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Chemical Synthesis of Complex Molecules Using Nanoparticle Catalysis

Huan Cong and John A. Porco Jr.*

Department of Chemistry and Center for Chemical Methodology and Library Development (CMLD-BU), Boston University, Boston, Massachusetts 02215, United States

Abstract

Nanoparticle catalysis has emerged as an active topic in organic synthesis. Of particular interest is the development of enabling methodologies to efficiently assemble complex molecules using nanoparticle catalysis. This Viewpoint highlights recent developments and discusses future perspectives in this emerging field.

Keywords

nanoparticles; catalysis; organic synthesis; heterogeneity; catalyst recycling

1. INTRODUCTION

The emerging field of nanoparticle catalysis represents a burgeoning area with increasing use in chemical synthesis,^{1–4} as a recent SciFinder search shows exponential growth of literature reports during the past decade (Figure 1).⁵ This rapidly expanding research subject has been built upon fruitful multidisciplinary collaborations between scientists in nanosciences and organic chemistry as well as the remarkable catalytic activities and selectivities of nanometric materials. Such features closely relate to the intrinsic size and shape-dependent properties^{6,7} of nanoparticles which may be subtly tuned by selection and modifications of preparation conditions, support materials, and capping agents. In addition, although widely utilized homogeneous catalysts remain as synthetic chemists' most powerful resources, heterogeneous, nanoparticle catalysis features the possibility for catalyst recycling, continuous processing, and ease of separation,⁸ thereby offering green and cost-effective alternatives. Despite the aforementioned promising attributes, nanoparticle catalysts have not yet found broad applications in complex molecule synthesis,^{9,10} with most applications thus far limited to cross-couplings¹¹ and oxidations/reductions.¹² In this Viewpoint article, we outline select examples employing nanoparticle catalysts to create new chemical bonds, with a special emphasis on applications and opportunities in complex molecule synthesis.

2. REPRESENTATIVE APPLICATIONS OF NANOPARTICLE CATALYSIS IN ORGANIC SYNTHESIS

2.1. Development of Tandem Reactions Based on Nanoparticle-Catalyzed Transformations

A number of notable studies have established nanoparticle-catalyzed cascade reactions, demonstrating an efficient approach to rapidly synthesize complex molecules from simple

*Corresponding Author: porco@bu.edu.

starting materials. The development of such tandem processes has also considerably broadened the utility and versatility of nanoparticle catalysis. For example, oxidations of alcohols to carbonyl compounds catalyzed by metal nanoparticles have been extensively investigated in the literature,¹² and have been frequently employed in tandem reaction processes. Shimizu and co-workers (Scheme 1)¹³ developed redox couplings of primary and secondary alcohols **1** and **2** catalyzed by alumina-supported silver nanoparticles (AgNP's) in combination with a mild base (cesium carbonate) to afford ketones **3**. The AgNP catalyst served dual roles in this highly creative tandem process which entailed AgNP-catalyzed dehydrogenation of alcohols^{14,15} **1** and **2** in the absence of molecular oxygen, base-mediated Claisen-Schmidt condensation of the derived carbonyl compounds **4** and **5**, and AgNP-mediated hydrogenation of the resulting α,β -unsaturated ketones **6**. Alcohols bearing α -aryl or heteroaryl groups generally afforded better yields than alkyl-substituted substrates, likely due to the inherent limitations of Claisen-Schmidt condensation. In addition, the supported AgNP catalyst displayed a high turnover number (TON) of up to 800 and remained active after two recycles.

Kobayashi and co-workers (Scheme 2)¹⁶ demonstrated a tandem aerobic oxidation-Michael addition process involving oxidation of allylic alcohol **8** followed by 1,4-addition of 1,3-dicarbonyl derivative **7** to Michael acceptor **9**. This multicatalytic reaction¹⁷ was built upon authors' earlier studies on polymer incarcerated gold nanoparticles (AuNP's)¹⁸ and a polymer/carbon black-incarcerated boron catalyst which promotes alcohol oxidation and Michael addition, respectively. The latter catalyst was prepared from NaBH₄ and PEGylated polystyrene to afford immobilized boron species which were characterized as tetravalent borates. The addition of porous carbon black as a support material optimized the catalyst preparation by reducing polymer cross-linking. Accordingly, a hybrid, heterogeneous catalyst containing polymer-incarcerated, bimetallic Au/Pd nanoclusters and boron was created and showed excellent dual catalytic activities after six recycles. The new catalyst also exhibited a broad substrate scope including cyclic, aliphatic, and aromatic-substituted starting materials. Since the heterogeneous support materials may minimize possible interactions and side reactions between multiple catalysts, the development of hybrid, supported catalysts containing orthogonal components should find broad applications in the synthesis of complex molecules.

2.2. Conversion of Homogeneous to Heterogeneous Reactions Employing Nanoparticle Catalysis

Another productive strategy for development of nanoparticle catalysis has taken advantage of the homogeneous transition metal catalysis. Reactions known to be catalyzed by transition metal complexes may also be facilitated by metal nanoparticles containing the same metal. This hypothesis has been proven true in many cases as highlighted in Scheme 3 with direct comparisons of nanoparticles and transition metal catalysts made for each reaction. In addition, heterogeneous nanoparticle catalysts have exhibited the capability of offering superior catalytic activities through artful design and modifications. It should be noted, nonetheless, that minimizing the possibility of nanoparticle leaching has become increasingly crucial in order to establish truly heterogeneous catalysis.¹⁹

In situ-generated nanoparticles in solution have shown remarkable catalytic properties in complex molecule synthesis. For example, the Wolff rearrangement has been conventionally initiated by thermal energy, UV light, and transition metal catalysis including silver(I) salts.²⁰ Sudrik and co-workers (Scheme 3a)^{21–23} found that AgNP's also served as an effective catalyst for rearrangement of diazo compounds **11** to form ketene intermediates **12** which further reacted with water to afford carboxylic acids **13**. The catalytically active AgNP's were generated *in situ* by chemical (e.g. triethylamine) or electrochemical reduction of silver(I) precursors. Another example by Han and co-workers (Scheme 3b)²⁴ showed that

in situ-generated AuNP's and homogeneous AuCl₃^{25–27} both catalyzed tandem alkyne activation/benzopyrylium formation/[3+2] dipolar cycloaddition of **14** to construct natural product-like polycycle **15** in a single step. In both studies, nanoparticles were unambiguously characterized by a number of instrumental analyses including UV-vis spectroscopy, powder X-ray diffraction (XRD), and transmission electron microscopy (TEM). However, using *in situ*-generated nanoparticles as catalysts has complicated accurate evaluations of the reactions' heterogeneity and nanoparticles' activity in terms of catalyst loading and TON. In light of the notable reaction complexity achieved in their studies, future investigations are warranted on related reactions employing supported nanoparticle catalysts.

In 2001, Chung and co-workers (Scheme 3c),²⁸ reported Pauson-Khand reactions catalyzed by cobalt nanoparticles (CoNP's). Building upon earlier studies using mesoporous silica and charcoal-supported cobalt catalysts,^{29,30} the CoNP catalyst exhibited improved activity for the intramolecular Pauson-Khand reaction of enyne **16** under a pressurized CO atmosphere. In addition, four catalyst recycles were conducted without particle agglomeration or loss of activity. Extending the CoNP catalyst to intermolecular reactions between norbornadiene and terminal alkynes afforded near quantitative yields..

Toste, Somorjai, and co-workers (Scheme 3d, e)³¹ recently reported the design and synthesis of electrophilic platinum nanoparticles (PtNP's) which were capped with either polyamidoamine dendrimers or polyvinylpyrrolidone (PVP), and further deposited onto mesoporous silica. The supported PtNP's initially showed no catalytic activity until the authors creatively devised an oxidative treatment of the nanoparticles employing a hypervalent iodine-based oxidant (PhICl₂). This mild oxidant selectively oxidized more than 25% of the Pt(0) atoms in the supported nanoparticles to higher oxidation states as confirmed by X-ray photoelectron spectroscopy (XPS), thereby converting the PtNP's into highly active electrophilic catalysts. This novel heterogeneous catalyst enabled a range of cyclization reactions including the hydroarylation of alkyne **18**³² and hydroamination of allene **20** *via* π -bond activation. In addition, the heterogeneity of the oxidized PtNP catalyst was unambiguously established by the "filtrate transfer" test.³³ This work is of particular impact due to the crafty post-synthetic modifications that induced the desired properties onto otherwise inactive nanoparticle catalysts.³⁴

Inspired by an AuCl₃-catalyzed intermolecular benzannulation between *o*-alkynylbenzaldehydes and alkynes,³⁵ Garcia, Corma, and co-workers (Scheme 3f)³⁶ developed a reusable cerium oxide-supported AuNP catalyst which is now commercially available. The catalyst efficiently facilitated the formation of naphthalene **24** from precursors **22** and **23** in near quantitative yield³⁷ and was validated to be heterogeneous by both the "filtrate transfer" test³³ and elemental analysis of the reaction solution. A series of in-depth control experiments led to interesting observations that product **24** was obtained in 94% yield using the optimal catalyst containing 4.5 weight percent (wt%) of AuNP's supported on CeO₂, in comparison to only 67% yield with 1.8 wt% AuNP/CeO₂ (both reactions were conducted under the otherwise same conditions with 5 mol% catalyst loading based on the amount of AuNP's). The same trends were also observed employing other support materials. The authors reasoned that most support materials can also function as adsorbents of organic molecules. Therefore a higher amount of support materials were added to reactions when using catalysts with lower AuNP content which caused decreased yields.

2.3. Exploration of Novel Activities of Nanoparticle Catalysts

In contrast to the homogeneous catalysis which has been extensively applied to a wide range of reaction types,³⁸ the identification of new catalytic activities of nanoparticles is highly underdeveloped. A brief survey of known nanoparticle-catalyzed transformations¹ has

revealed that most of these reactions involve redox processes, which is echoed by the distinctive electrochemical properties of nanoparticles including size and shape-dependent redox potentials⁶ and multiple available oxidation states.^{39,40} Based on these promising characteristics, nanoparticle catalysis should offer broad opportunities for mining new chemical transformations, in particular, those which enable the synthesis of otherwise challenging complex molecules.

Chattopadhyay and co-workers (Scheme 4)⁴¹ reported oxidative couplings of phenols catalyzed by chitosan-supported AgNP's. In the presence of molecular iodine as an oxidant, unsubstituted phenol (**25**) underwent an iodine-incorporated, oxidative C-C coupling to afford biphenyl **26** in 75% yield. The products of the AgNP-catalyzed oxidative couplings were highly regioselective and substrate dependent, with α -(**27**) and β -(**29**) naphthols affording exclusive 2,2'-(**28**) and 3,3'-(**30**) *bi*-naphthols, respectively, under the same conditions. The formation of *bi*-naphthol **30** differed in the regioselectivity for oxidative coupling of **29** using homogeneous catalysis.^{42–46} These intriguing observations implied subtle mechanistic variations related to specific phenol starting materials, which warranted further investigation. Besides the above notable features, the novel AgNP-catalyzed reactions showcased low catalyst loading and mild reaction conditions.

Aromatic azo compounds have broad industrial applications including drugs, dyes, and food additives.⁴⁷ Corma, Garcia, and co-workers (Scheme 5)⁴⁸ developed a catalytic, oxidative synthesis of azobenzenes directly from anilines which represented a major improvement in comparison to traditional synthetic methods.^{49–51} Employing the commercially available titanium dioxide-supported AuNP's as catalyst and molecular oxygen as terminal oxidant, a number of symmetrically substituted azobenzenes were prepared in greater than 90% yield regardless of the electron donating or withdrawing substitutions of the starting materials. Notably, the reaction between equimolar electron-rich (**31**) and electron-poor (**32**) anilines afforded unsymmetrical product **33** (methyl orange) in 91% yield in a single step.

The proposed reaction mechanism entailed AuNP-mediated single electron transfer (SET) of aniline **34** to generate radical cation **35**, followed by formation of intermediate **36** through the coupling between **35** and aniline **34**. Key supporting evidence included electron paramagnetic resonance (EPR) data for radical trapping of **35**.⁵² Subsequent AuNP-mediated, stepwise oxidative electron transfer processes afforded hydrazine **37** and finally the desired azobenzene **38**.

Porco and co-workers (Scheme 6)⁵³ recently demonstrated the utility of silica-supported AgNP's as an active catalyst for Diels-Alder cycloadditions of 2'-hydroxychalcones, a biomimetic and straightforward access to the core structure shared by over fifty biologically active natural products.⁵⁴ In this study, the authors accomplished the total synthesis of panduratin A (**42**), establishing the first example of a natural product synthesis employing nanoparticle catalysis. The key AgNP-catalyzed cycloaddition step was carried out using 0.5 mol% catalyst loading with chalcone **39** and the acid-labile trans- β -ocimene (**40**) in 85% yield and 19:1 d.r., thereby showcasing the catalytic activity and selectivity that has not been achieved by other methodologies.⁵⁵ Final acetate deprotection of cycloadduct **41** afforded the natural product **42** in 87% yield.

In addition, a series of mechanistic studies were conducted including EPR measurements of radical trapping (confirming SET processes between AgNP's and 2'-hydroxychalcones) and deuterium-labeling experiments between chalcone **43** and deuterium-labeled diene **44** (Scheme 7a) supporting a concerted cycloaddition mechanism. These results suggested a working mechanism (Scheme 7b) starting with proton removal and SET from the adsorbed chalcone **46** to AgNP's. The resulting AgNP-stabilized phenoxyl radical **47a** and its

resonance form **47b** may further undergo concerted cycloaddition with diene **48** to generate intermediate **49**, which afforded cycloadduct **51** *via* back electron transfer, protonation, and product desorption.

Stratakis and co-workers (Scheme 8)⁵⁶ have reported a AuNP-catalyzed dehydrogenative, formal [3+2] cycloaddition between tetramethyldisiloxane **52** and acetylene **53** which was conducted at room temperature with 0.3 mol% catalyst loading leading to the production of dihydrooxadisole **54** in 95% isolated yield. The substrate scope of the methodology was established employing a range of functionalized aromatic, aliphatic, and internal alkynes. Generally, most reactions were completed within an hour regardless of the electron donating or withdrawing substitutions of the alkynes. In comparison, starting materials **52** and **53** underwent alkyne hydrosilylation catalyzed by homogeneous *t*-Bu₃P-modified Pt(0) catalyst,⁵⁷ thereby highlighting the unique catalytic activity of the AuNP's.

3. SUMMARY AND FUTURE OUTLOOK

In this Viewpoint article, we have briefly summarized the utility of nanoparticle catalysis in organic synthesis through a critical overview based on recent literature examples. With increasing research endeavors being devoted to this field, new methodology development based on nanoparticle catalysis is emerging as a valuable addition to chemists' existing tools for complex molecule synthesis.

As outlined in this article, an evaluation of the possibility of catalyst leaching is crucial for the investigation of supported nanoparticle catalysts. Current studies mainly employ the "filtrate transfer" test³³ and/or elemental analysis of the reaction solution to determine catalyst leaching. In addition to these indirect methods, real-time monitoring of catalyst surface using *in situ* X-ray absorption spectroscopy (XAS) techniques provides unambiguous proof of catalyst heterogeneity.^{58–60} Although there is no strict rule for the nanoparticle-catalyzed reactions, the absence of evidence against catalyst leaching may lead to questioning of reaction heterogeneity as well as the identity of actual catalytic species.

Future development of nanoparticle catalysis may also significantly benefit from further understanding of reaction mechanisms which will ultimately require interdisciplinary collaborations, for example, between organic chemists and material scientists. Such mechanistic studies may include experiments on reaction kinetics, theoretical modeling, catalyst surface characterization, and validation of reaction intermediates.

In the future, we anticipate further discovery of new nanoparticle catalysts, including bimetallic and hybrid systems,^{61,62} and their applications in complex molecule synthesis in an effort to identify novel chemical reactions and tandem reaction sequences. Such opportunities should offer a strong stimulus to the continuing efforts in this vigorously advancing area.

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Figure 1.
Publications on nanoparticle catalysis from 1994 to 2010.

Scheme 1.
AgNP-Catalyzed Coupling of Alcohols

Scheme 2.
Sequential Oxidation/Michael Additions of Allylic Alcohols

Scheme 3.
Select Examples of Nanoparticle Catalysis from the Recent Literature

Scheme 4.
AgNP-Catalyzed Oxidative Coupling of Phenols

Scheme 5.
AuNP-Catalyzed Synthesis of Aromatic Azo Compounds

Scheme 6.

AgNP-Catalyzed Diels-Alder Cycloaddition of 2'-Hydroxychalcones

(b) Proposed mechanism

Scheme 7.
Mechanistic Evidence and Proposed Mechanism for AgNP-Catalyzed Diels-Alder Cycloadditions

Scheme 8.

AuNP-Catalyzed Synthesis of Dihydrooxadisiloles *via* Oxidative, Formal [3+2] Cycloadditions.