), showcasing the methodology with the $AgNO_3$–SiO_2-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.

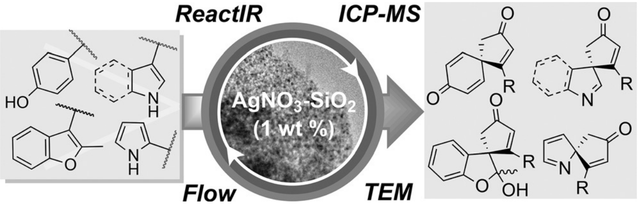

Figure 1. $AgNO_3$–SiO_2 mediated dearomatizing spirocyclization.

To start, we examined the conversion of ynone **1a** into spirocyclic indolenine **2a**.[10] Commercial $AgNO_3$–SiO_2 (10 wt % $AgNO_3$ 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] $AgNO_3$–SiO_2 with a reduced $AgNO_3$ 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 % $AgNO_3$–SiO_2 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 $AgNO_3$ (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 % $AgNO_3$–SiO_2 was used, $AgNO_3$ 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 % $AgNO_3$–SiO_2 catalyst, ynone **1a** was converted into spirocycle **2a** in 30 min (blue line, **A**, Figure 2),

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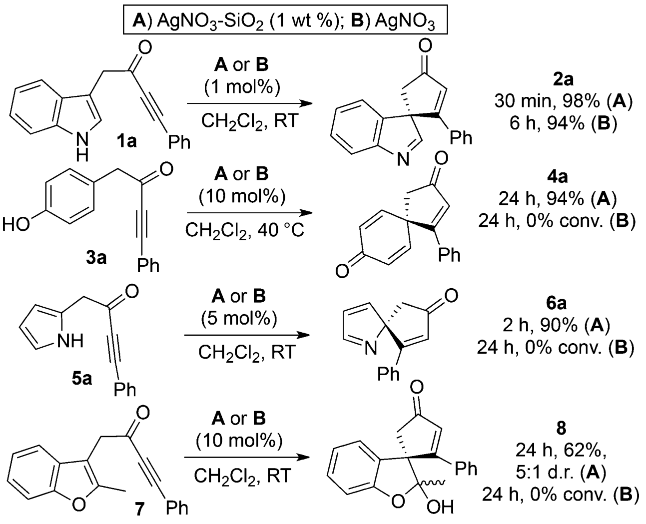


Scheme 1. Supported and unsupported Ag^{I}-catalyzed spirocyclization.

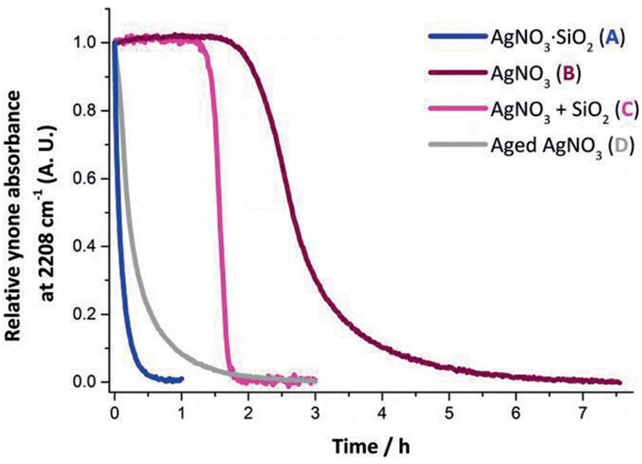


Figure 2. 2D ReactIR plots of the conversion of **1a** into **2a** using catalysts **A**–**D** (1 mol%) in CH_2Cl_2 at RT.

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, $AgNO_3$ and silica were both added to a solution of **1a** in CH_2Cl_2 (i.e. the $AgNO_3$ 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 $AgNO_3$–SiO_2 reaction (blue line, **A**). Silica is not able to promote spirocyclization on its own (stirring ynone **1a** in silica in CH_2Cl_2 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 $AgNO_3$–SiO_2 catalyst and unsupported $AgNO_3$ in the presence of silica (which should have the same elemental composition). This led us to propose that $AgNO_3$ 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 $AgNO_3$ was "aged" by stirring the standard reaction dose in CH_2Cl_2 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 $AgNO_3$ 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); $AgNO_3$ was stirred for 24 h at RT in CH_2Cl_2 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 CH_2Cl_2 had evaporated was then analyzed using TEM, and Ag-NPs were found to be present (Figure 3).

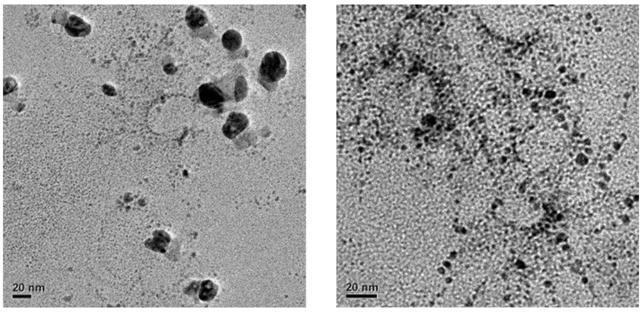


Figure 3. TEM images for $AgNO_3$ "aged" in CH_2Cl_2.

In view of the above results, we considered it likely that Ag-NPs were also present in our standard supported $AgNO_3$–SiO_2 (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 *Fm*3*m*) 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.

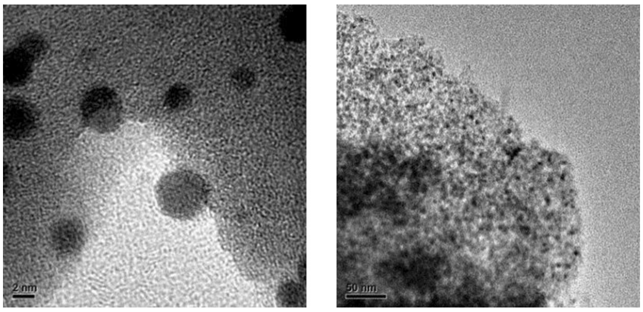


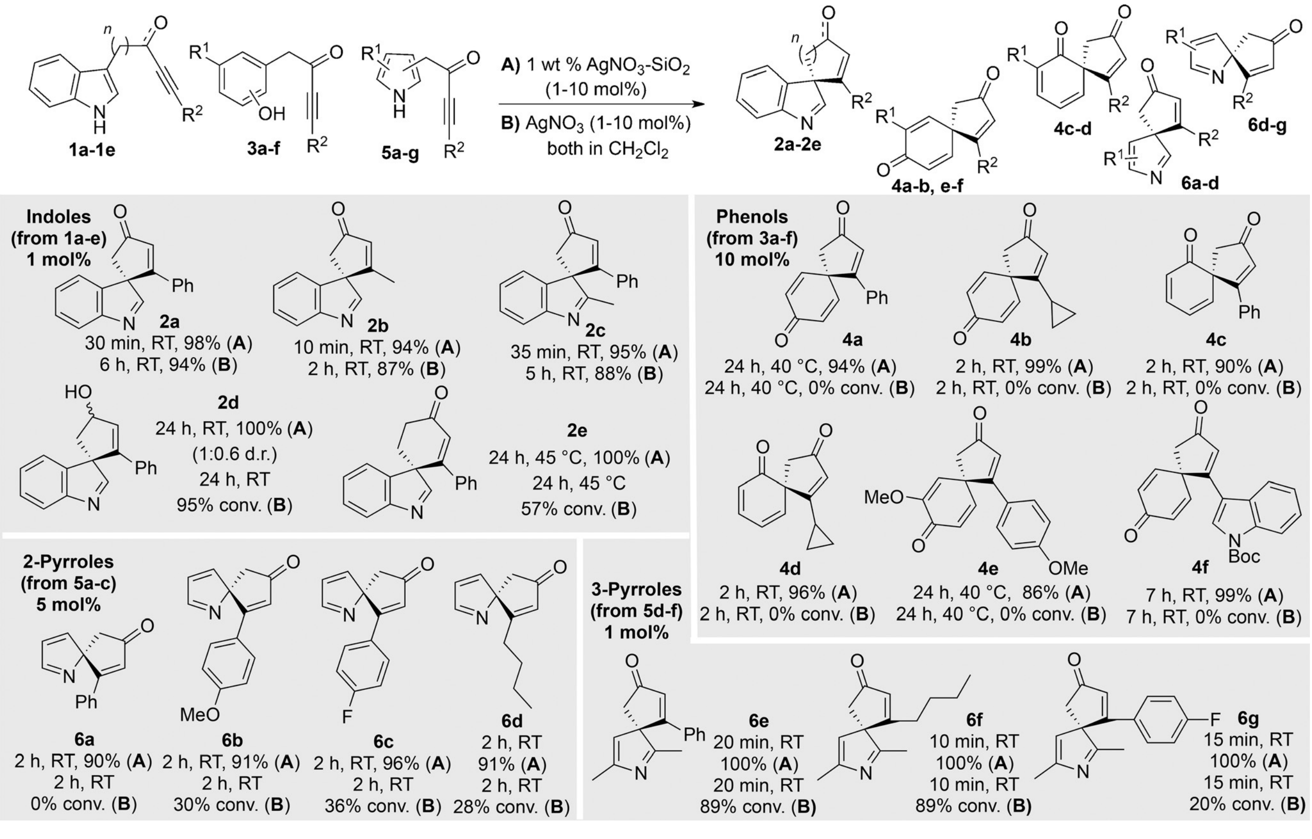
Figure 4. TEM images for $AgNO_3$–SiO_2.

Next, to more fully evaluate the synthetic utility of our $AgNO_3$–SiO_2 catalyst, the optimized spirocyclization conditions were applied to other alkyne-tethered aromatics, and compared to unsupported $AgNO_3$ in each case (Scheme 2).

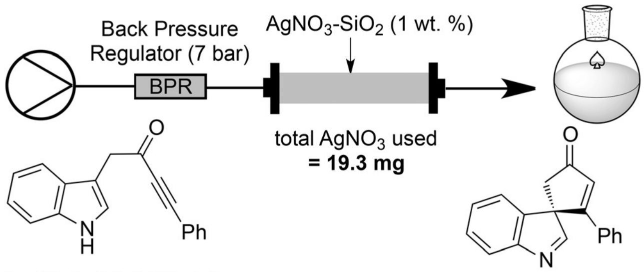
Indolyl spirocyclic products **2a–e** were all obtained in excellent yields (94–100 %), with $AgNO_3$–SiO_2 promoting a faster transformation than with unsupported $AgNO_3$ in all cases. More pronounced differences in reactivity were observed for 2- and 4-phenol derivatives **3a–f**; these substrates did not react at all using unsupported $AgNO_3$, but using $AgNO_3$–SiO_2 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 $AgNO_3$–SiO_2 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 $AgNO_3$–SiO_2 catalyst in a continuous flow reaction[22] has been demonstrated. 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 $AgNO_3$) at a flow rate of 0.3 mL min^{-1}, concentrated in vacuo, and analyzed using ^{1}H 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 % $AgNO_3$–SiO_2 is a very effective catalyst for the dearomatizing spirocyclization 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. It is much more reactive than unsupported $AgNO_3$, 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 Ag^{I}-catalyzed spirocyclization. Isolated yields (following catalyst removal) are quoted, or for incomplete reactions, conversion (conv.) was calculated based on analysis of the ^{1}H NMR spectrum on the unpurified product mixture.



1a (**23.6 g**) 0.1 M in toluene **2a**, 100% (**23.6 g**)

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 CH_2Cl_2, 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 $AgNO_3$–SiO_2 also benefitted from the presence of Ag-NPs, while moving forwards, $AgNO_3$–SiO_2 may also represent a more convenient source of Ag-NPs than those prepared by conventional methods.

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[12] 1 wt% $AgNO_3$–SiO_2 was prepared by adding $AgNO_3$ (100 mg) to a slurry of Fluka silica gel (9.90 g, pore size 60 Å, 220–440 mesh particle size) in deionized 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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[18] The reaction of ynone **1a** with unsupported $AgNO_3$ was allowed to proceed to ca. 50% conversion, before mercury was added (200 equivalents with respect to $AgNO_3$), which stopped any further reaction.

[19] Qualitatively, the supported Ag-NPs appear to be much more uniform in size than those obtained from aged $AgNO_3$ in CH_2Cl_2; more detailed studies will be required in future to probe this observation and its implications more rigorously.

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[23] Silica-supported Ag-NPs synthesized by literature methods (references [6a] and [8b]) were tested in the transformation of ynone **1a** into spirocycle **2a**, resulting in 45% and 28% conversion into **2a**, respectively, with unreacted starting material accounting for the remainder of the mass balance.

[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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