Латвийский институт органического синтеза

Химия гетероциклических соединений **2018**, *54*(3), 241–248

Химия гетероциклических соединений

Gold and silver nanoparticle-catalyzed synthesis of heterocyclic compounds

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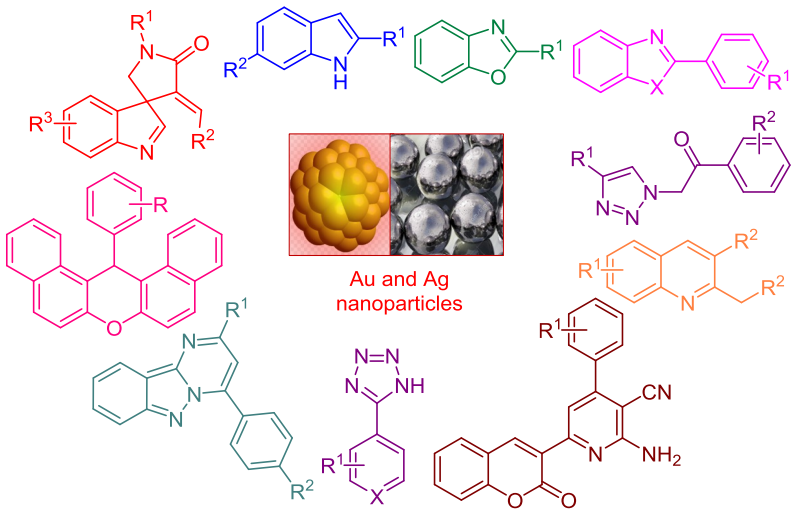
Submitted March 1, 2018
Accepted March 28, 2018



In recent years, metallic nanoparticles have been a constant subject of attention for researchers. The transition of metal from microparticles to nanoparticles leads to a substantial change in its physical and chemical properties. Nanoparticles as catalyst in organic reactions provide additional benefits such as catalyst recycling, scale-up of reactions using continuous flow processes, and easy purification of the reaction mixture offering green and cost-effective alternatives. This review highlights some of the significant gold and silver nanoparticle-catalyzed reactions for the synthesis of various heterocyclic compounds. A brief synthetic methodology for different heterocyclic compounds is discussed along with the scope of the reaction.

Keywords: heterocyclic compounds, indole, spiroindoline, triazole, nanoparticle.

Heterocyclic compounds are of great importance due to their biological properties. From an industrial point of view, the majority of the pharmaceuticals, bioactive agrochemicals, additives, and modifiers are heterocyclic in nature. The high prevalence of heterocycles as pharmaceuticals is because of their vast distribution in nature and their abundance as building block for biomacromolecules such as DNA or RNA. The designing of new therapeutic molecules is usually to mimic the natural ligands or substrates of receptors or enzymes with the aim to improve the potency of the ligand by enhancing its pharmacokinetic profile.[1] Therefore, researchers are in a continuous pursuit to find new and efficient synthetic transformations for heterocyclic compounds.

The field of nanocatalysis has undergone an explosive growth in recent years involving the application of nanomaterials as catalysts under various homogeneous and heterogeneous conditions.[2] The efficacy of nanomaterials is

very high compared to conventional catalysts due to their high activity, selectivity, excellent stability, low energy consumption, and long shelf life. Their extremely small size (typically 10–80 nm) and shape provides exceptionally large surface-to-volume ratio and leads to unique and immense changes in the physical and chemical properties of the material.[3]

Metal nanoparticles (MNPs) confer great potential in areas such as medicine and catalysis.[4] The large surface area of MNPs has a positive influence on the reaction rate and is the main explanation of their higher catalytic activity. MNP catalysis provides rapid and selective chemical transformations with excellent product yields combined with the ease of catalyst separation and recovery.[5] The first example of gold NPs use was reported in 1989 by Haruta et al. for the oxidation of carbon monoxide and hydrogen at low temperatures.[6]

Importantly, among metal-based NPs, gold and silver NPs as catalyst have attracted the attention of the scientific community owing to their exceptional reactivity, selectivity, stability, and recyclability in catalytic reactions.[4a,7] Over the past few years, there have been several books and reviews published on gold- and silver-catalyzed organic reactions.[8] Various comprehensive reviews on gold NP catalysis have been published covering the physical properties and characterization of gold NPs, the formation of the carbon–heteroatom bond, the preparation of supported gold catalysts as well as both homogeneous and heterogeneous catalysis.[8b–d,f,g,i]

Gold as a catalyst is of great importance in organic synthesis, as it promotes the construction of C–C and C–heteroatom bonds (C−O, C−N, and C−S) by nucleophilic attack on multiple reactive bonds.[9] Similarly, silver NPs have gained interest due to their catalytic properties for some important organic reactions such as multicomponent (A^3-coupling) reactions, Diels–Alder [4+2] cycloaddition reactions, etc.[10] In 2009, a review appeared on the green synthesis of silver NPs and their antimicrobial applications against gram-positive and gram-negative bacteria.[11]

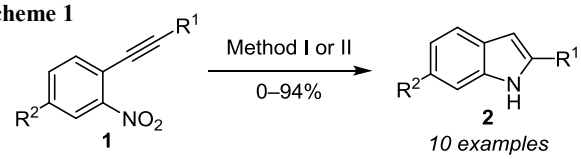
This small review summarizes some important reports of gold or silver NPs used as catalyst for the construction of heterocyclic compounds. We have covered the literature from last 3 years, although only prime reports are highlighted. The main aim of this review is to provide a platform to further explore gold and silver NPs for the synthesis of new heterocycles. For better understanding, the report is subdivided into two parts as given below: 1) gold NP-catalyzed synthesis of heterocycles, 2) silver NP-catalyzed synthesis of heterocycles.

Au NP-catalyzed synthesis of heterocycles

Au NPs have received immense interest due to their well-characterized electronic and physical features. The characteristic features of Au NPs are their small size (1–100 nm) and correspondingly large surface-to-volume ratio. Their physical and chemical properties can be altered as per the requirements of size, composition, and shape, high robustness, and unique target-binding properties.[4c,12] These features have made Au NPs one of the most widely used nanomaterials for catalysis, imaging, disease diagnostics, and gene expression. Features that made Au NPs as catalyst of choice include their ability to be active under mild conditions, even at ambient temperature or less, and to increase the selectivity of the reaction, as well as the fact that they are durable and resistant to poisoning.[13]

Indoles are important heterocycles with characteristic properties due to the presence of an electron-rich pyrrole ring that can interact noncovalently with other molecules by hydrogen bonding through the NH group and by π–π stacking. The indole ring is a constituent of proteins in the form of tryptophan residues and exhibits a range of pharmacological activities.[14] Tokunaga and coworkers have reported a one-pot reaction of (2-nitrophenyl)alkynes **1** to form indoles, catalyzed by Au NPs supported on Fe_2O_3 under hydrogenation conditions.[15] Two methods were reported for the synthesis of indoles. The first method involves one-step synthesis of indoles from (2-nitrophenyl)-alkynes **1** using Au NPs supported on Fe_2O_3 at 120°C in toluene (Scheme 1). The second method includes the one-pot two-step reaction, where the first step was performed at 60°C, 2.0 MPa H_2 for 1 h, followed by release of H_2 at atmospheric pressure (0.1 MPa). Then the second step involves the heating of the reaction mixture at 120°C for 1 h. It was observed that the second method affords slightly better yields. Under the optimized conditions, a wide variety of alkynes substituted with large steric groups such as *p*-Tol, *t*-Bu, and cyclohexenyl, underwent the reaction to give the corresponding indoles **2** in excellent yields. However, an electron-withdrawing group on the alkyne, such as a trifluoromethylphenyl, gave the corresponding indoles in moderate yields, whereas a TMS group was found incompatible in the reaction and led to complete loss of the product. Substituent on the benzene ring does not affect the yield of the desired product.

Scheme 1

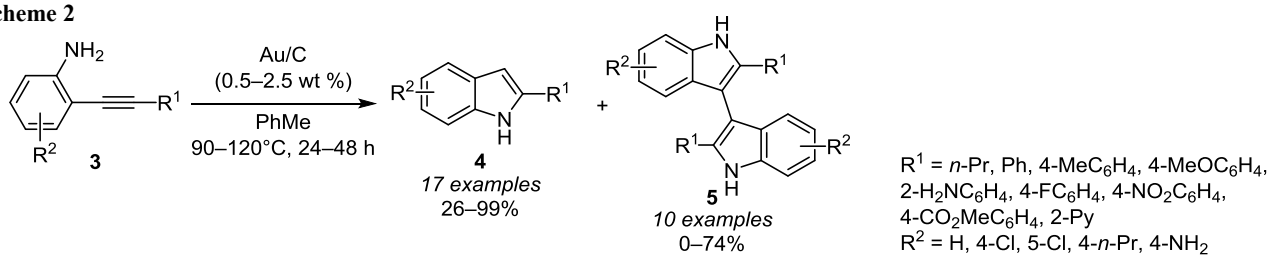


Method I: H_2 (2.0 MPa), Au/Fe_2O_3, 120°C, 1 h
Method II: H_2 (2.0 MPa), Au/Fe_2O_3, PhMe, 60°C, 1 h, then H_2 (0.1 MPa), Au/Fe_2O_3, PhMe, 120°C, 1 h

R^1 = Ph, *p*-Tol, 4-FC_6H_4, 4-$MeOC_6H_4$, 4-$CF_3C_6H_4$, *t*-Bu, Cy, cyclohexenyl, TMS; R^2 = H, Me

Lopez-Sanchez, Helaja, and coworkers have reported an efficient method for the synthesis of indoles **4** by heterogeneous cycloisomerization of 2-alkynylanilines **3** catalyzed by carbon-supported Au NPs at 90°C in toluene within 24 h (Scheme 2).[16] Under the optimized reaction conditions, substrates with various substituents on the alkyne and/or aryl ring underwent the cycloisomerization reaction in high to excellent yields. The presence of an electron-deficient substituent R^1 in the substrate led to a decrease in reactivity and catalytic performance, whereas an electron-rich *p*-methoxyphenyl group R^1 increased the

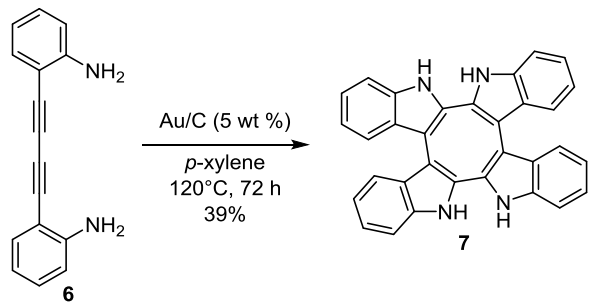
Scheme 2



reactivity. However, the use of an aliphatic alkyne resulted in a low product yields, and had detrimental effect on the catalytic activity. The presence of chlorine at the C-4 or C-5 atoms of the aniline (R^2) was found to be beneficial for the catalytic activity. Most of the substrates provided excellent yields of the desired product **4**, except 2-alkynyl-4-nitroanilines. Interestingly, the use of a high catalyst loading at low temperature (90°C) affords product of the homocoupling, e.g., 3,3'-bisindoles **5**, in good yields with the exception of 4-propyl- and 4-amino-2-alkynylaniline substrates.

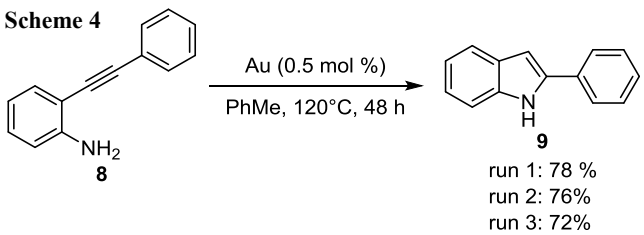
Further, the authors reported an unprecedented synthesis of cyclooctatetraene condensed with four indole rings **7** using 2,2'-(buta-1,3-diyne-1,4-diyl)dianiline **6** as a substrate. For the completion of this reaction, a higher catalytic loading (5 wt %) along with high temperature were required in comparison with the above-mentioned cycloisomerization of 2-alkynylanilines **3** (Scheme 3).

Scheme 3



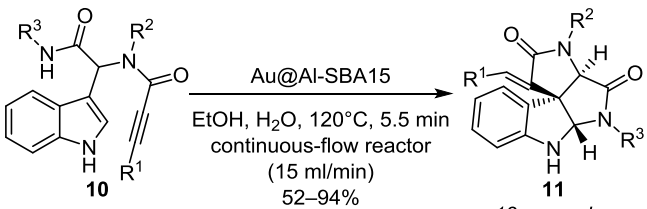
Savva and coworkers have prepared Au NPs-containing polyvinylpyrrolidone-crosslinked electrospun fibers and investigated their catalytic efficiency in the intramolecular cyclization of 2-(phenylethynyl)aniline **8** to give access to 2-phenyl-1*H*-indole **9** (Scheme 4).[17] It has been observed that the catalytic performance of the Au NPs-containing fibers is directly influenced by the size of the Au NPs, where small-sized Au NPs gave the best results. The catalytic efficiency was found to decrease after three consecutive reaction cycles. This may be attributed to the morphological changes in the fibers merging.

Scheme 4



Spiroindolines have attracted immense interest due to their presence in various natural products and drug-like molecules. Van der Eycken and coworkers have reported an expeditious synthesis of spiroindolines **11** catalyzed by supported Au NPs *via* cycloisomerizations and C–C bond formations under microflow conditions.[18] The heterogeneous gold catalyst Au@Al-SBA15 was prepared *via* a ball-milling process. The sterically hindered Ugi-adducts **10** were cyclized to spiroindolines **11** in a stainless steel packed-bed microreactor filled with Au@Al-SBA15 at 120°C in a mixture of EtOH and water as solvent, using hexafluoroisopropyl alcohol (HFIP) as proton shuttle (Scheme 5). Under the optimized conditions, substrates **10** bearing aliphatic and aromatic substituents afforded the corresponding spiroindolines **11** in good to excellent yields. *p*-Methoxybenzyl and various aliphatic moieties as the R^2 substituents were well tolerated. The presence of a *t*-Bu or a Cy group as the R^3 substituents gives good product yields. Also, the effect of water on the selectivity of the reaction was investigated, indicating that the presence of water expediates the protodecoordination of the Au NPs and thus, stimulates the formation of spiroindoline by improving the catalytic process. Furthermore, deactivation of the catalyst occurs only after an extended use, and leaching was not detected from the Au@Al-SBA15 catalytic bed.

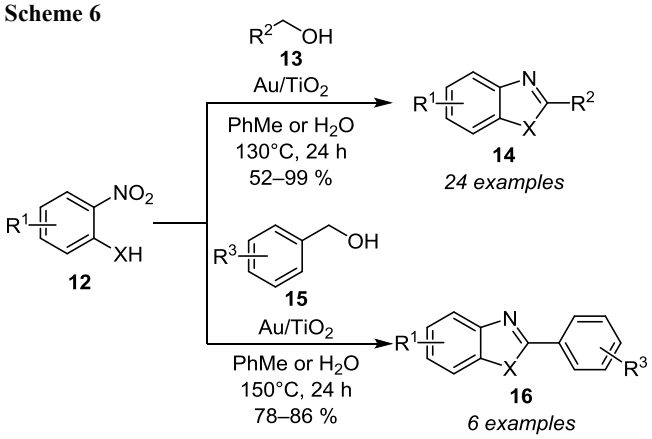
Scheme 5



The benzoxazole and benzimidazole cores are common structural units in many marketed pharmaceuticals and drug candidates.[19] Wang and coworkers have described a highly efficient synthesis of 2-substituted benzoxazoles **14** and benzimidazoles **16** using Au NPs supported on titanium dioxide (Au/TiO_2) in toluene or water.[20] 2-Arylbenzoxazoles **14** were selectively synthesized using Au/TiO_2 as a catalyst in a reaction of 2-nitrophenols **12** with alcohols **13** (Scheme 6). Under the optimized reaction conditions, substituted benzylic alcohols (electron-donating

or electron-withdrawing groups) furnished the desired products in excellent yields. However, the steric hindrance of the substituents at *ortho* position of the benzene ring hampers the reaction. Replacement of the benzene ring with that of naphthalene provided access to the desired product in excellent yield. The presence of either electron-donating or electron-withdrawing groups on the phenyl ring of nitrophenol **12** was well tolerated. Under similar reaction conditions, using toluene or water as a solvent, *o*-nitroanilines **12** and benzyl alcohols **15** were converted to 2-arylbenzimidazoles **16** in high to excellent yields. Interestingly, the use of *N*-methyl-*o*-nitroaniline as substrate led to an improved product yield. The catalytic activity of Au/TiO_2 catalyst was decreased after six catalytic cycles.

Scheme 6



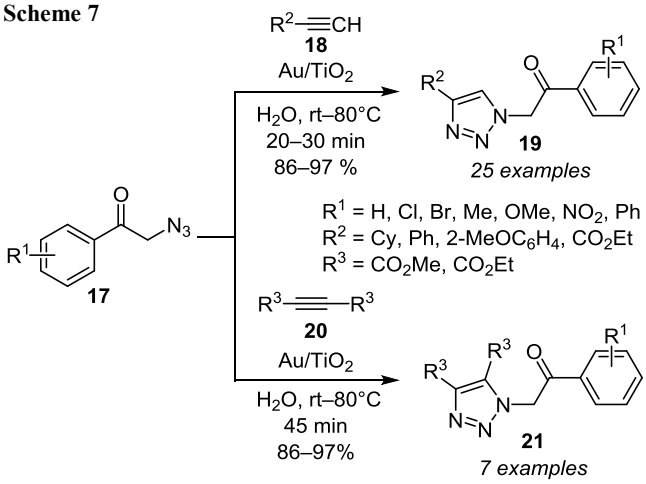
14 X = O; R^1 = H, 4-Me, 5-Me, 4-OMe, 5-F, 4-F, 4-Cl; R^2 = Me, *t*-Bu, *n*-Pent, Cy, Ph, 4-MeC_6H_4, 3-MeC_6H_4, 2-MeC_6H_4, 4-FC_6H_4, 3-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-$CF_3C_6H_4$, 1-Naphth

16 X = NH, NMe; R^1 = H; R^3 = H, 4-Me, 4-OMe, 4-F, 4-Cl

1,2,3-Triazoles are valuable heterocyclic motifs that have a widespread occurrence in different compounds characterized by several pharmacological applications.[21] Muthusubramanian and coworkers have employed nanoporous titania-supported Au NPs for the green synthesis of 1,2,3-triazoles **19** in aqueous medium.[22] The Huisgen [3+2] cycloaddition was achieved by reaction of substituted phenacyl azides **17** with alkynes **18** in the presence of Au/TiO_2 in water alone or in a *t*-BuOH/water mixture providing an excellent yield of 1,4-disubstituted 1,2,3-triazoles **19** as a single regioisomer (Scheme 7). Under the optimized reaction conditions, various aliphatic and (un)substituted aromatic 1-alkynes underwent the regioselective reaction with different azides affording products **19** in excellent yields. The use of symmetrical internal alkynes **20** in this reaction was also evaluated. It was found that in contrast to the noncatalytic reaction, the presence of the Au/TiO_2 catalyst provided excellent yields of products **21** in a short time. This increase in the product yield can be attributed to the alkynophilic nature of the gold that activates the internal alkyne leading to an enhancement in the reaction rate.

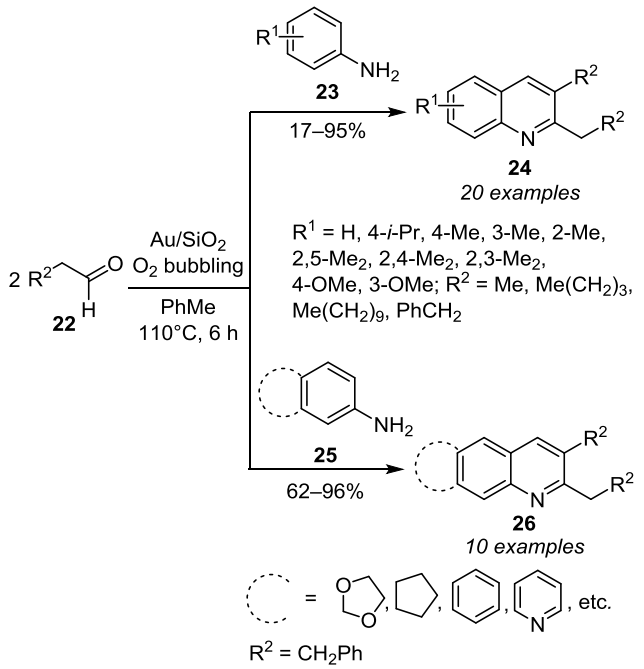
Quinolines have attracted much attention due to the broad range of their pharmacological properties.[23] Che and

Scheme 7



coworkers have developed a new one-pot protocol to access nitrogen-containing heterocycles **24** and **26** *via* silica-supported Au NPs catalytic system by reacting anilines **23** or polycyclic aniline **25** with aldehydes **22** using oxygen as an oxidant in toluene at 110°C (Scheme 8).[24] Under the optimized reaction conditions, a variety of electron-donating substituents on aniline **23** provided good to excellent product yields. However, electron-deficient substituents have a detrimental effect on the product yield. Hydrocinnamaldehyde and high-boiling aldehydes were found to be good substrates and provided good to excellent product yields. For the synthesis of polycyclic anilines, bulky anilines were found suitable under this reaction conditions and provided the desired product in good yields. An additional advantage of this method is the easy recovery of the silica-supported gold catalyst, which can be reused for seven consecutive runs without significant loss of catalytic activity.

Scheme 8

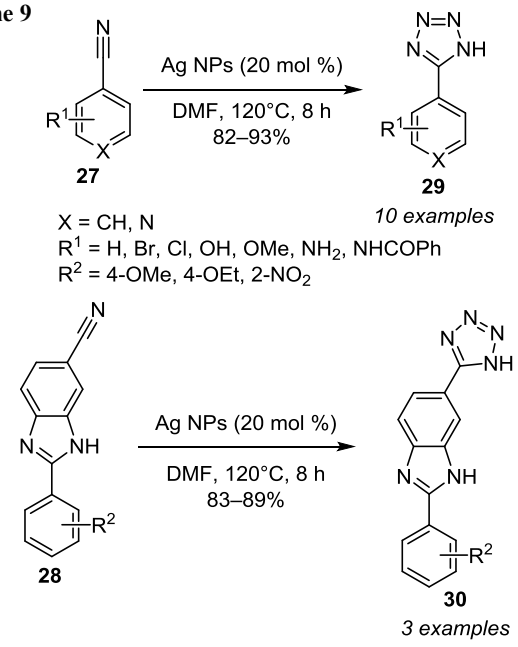


Ag NP-catalyzed synthesis of heterocycles

Among the various metal catalysts, silver has higher accessibility for industrial and heterogeneous catalysis because of its relatively low price (as less than 1/50 of gold, and about 1/25 of palladium) and is being relatively more friendly to the environment.[25] Ag NPs as catalyst have distinct physical and chemical properties compared to the bulk material due to their small size. The researcher's interest in silver nanoparticles has expanded rapidly in the last few years because of their distinct reactivity, stability, and recyclability in catalytic reactions. Silver nanoparticle catalysis has great potential in organic transformations and play an important role in the total synthesis of natural products and pharmaceutical molecules.[10a]

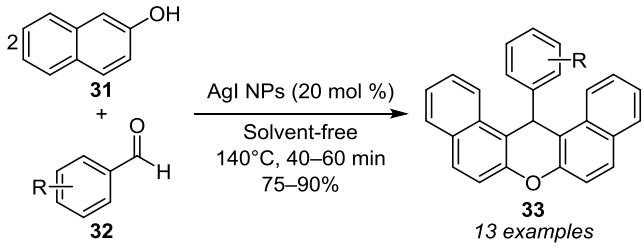
Tetrazoles are widely used in drug discovery as isosteric replacement for carboxylic acids, and owing to their wide range of biological and commercial applications.[26] Awasthi and coworkers have developed an efficient synthetic methodology for the synthesis of 5-substituted 1*H*-tetrazoles **29** and **30** using Ag nanoparticles as catalyst *via* [3+2] cycloaddition reaction of benzonitriles **27** or **28** and sodium azide in DMF at 120°C (Scheme 9).[27] Under the optimized conditions, benzonitriles bearing electron-withdrawing and electron-donating substituents on the aromatic ring were efficiently converted. However, electron-withdrawing substituents provided better product yields. Heterocyclic nitriles are also well tolerated in this reaction and provided access to the corresponding tetrazoles in moderate to high yields. Interestingly, the Ag catalyst can be reused up to four catalytic cycles without significant loss of catalytic activity.

Scheme 9



Xanthene derivatives exhibit a diverse range of biological applications. Xanthene dyes have been used for diagnostic and imaging purposes.[28] Safaei-Ghomi and coworkers have reported an efficient, facile, and economical method for the preparation of 14-aryl-14*H*-dibenzo-[*a*,*j*]xanthenes **33** under solvent-free conditions using AgI NPs as a catalyst by the reaction of 2-naphthol (**31**) and benzaldehydes **32** at 140°C (Scheme 10).[29] The reaction time was significantly reduced by using AgI NPs compared to using bulk AgI. This efficient method furnishes the products with diversely substituted benzaldehydes **32** in excellent yields and high purity (≥95%). Aldehydes bearing electron-withdrawing groups (NO_2, Cl, and Br) at the *para* position provided better results with respect to yield and rate of the reaction. The present method offers high yields, short reaction times, easy purification, and low catalyst loading along with recyclability of the catalyst. The latter was recovered by simple filtration followed by washing with chloroform and methanol and then drying at 70°C for 10 h.

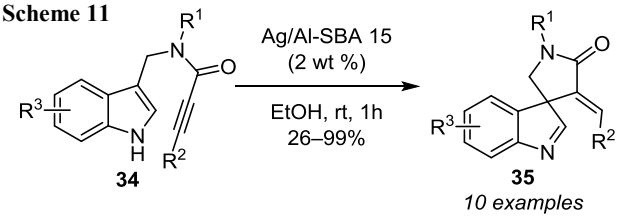
Scheme 10



R = H, 4-Me, 3-Me, 4-OMe, 4-*i*-Pr, 4-Cl, 4-Br, 4-NO_2, 3-NO_2, 3-OH, 2-F, 4-SMe

Van der Eycken and coworkers have described an Al-SBA-supported Ag NP-catalyzed 5-*exo-dig* cyclization reaction of 3-substituted indoles **34** bearing a side-chain alkynyl group to provide access to 3-spiroindolenines **35** in high to excellent yields (Scheme 11).[30] The substrates comprising terminal alkyne group (R^2 = H) gave better results with respect to yield and reactivity as compared to the internal alkynes (R^2 = Me, Et) which cyclized slowly and required longer reaction times, high temperature, and high catalyst loading for completion of the reaction. Surprisingly, 6-*endo-dig* cyclization products were also formed, which were difficult to separate from the *exo* products. The presence of electron-withdrawing or electron-donating substituents on the C-5 position of the indole produces negligible impact, although a chlorine atom at the C-6 position has detrimental effect on the yield. Substitutions on the amide N atom (R^1) have insignificant effect on the yield of desired product.

Scheme 11

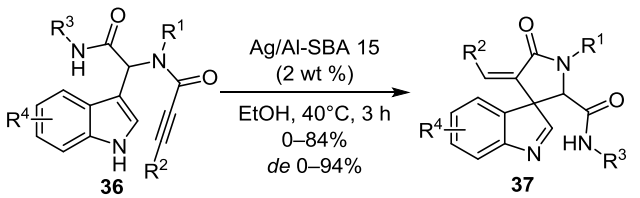


R^1 = PMB, Me, CH_2Cy; R^2 = H, Me, Et; R^3 = F, Cl, OMe

Further, Van der Eycken and coworkers have reported a post-Ugi cyclization of Ugi-adducts **36** using Al-SBA-supported Ag NPs as catalyst to get access to spiro-

indolenines **37** at 40°C in good to excellent yields and with satisfactory diastereoselectivity (Scheme 12).[30] The substrates comprising a terminal alkynyl group (R^2 = H) provided good yields with trace amounts of the undesired tetracyclic product. Substrates comprising internal alkynyl group (R^2 = Me) were not converted under these conditions. Substituents on both C-5 and C-6 atoms of the indole were well tolerated. However, a sterically demanding R^3 substituent such as butyl, has been found deteriorating for the product yield. Further, various R^1 alkyl substituents were well tolerated and had minimal effect on the reaction outcome. The above catalyst could be used up to ten catalytic cycles without having desactivation of crystal ripening and with extremely low leaching.

Scheme 12

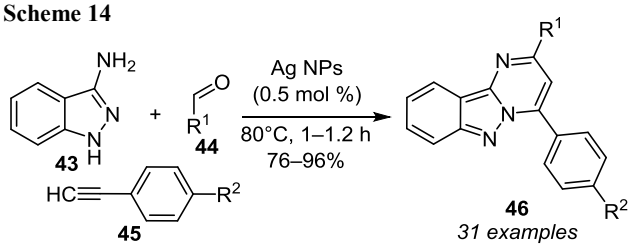


R^1 = PMB, Me, Bn, CH_2Cy; R^2 = H, Me
R^3 = *t*-Bu, *n*-Bu, *i*-Pr, Bn; R^4 = H, F, Cl, OMe

Maleki and coworkers have developed an eco-friendly method for the synthesis of 2-amino-4-aryl-6-(2-oxo-2*H*-chromen-3-yl)nicotinonitriles **42** catalyzed by magnetic cellulose/Ag nanobiocomposite.[31] The synthetic methodology for the preparation of chromene-linked nicotinonitriles **42** commenced with the MCR reaction of 3-acetylcoumarin **38**, benzaldehydes **39**, malononitrile (**40**), and ammonium acetate (**41**) in the presence of a catalytic amount of magnetic cellulose/Ag nanobiocomposite in ethanol at 60°C (Scheme 13). The magnetic cellulose/Ag nanobiocomposite comprises γ-Fe_2O_3 NPs supported onto the cellulose layers and Ag NPs immobilized on the surface of the cellulose. Under the optimized conditions, different benzaldehydes **39** substituted with electron-donating or electron-withdrawing groups furnished the corresponding products **42** in high yields. Aldehydes bearing electron-withdrawing substituents underwent the reaction faster. This approach has the advantages of using an inexpensive catalyst, catalyst recyclability (up to five times), easy separation of catalyst from the reaction mixture, an environment friendly procedure, short reaction times, avoiding hazardous organic solvents, and high yields.

Jeong and coworkers have reported a convenient and efficient approach for the synthesis of pyrimido[1,2-*b*]-indazoles **46** catalyzed by Ag NPs under solvent-free conditions.[32] The authors have prepared environment friendly Ag NPs from the extract of the plant *Radix Puerariae via* a novel chemical route. One-pot three-component coupling reaction between 3-aminoindazole (**43**), aldehydes **44**, and alkynes **45** catalyzed by Ag NPs under solvent-free conditions at 80°C furnished pyrimido-[1,2-*b*]indazoles **46** in excellent yields (Scheme 14). Under the optimized reaction conditions, a wide range of aldehydes were well tolerated and provided access to the desired products **46** in high yields. Alkyne substrates, such as 1-ethynylbenzene and 1-ethynyl-4-methylbenzene gave pyrimido[1,2-*b*]indazoles in good to excellent yields. However, aliphatic alkynes failed to give the desired products. The promising points of this approach include ease of the catalyst preparation and reusability, simple workup procedure, higher reaction rates, and avoiding the use of hazardous solvents.

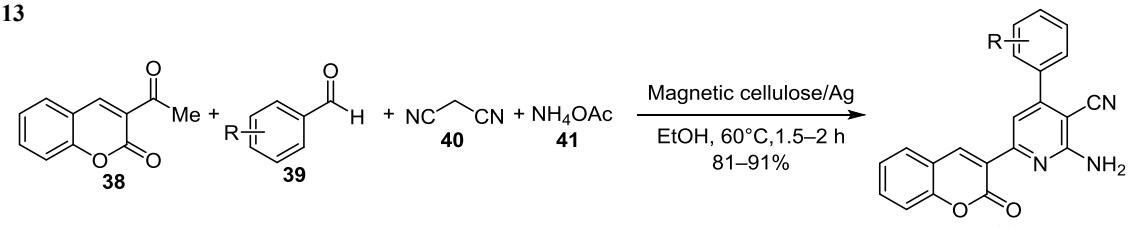
Scheme 14



R^1 = 2-$MeOC_6H_4$, 3-$MeOC_6H_4$, 4-$MeOC_6H_4$, 4-*i*-PrC_6H_4, 2,5-$Me_2C_6H_3$, 2-Cl-6-FC_6H_3, 4-ClC_6H_4, 3-ClC_6H_4, 2-ClC_6H_4, 2-FC_6H_4, 3-FC_6H_4, 4-FC_6H_4, 3-BrC_6H_4, 4-BrC_6H_4, 4-CNC_6H_4, 2-thienyl, 2-furyl, 1-Naphth, Cy; R^2 = H, 4-Me

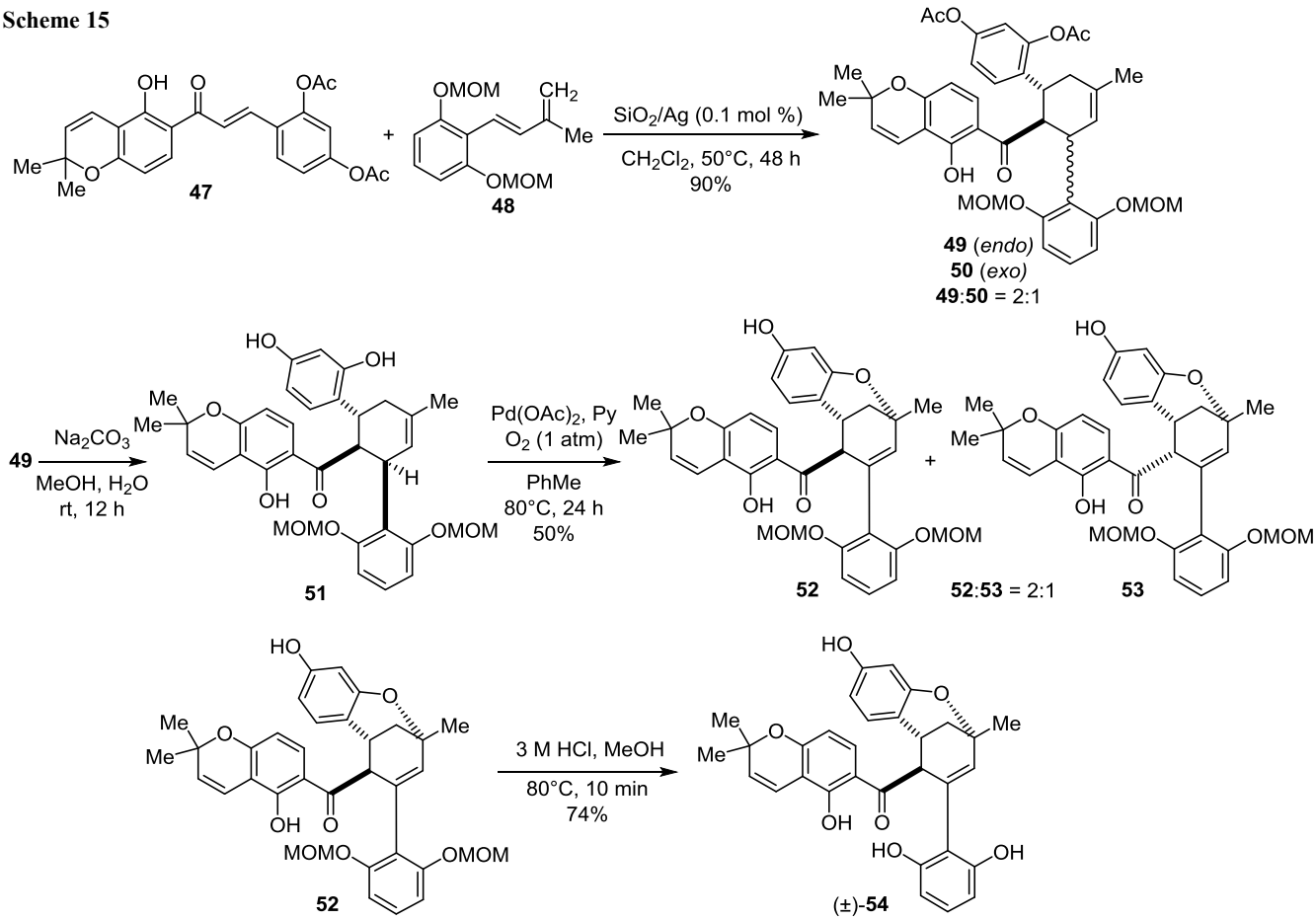
Sorocenol B, an isoprenylated phenol, was isolated from the root bark of *Sorocea bonplandii* Baillon (Moraceae). Chemically, soracenol comprises of a bicyclo[3.3.1] core which is biosynthetically derived from oxidative cyclization of 2'-hydroxychalcone-derived Diels–Alder cycloadduct.[33] Porco and coworkers have developed a method for the total synthesis of (±)-sorocenol B **54** utilizing silver nanoparticles as catalyst.[34] Diels–Alder cycloaddition reaction between 2'-hydroxychalcone **47** and diene **48** was catalyzed by silica-supported Ag NPs (0.1 mol %). The desired cycloadduct was obtained in 90% yield as a separable mixture of *endo*/*exo* diastereomers **49** and **50** in 2:1 ratio (Scheme 15). Further, the bicyclo[3.3.1] framework was constructed by using Pd(II)-catalyzed oxidative cyclization. Substrate **51** was synthesized from *endo*

Scheme 13



R = H, 3-NO_2, 4-NO_2, 4-Cl, 4-Br, 2-Cl, 4-CN, 4-OH, 4-Me, 4-OMe, 3-OMe, 4-F

Scheme 15



diastereomer **49**, using Stoltz's conditions for oxidative Wacker cyclization (the $Pd(OAc)_2$/pyridine catalytic system in toluene under O_2 atmosphere).[35] This afforded the desired bicyclic product **52** and its C-4 epimer **53** (in 2:1 ratio) in 50% yield. Finally, (±)-sorocenol B **54** was accessed in 74% yield by hydrolyzing MOM ether **52** in refluxing acidic MeOH. The synthetic natural product displayed low micromolar cytotoxic activity, particularly against prostate cancer PC-3 (GI_{50} 1.1 μM), melanoma LOX IMVI (GI_{50} 1.4 μM), leukemia MOLT-4 (GI_{50} 1.4 μM), and colon cancer HCC-2998 (GI_{50} 1.4 μM).

Several protocols for the synthesis of heterocyclic compounds catalyzed by Au and Ag NPs were summarized. Rapid and green synthetic methods using microflow conditions have shown great potential for the synthesis of heterocyclic compounds using NPs as a catalyst. The use of supported materials such as Fe_2O_3, TiO_2, SiO_2, and carbon enhances the reactivity of Au NPs. The Au and Ag NP-catalyzed synthetic methods for heterocyclic compounds are environmentally friendly procedures and provide several advantages including increased reaction rates, higher yields, simple workup procedure, and reusability of the catalyst. We strongly believe that NP-catalyzed reactions have great potential for the synthesis of heterocyclic compounds and will attract the attention of organic chemists. We also expect an exponential increase in NP-catalyzed reactions in the near future.

The authors are thankful to ISF College of Pharmacy, Moga, Punjab, India, University of Nebraska Medical Center, Omaha, NE, USA, KU Leuven, Belgium and for support of RUDN University, Moscow, Russia (Program 5-100).

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