Continuous centrifugation and filtration for assessing the catalytic significance of metal nanoparticles forming in situ during the palladium-catalyzed arylation of *N*-methylindole

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We demonstrate that continuous centrifugation of the reaction mixture can alter the trajectory of a palladium catalyzed C-H functionalization reaction in which nanoparticles are forming in situ from molecular precatalysts. By the action of the centrifuge the nanoparticles are sequestered in an immiscible layer as they form, preventing them from interacting with the substrate or forming equilibria with molecular catalyst species. The use of continuous centrifugation to assess the catalytic relevance of nanoparticles that are forming in situ is compared to a more conventional filtration strategy.

Introduction

It is well established that palladium nanoparticles can form in situ from molecular precatalysts during catalysis and that equilibria among various palladium species can occur.[1–5] The presence of nanoparticles in reactions with molecular precatalysts naturally raises questions about whether the nanoparticles are simply a decomposition product or whether the nanoparticles have catalytic relevance either as active catalysts themselves or by serving as a reservoir for the active form(s) of the catalyst. The many methods of assessing the catalytic contributions of nanoparticles vs molecular species in reactions where both present, and the challenges associated with the existing methods, have been reviewed. [6 ,7]

In the nanoparticle synthesis community, centrifuges are a widely used tool for the isolation and purification of metal nanoparticles. While large nanoparticles sediment at the bottom of the centrifuge tube, molecular species and the smallest nanoparticles remain in the supernatant.[8] The use of multiple liquid phases, aqueous[9] or aqueous-organic,[10] can further aid in the separation of metal nanoparticles from other species. In the context of a catalytic reaction in which nanoparticles are forming in situ it is then plausible that continuous centrifugation during the reaction could separate the various forms of the metal that may be contributing to the observed catalysis.[1–5]

Our work investigates the use of a centrifuge to continuously sediment nanoparticles as they are forming, by performing a metal-catalyzed reaction that is actively forming nanoparticles under continuous centrifugal force. Addition of a second liquid phase under the reaction mixture allows the sedimented nanoparticles to be sequestered and prevented from engaging in any catalytic activity or forming equilibria with catalytically active species. If those nanoparticles were catalytically relevant, the trajectory of the catalyzed reaction should be impacted by centrifugation. Conceptually similar to the hot filtration test,[11,12] the continuous centrifugation test should have the advantage of minimal perturbation to the reaction medium. Perturbations to the reaction, particularly changes in temperature, have been shown to impact the results of the hot filtration test in the context of studies investigating the leaching of molecular species from heterogeneous catalysts.[13–15] In the context of nanoparticles forming in situ from molecular precatalysts, there is the added complication that any molecular precatalyst that remains in solution after a discrete separation procedure can simply generate more nanoparticles.

There have been a few isolated examples where centrifugation of a reaction mixture was used to manipulate the trajectory of the reaction such as in the formation of humin during acid-catalyzed reactions involving fructose[16] and the radiation-induced polymerization of vinyl chloride.[17] These examples and our work are distinct from the more common application of centrifugal forces to affect reactions by moving or mixing solutions in the context of microfluidics[18] or applications in which centrifugation prior to a reaction is used to create gradients or otherwise organize materials in a way that impacts the outcome of a future reaction.[19]

As a model reaction for the proposed centrifugation studies we chose the palladium-catalyzed C–H arylation of *N*-methylindole with a diaryliodonium salt (Figure 1), originally reported by Sanford and coworkers in 2006.[20] Sanford and coworkers reported that both $Pd(OAc)_2$ and $IMesPd(OAc)_2$ (IMes=1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene)[21] were

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Supplementary Information available: Detailed experimental procedures and additional characterization data. See DOI: 10.1039/x0xx00000x effective precatalysts and suggested a mechanism involving a $Pd^{II/IV}$ catalytic cycle. Iodonium reagents were known to oxidize Pd^{II} to Pd^{IV}.[22] Later mechanistic studies on C–H arylation of related substrates supported the involvement of a bimetallic, high oxidation state species in the key bond forming step.[23]

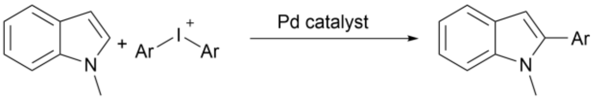

Figure 1. C–H arylation of *N*-methylindole with a diaryliodonium salt.

Since the initial report, various groups have reported that the C-H arylation of indoles by diaryliodonium reagents can be promoted with other palladium precatalysts including $Pd(OTf)_2$,[24] $PdCl_2$,[24] $(PPh_3)_2PdCl_2$,[24] $Pd_2(dba)_3$,[25] palladium nanoparticles,[26–28] and Pd on carbon.[29] To our knowledge there were no reports of interconversion among the different forms of palladium during a C–H arylation reaction specifically involving an iodonium salt, however the generation of palladium nanoparticles from palladium acetate during other C–H functionalization reactions has been reported.[2 4, 30–32] These reports indicate that various forms of palladium may have catalytic relevance, either as catalysts themselves or in equilibrium with catalytically active species, thus making the system an attractive target for centrifugation studies that would remove nanoparticles selectively from the catalytic reaction mixture.

Here we report our efforts toward the development of a procedure that uses a centrifuge to disambiguate the roles of molecular and nanoparticulate forms of palladium during the C–H arylation of *N*-methylindole using a diaryl iodonium salt. We compare our novel centrifugation test with the more conventional method of performing a filtration at a single point during the reaction.

Results and discussion

Prerequisite to the centrifugation studies, all other reactants and reagents must be fully soluble in the reaction medium. In our hands, under the originally reported conditions for C–H arylation of *N*-methylindole[20] the iodonium salt was not fully soluble. The solubility of the iodonium salt in acetic acid was improved by selecting an iodonium salt with a tosylate or triflate anion and *tert*-butyl substituents to the aryl rings.

To ensure that the sedimented nanoparticles are completely isolated from the reaction mixture, a second liquid phase was added below the reaction mixture. The requirements for the second phase are that it have a higher density than the reaction mixture, be immiscible with the reaction mixture, be non-reactive, and not electrostatically repulsive toward nanoparticles. Polyfluorinated compounds appeared to be attractive options because of their high densities. We found that hexafluorobenzene was soluble in acetic acid. In trials with perfluoro-n-octane and perfluoro-2-butyltetrahydrofuran we found that nanoparticles did not reliably penetrate the perfluoro layer after 5 minutes at 39000 g. We found that MOLYKOTE® high vacuum grease met our criteria for nanoparticles forming in situ during a C–H arylation reaction with a $Pd(OAc)_2$ pre catalyst (vide infra) however it was necessary to add ethanol to the acetic acid (1:5 v/v) in order to decrease the density of the reaction mixture below the density of the vacuum grease. While the high vacuum grease proved effective for the C–H arylation reaction reported here it may not be appropriate for all systems. For example, when we attempted to employ high vacuum grease to sequester nanoparticles in a Pd-catalyzed alkene oxidation reaction in a mixture of DMSO, ethanol, and water we found that the nanoparticles generated failed to fully penetrate into the high vacuum grease under centrifugation (see supporting information).

With suitable reaction conditions for C–H arylation studies identified we then sought to document the impact of centrifugation on the trajectory of a C–H arylation reaction using preformed nanoparticles as the precatalyst. Pd nanoparticles in a polyvinylpyrrolidone matrix were prepared using the procedure reported by the Fairlamb group.[4] Washing the isolated particles with a cetrimonium bromide solution allowed for STEM characterization of minimally aggregated particles (Figure 2a). Size distribution analysis using ImageJ[33] confirmed that the majority of the particles were between 3 nm and 6 nm in diameter with an average diameter of 5 ± a1 nm (see supporting information).

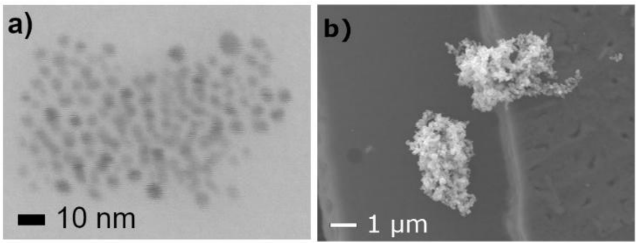

Figure 2. a) STEM image of Pd nanoparticles that were synthesized in polyvinylpyrrolidinone matrix; **b)** SEM image of nanoparticles formed in situ during the reaction of *N*-methylindole and an aryl iodonium salt in the presence of a $Pd(OAc)_2$ pre-catalyst.

These nanoparticles were used as a precatalyst in C–H arylation reactions. Time course data on the conversion of *N*-methylindole to 2-(4-(*tert*-butyl)phenyl)-1-methyl-1H-indole was recorded for reactions at two temperatures with and without continuous centrifugation during the reaction. The centrifuge was equipped with a refrigeration unit and a heating mechanism separate from the motor giving temperature control rated to be within 2 °C of the specified value and allowing elevated temperatures to be maintained even at low centrifuge speeds. This level of temperature control bypasses the previous suggestion that centrifugation could only give “post operandum information” about speciation in catalytic reactions.[6] With the goal of maximizing the time that each sample spent at the stated relative centrifugal force (RCF) while minimizing the time when the reaction could be proceeding at a lower RCF we opted to collect each time point from an independent reaction rather than taking aliquots from a single reaction mixture. To monitor the progress of the organic reaction, samples were quenched with a saturated solution of aqueous sodium bicarbonate immediately upon removal from the centrifuge. The product was quantified by GC-FID relative to a benzophenone internal standard.

We found that the action of the centrifuge resulted in less product formation, consistent with the removal of the nanoparticles that were the catalyst and/or precatalyst for the C–H arylation of *N*-methylindole. However, the magnitude of the difference between the centrifuged and uncentrifuged reactions varied with temperature. After one hour at 70 °C the yield of the C–H arylation in an uncentrifuged reaction was approximately 45 % while a reaction centrifuged at 39,000 g had a yield of approximately 40 % (as determined by integration of a GC-chromatogram relative to an internal standard, see supporting information). This result could be interpreted as indicating that the mass transfer of the nanoparticles into isolation is slow relative to the rate of the catalysis. For particles of known size, the velocity at which the particles are traveling during centrifugation has been approximated using classical sedimentation theory.[34] Assuming a particle radius of approximately 2.5 nm mass transit times for the particles with the furthest travel distance could take on the order of 30 minutes (see supporting information), however particles that start closer to the interface will be sequestered faster.

Alternatively, the activity observed during centrifugation could be indicative of a situation where the nanoparticles are a precatalyst that rapidly converts into small molecules that are the active form of the catalyst. When the experiment was repeated at 50 °C the uncentrifuged reaction had a yield of approximately 17% after one hour while the reaction centrifuged at 39000 g had a yield of approximately 4 % (Figure 3). Notably at longer reaction times the yield of the uncentrifuged reaction continued to increase while the yield of the centrifuged reaction remained 4 %. This result demonstrates that if the rate of catalysis or rate at which nanoparticles generate non-nanoparticle active species is slow it is possible for the centrifuge to significantly limit the progress of a reaction in which nanoparticles are catalytically relevant. The action of the centrifuge causes nanoparticles to aggregate in the grease layer. This aggregation can be detected visually and by computed tomography scans, see supporting information.

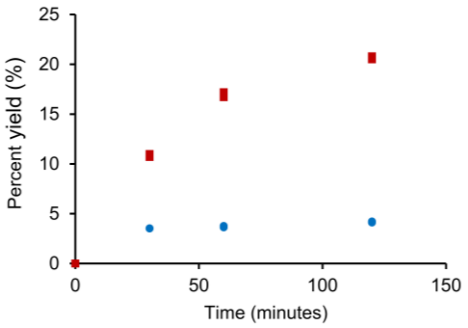

Figure 3. Time course for the formation of 2-(4-(*tert*-butyl)phenyl)-1-methyl-1H-indole from *N*-methylindole at 50 °C in the presence of high vacuum grease, with Pd nanoparticles in polyvinylpyrrolidone matrix as the pre-catalyst. Blue circles (•) indicate a reaction with the centrifuge on (RCF = 39677 g) and red squares (▪) represent a reaction at RCF = 1 g.

With proof of concept that a centrifuge could impact the trajectory of a C–H arylation reaction we turned our attention to reactions with molecular precatalysts. Initial reactions were done in the absence of MOLYKOTE® high vacuum grease and centrifugation. During the reactions in which $Pd(OAc)_2$ or $IMesPd(OAc)_2$ was used as the precatalyst the reaction mixture became noticeably darker. When the reactions were complete a dark solid could be sedimented from the reaction mixture by centrifugation. The precipitate was washed with ethanol, suspended in ethanol by sonication, and deposited on a 400 mesh copper/carbon grid. SEM analysis revealed aggregated nanoparticles (Figure 2b). The size distribution determined by DLS in situ in the absence of centrifugation or purification (vide infra) suggests that the observed aggregation is not fully attributable to the isolation and purification procedure. EDS analysis confirmed that the nanoparticles contained palladium as the major component by weight (see supporting information).

Monitoring reactions with $Pd(OAc)_2$ or $IMesPd(OAc)_2$ precatalysts by DLS[35,36] showed the nanoparticle aggregates forming and increasing in size at early reaction times (Figure 4). As expected for a ligated species, the formation of nanoparticles from the ligated $IMesPd(OAc)_2$ (Figure 5) precatalyst required a higher temperature. While there is likely systematic error in the absolute magnitudes of the particle sizes owing to the non-standard solvent mixture, the DLS data indicate that particles are forming at early reaction times then growing and aggregating.

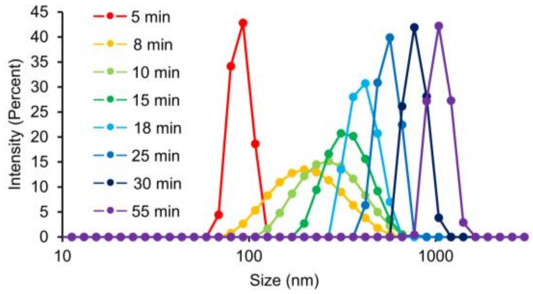

Figure 4. DLS data recorded during the reaction of *N*-methylindole and an aryl iodonium salt in the presence of a $Pd(OAc)_2$ pre-catalyst at 30 °C.

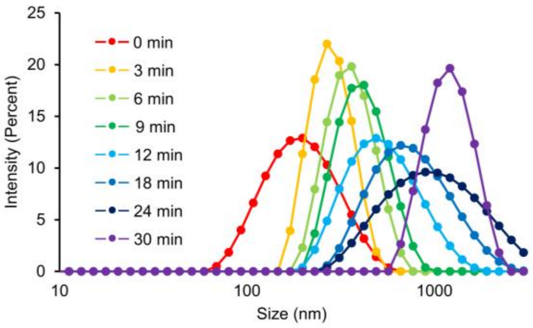

Figure 5. DLS data recorded during the reaction of *N*-methylindole and an aryl iodonium salt in the presence of a $IMesPd(OAc)_2$ pre-catalyst at 60 °C.

The question then is whether these particles are catalytically relevant to the C–H arylation as an active catalyst or as a reservoir in equilibrium with active species, or whether they are simply an inactive decomposition product. If the latter is correct, then continuously removing these particles by centrifugation should have no impact on the trajectory of the catalytic reaction.

Reaction time course studies for C-H arylation using both $Pd(OAc)_2$ (Figure 6) and $IMesPd(OAc)_2$ (Figure 7) precatalysts were conducted in the presence of MOLYKOTE® high vacuum grease. In both cases the reactions were inhibited by the action of the centrifuge, most notably at later reaction times. The inhibition was more pronounced in the reaction with the unligated $Pd(OAc)_2$ precatalyst. The observed inhibition indicates that in both reactions the nanoparticles are more than a decomposition product. The nanoparticles are either themselves an active catalyst or are in equilibrium with an active form of the catalyst. The modest inhibition compared with the control experiment using pre-formed nanoparticles (vide supra) could be explained by reaction rates that are fast relative to the mass transfer of the centrifuge, especially at early reaction times, or could be consistent with a system in which both molecular species and nanoparticles are contributing to the observed catalysis at meaningful rates. For these reactions in which the nanoparticles are forming and aggregating in situ the varied and non-static particle sizing precludes estimation of the mass transfer time.

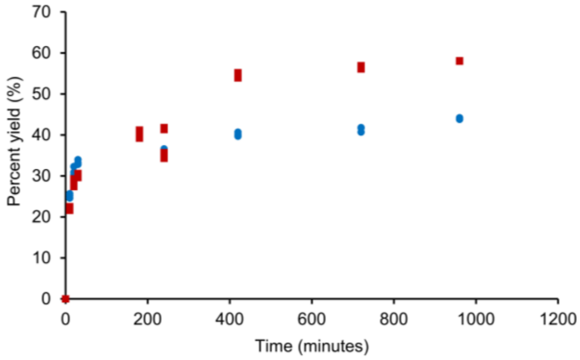

Figure 6. Time course for the formation of 2-(4-(*tert*-butyl)phenyl)-1-methyl-1H-indole from *N*-methylindole at 30 °C in the presence of high vacuum grease with $Pd(OAc)_2$ as the pre-catalyst. Blue circles (•) indicate a reaction with the centrifuge on (RCF = 39677 g) and red squares (▪) represent a reaction at RCF = 1 g.

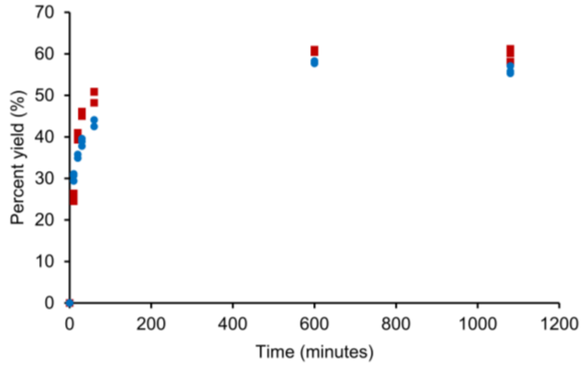

Figure 7. Time course for the formation of 2-(4-(*tert*-butyl)phenyl)-1-methyl-1H-indole from *N*-methylindole at 60 °C in the presence of high vacuum grease with $IMesPd(OAc)_2$ as the pre-catalyst. Blue circles (•) indicate a reaction with the centrifuge on (RCF = 39677 g) and red squares (▪) represent a reaction at RCF = 1 g.

If the modest inhibition were entirely due to mass transfer however it would be surprising for the reaction with $Pd(OAc)_2$ precatalyst at 30 °C to have a different level of inhibition from the reaction of $IMesPd(OAc)_2$ precatalyst at 60 °C given that the reaction time scales are similar, the DLS results suggest that the sizes of any aggregates that form are comparable, and the rates of mass transport in the same solvent could be expected to be on the same order of magnitude. The differing levels of inhibition in the different reactions are thus most consistent with differing relative contributions among various catalyst forms in the ligated and unligated systems. In the ligated system the majority of the observed catalysis is best explained by molecular species or small clusters, either because of their greater rate constants or greater abundance. In contrast, in the unligated system with the $Pd(OAc)_2$ precatalyst the nanoparticles are contributing more substantially to the observed catalysis as an active species or a reservoir for the active species.

Next we sought to compare the centrifugation test with a conventional filtration test.[11] For these tests we opted for $Pd(OAc)_2$ as the precatalyst. In our initial filtration test the reaction was filtered after 120 minutes (Figure 8). In the filtered sample a 40 % yield was obtained compared with 53 % in the unfiltered sample. This difference in yield is comparable to the difference caused by continuous centrifugation at 39677 g (Figure 6). We selected the filtration time of 120 minutes with full reaction time course data in hand. Recognizing that filtration tests are sometimes performed without the benefit of full reaction time course data we repeated the hot filtration test two more times, once with filtration after 15 minutes (Figure 9) and once with filtration after 360 minutes (Figure 10). In these cases, the effect of the filtration was noticeably less, demonstrating that an ill-timed filtration could lead to an underreporting of the catalytic significance of the filtered nanoparticles.

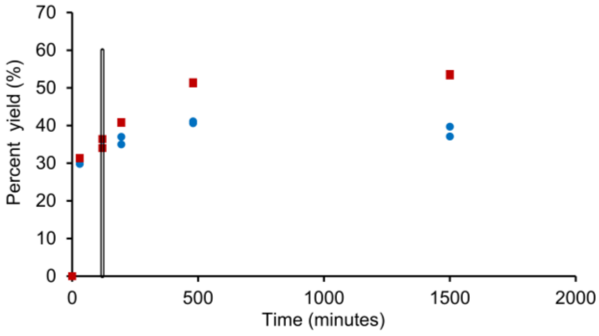

Figure 8. Time course for the formation of 2-(4-(*tert*-butyl)phenyl)-1-methyl-1H-indole from *N*-methylindole at 30 °C in the presence of high vacuum grease with $Pd(OAc)_2$ as the pre-catalyst. Blue circles (•) indicate a reaction that was filtered through a plug of diatomaceous earth after 120 minutes and red squares (▪) represent an unfiltered reaction.

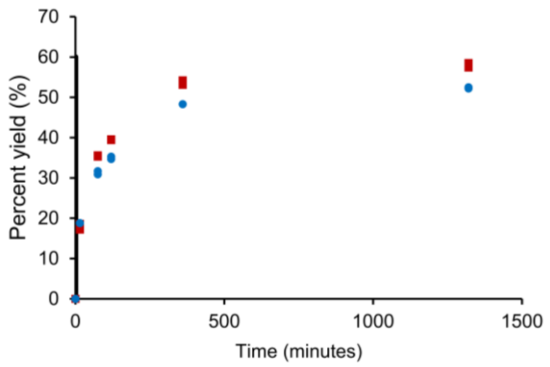

Figure 9. Time course for the formation of 2-(4-(*tert*-butyl)phenyl)-1-methyl-1H-indole from *N*-methylindole at 30 °C in the presence of high vacuum grease with Pd(OAc)$_2$ as the pre-catalyst. Blue circles (•) indicate a reaction that was filtered through a plug of diatomaceous earth after 15 minutes and red squares (▪) represent an unfiltered reaction.

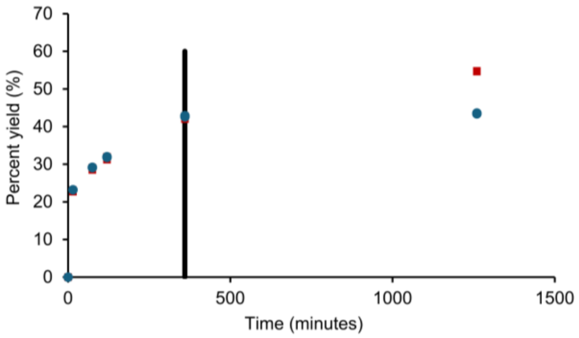

Figure 10. Time course for the formation of 2-(4-(*tert*-butyl)phenyl)-1-methyl-1H-indole from *N*-methylindole at 30 °C in the presence of high vacuum grease with Pd(OAc)$_2$ as the pre-catalyst. Blue circles (•) indicate a reaction that was filtered through a plug of diatomaceous earth after 360 minutes and red squares (▪) represent an unfiltered reaction.

Conclusions

We have demonstrated that continuous centrifugation can impact the trajectory of a catalytic reaction in which nanoparticles are catalytically relevant either as an active catalyst or in equilibrium with an active form of the catalyst. The impact of the centrifugation is most pronounced in a reaction using preformed nanoparticles as a precatalyst and least pronounced in a reaction using a ligated organometallic precatalyst consistent with the magnitude of the impact being proportional to the catalytic contribution of the atoms whose resting state is in a nanoparticle. In the context of C–H arylation this implies that as with cross coupling,[5] the formed nanoparticles are catalytically relevant and are not simply a decomposition product while suggesting that the level of contribution of the nanoparticles is dependent on the precatalyst.

We anticipate that this method could be applied in a range of catalytic contexts provided that the reaction components are soluble in the medium, the nanoparticles that form are able to penetrate the inert layer, and that the rate of mass transport under centrifugation is sufficiently fast relative to the rate of reaction. The latter criterion could be problematic with very small nanoparticles, viscous reaction media, and fast reactions.

While the impact of continuous centrifugation was found to be comparable to a well-timed filtration test for the system we studied, a filtration that is performed too early, or too late can underestimate the catalytic significance of the material that was removed in the filtration. Predicting optimal timing for a filtration in advance is challenging. Reactions with an evolving catalyst will have a complex kinetic profile potentially with different species predominating at different times. Thus, when filtration is used as a strategy to screen for catalytically relevant nanoparticles, reporting multiple filtration experiments at different time points would be appropriate.

In addition to disambiguating the role of nanoparticles that form in situ as we demonstrated here, continuous centrifugation of a reaction mixture could have synthetic utility by impacting selectivity in reactions where nanoparticles and molecular species favor the formation of different products.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the Supplementary Information.

Acknowledgements

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