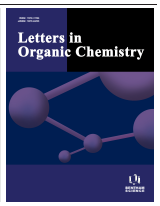
Letters in Organic Chemistry, 2023, *20*, 18-27

MINI-REVIEW ARTICLE



Use of Gold Nanoparticles in the Synthesis of Heterocyclic Compounds

Biswajit Panda[1,*]

[1]*Department of Chemistry, City College, 102/1 Raja Rammohan Sarani, Kolkata-700009, India*

ARTICLE HISTORY

Received: April 15, 2022
Revised: June 23, 2022
Accepted: June 28, 2022

DOI:
10.2174/1570178619666220826115245

Abstract: Nanoparticles have been proven to be efficient catalysts for a variety of chemical reactions, with added advantages such as the reuse of catalysts, increasing the scale of reactions employing continuous flow techniques, and simple separation of the reaction milieu, making them green, efficient, and lucrative choices. Over the last decade, gold nanoparticles (AuNPs) have appeared as promising and efficient catalysts in the field of sustainable organic synthesis. On the other hand, heterocycles are significant scaffolds in a variety of natural products and other biologically active molecules, as well as useful compounds for organic and material chemistry. Therefore, the progress of proficient techniques for the synthesis of heterocyclic compounds is always of major significance. This mini-review focuses on some of the most important AuNPs catalyzed heterocyclic compound synthesis processes. Wherever essential, the exclusivity of the approaches has been discussed by emphasizing substrate diversity, selectivity, product yields, and mechanistic features.

Keywords: Nanocatalysis, AuNPs, heterocycles, gold catalysis, agrochemicals, nanoparticles.

1. INTRODUCTION

Heterocycles and their synthesis, transformation, and characteristics are very important in organic chemistry. The majority of medicines, natural products, agrochemicals, additives, conductive polymers, and other products contain heterocyclic moiety(s) [1-5]. New therapeutic compounds are often designed to increase ligand efficacy by improving their pharmacokinetic profile. At least one heterocyclic ring can be found in around 70% of all medicines and agrochemicals. The primary reason for the enormous usefulness of heterocycles in pharmaceuticals is due to drug heterocyclic scaffold, which frequently has a favourable influence on its synthetic accessibility and physicochemical characteristics, bringing lipophilicity and solubility values into the ideal balanced range in terms of absorption and bioavailability. As a result, researchers are always looking for novel and efficient heterocyclic compound synthesis methods.

In recent years, the area of nanocatalysis has exploded, incorporating the use of nanomaterials as catalysts in a variety of homogeneous and heterogeneous conditions [6]. Nanomaterials have very high efficacy as compared to typical catalysts because of their enhanced activity, specificity, superior stability, minimal energy usage, and extended shelf life. Because of their tiny size (about 10-80 nm) and form, they have a high surface-to-volume ratio, which results in distinct and massive changes in the material physicochemical characteristics [7, 8].

Metal nanoparticles (MNPs) have a lot of promise in fields like medicine and catalysis [9, 10]. MNP greater surface area has a beneficial effect on reaction rate, which is the primary reason for the increased catalytic activity of these NPs. MNP catalysis allows for quick and selective chemical conversions with good yields, as well as easy catalyst separation and recovery [11].

Particularly, AuNPs as catalysts have drawn the scientific community's attention due to their remarkable catalytic activity, specificity, stability, and reusability in catalytic processes [12-15]. In recent years, a series of books and review articles addressing gold catalyzed organic processes have been published [16-21]. Several comprehensive reviews on AuNP catalysis have covered the physical properties and analysis of AuNPs, as well as the formation of various carbon-heteroatom bonds.

Gold is an important catalyst for the formation of carbon-carbon and carbon-heteroatom bonds (C-O, C-N, and C-S) through the addition of unsaturated reactive π-bonds by suitable nucleophiles. This brief overview highlights several key findings on the employment of AuNPs as efficient catalysts for the formation of heterocyclic compounds. After careful analysis of literature reports on this area over the last ten years, only significant discoveries have been highlighted here. The major goal of this review is to offer a foundation for ongoing research into AuNPs for the production of novel heterocycles.

*Address correspondence to this author at the Department of Chemistry, City College, 102/1 Raja Rammohan Sarani, Kolkata-700009, India;
E-mail: biswajitchem@gmail.com

1875-6255/23 $65.00+.00

2. AuNPs CATALYZED HETEROCYCLES SYNTHESIS

Because of their well-defined electrical and physical properties, AuNPs have generated considerable attention. The tiny size of AuNPs (1-100 nm) and hence the high surface-to-volume ratio distinguish them. Their physical and chemical properties may be modified to meet the criteria for size, composition, and shape, as well as high resilience and specialized target-binding qualities. Because of the features mentioned above, AuNPs are one of the most frequently used nanomaterials for catalytic reactions, imaging, illness diagnostics, and gene expression [22-28].

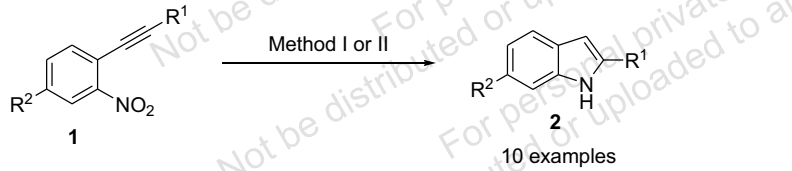
3. SYNTHESIS OF NITROGEN-HETEROCYCLES

Nitrogen-based heterocyclic chemistry is a prominent and distinct domain of modern organic chemistry, with substantial research devoted to the production of new compounds and composites. The quest for novel therapeutic drugs has been assisted by the N-heterocyclic frameworks' great structural diversity in terms of pharmacokinetics and other physicochemical characteristics [29]. The study and development of nitrogen-based molecules for medical purposes is now a fast-expanding and active area of research.

Indoles are important heterocycles with distinct properties due to the existence of an electron-rich pyrrole ring, which may bind noncovalently with the other molecules through hydrogen bonding *via* the NH group and π-π stacking [30, 31]. Tokunaga and coworkers described an AuNPs catalyzed one-pot hydrogenation followed by a cyclization reaction of (2-nitrophenyl)alkynes **1** to produce indoles derivatives **2** [32]. Two methods were used to synthesize the indoles **2**. The first technique uses Fe_2O_3 supported AuNPs to catalyze the reaction of (2-nitrophenyl)alkynes **1** to the synthesis of indoles **2** in a single step (Scheme **1**). The second technique uses a two-step reaction in one pot where the first phase is carried out at 60°C with 2.0 MPa H_2 for 1 h, followed by H_2 release at 0.1 MPa pressure. The reaction mixture is then heated for 1 h at 120°C in the second stage. The second approach produces somewhat higher yields compared to the first approach. A diverse array of alkynes **1** bearing bulky groups, like *p*-Tol, *tert*-Bu, and cyclohexenyl, have undergone the reaction to generate the respective indoles **2** in good yields under the optimum conditions. Conversely, an electron- deficient group substituted on the alkyne, for example a trifluoromethylphenyl, produced moderate yields of the corresponding indoles. On the other hand, an alkyne containing a TMS group was not compatible with the reaction and resulted in the complete decomposition of starting materials. It was found that the yield of the expected product **2** was unaffected by substituents on the benzene ring. In their study, gold particles with an average diameter of 2-3 nm were seen in TEM pictures of the Au/Fe_2O_3 catalysts. After the catalytic process, the size of the gold particles marginally increased. Actually, the catalysts that had been used previously had slightly lower activity and provided a product with low yields. The performance might be negatively impacted by a small change in the catalyst condition along with the size of the gold nanoparticles.

Quinolines have received a lot of interest because of their wide variety of pharmacological properties [33-35]. In 2011, Che and coworkers published a novel one-pot method for accessing nitrogen-containing heterocycles **5** and **7** through an AuNPs catalyzed reaction of anilines **4** and polycyclic aromatic amines **6** with aldehydes **3** in toluene at 110°C with oxygen as an oxidant (Scheme **2**) [36]. A range of electron-donating functional groups on anilines **4** gave good yields of the desired products **5** under the optimum reaction conditions. On the other hand, electron-deficient substituents have a negative impact on the yield of the product formed. Hydrocinnamaldehyde and aldehydes with high boiling points were revealed to be suitable substrates with excellent yields. Bulky anilines were found to be appropriate for the synthesis of polycyclic quinolines **7** under these reaction conditions and produced the required product in good yields. The marking indicates the connection points in product **7**. The image obtained using transmission electron microscopy (TEM) showed that the spherical AuNPs were equally dispersed over the silica surface. The average AuNPs had a diameter of 27.7 ± 2.9 nm and a dispersion of 10.5%, respectively. The distinct diffraction spots in the supported AuNPs' fast-Fourier transform (FFT) images further demonstrated the single crystal structure and outstanding crystallinity of the AuNPs. The identification of Au, Si, and O peaks during energy-dispersive X-ray (EDX) microanalysis provided more evidence that Au was present on silica. The easy recovery of the catalyst, which can be successfully reused for the next seven consecutive cycles without the substantial defeat of catalytic activity, is another benefit of this protocol.

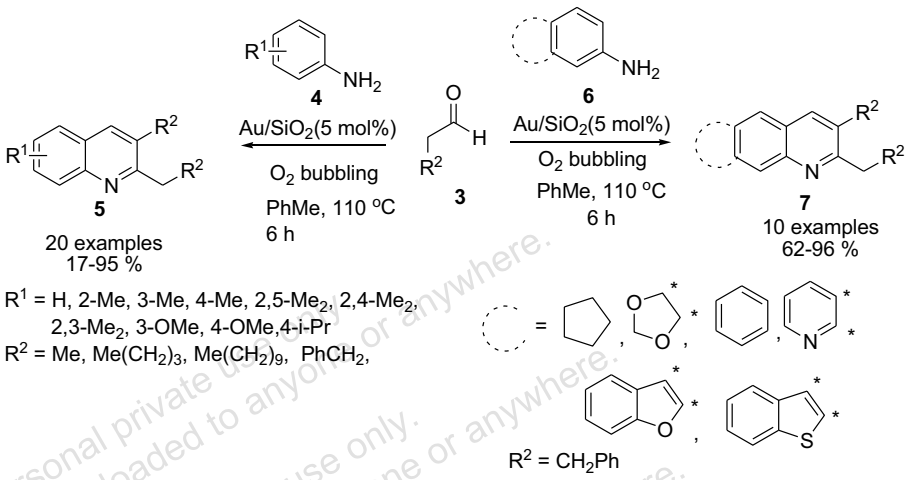
Iborra and co-workers described the AuNPs catalyzed synthesis of quinoxalines **10** from the reaction of *o*-phenylenediamines **8** and glycols or vicinal diols **9** at 140°C in the absence of base (Scheme **3**) [37]. The catalyst reusability was investigated for as far as four catalytic cycles; and after



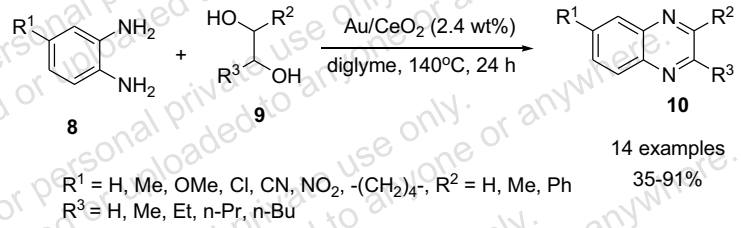
R^1 = Ph, *p*-Tol, 4-$MeOC_6H_4$, 4-FC_6H_4, 4-$CF_3C_6H_4$, t-Bu, Cy, cyclohexenyl, TMS
R^2 = H, Me

Method I: H_2 (2 MPa), Au/ Fe_2O_3 (5.0 atom % Au/(Au +Fe), 2.3 mol % Au/**1**), 120°C, 1 h
Method II: H_2 (2 MPa), Au/ Fe_2O_3(5.0 atom % Au/(Au +Fe), 2.3 mol % Au/**1**), PhMe, 60°C, 1 h then H_2 (0.1 MPa), PhMe, 120°C, 1 h

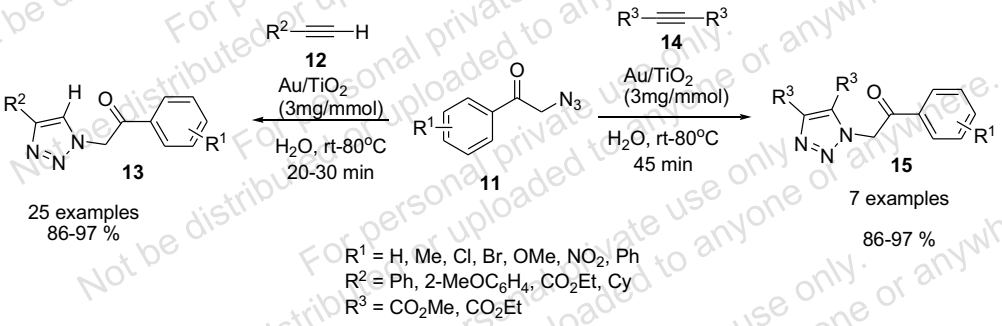
Scheme 1. AuNPs catalyzed synthesis of indoles **2**.



Scheme 2. AuNPs catalyzed synthesis of quinolines **5** and **7**.



Scheme 3. AuNPs catalyzed preparation of quinoxalines **10**.



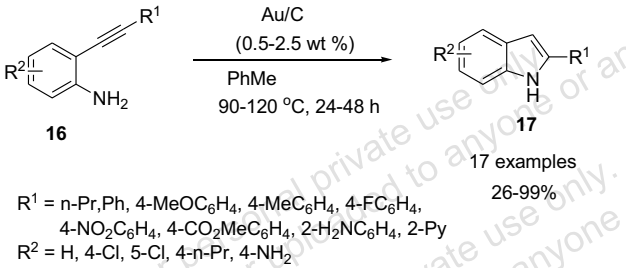
Scheme 4. AuNPs catalyzed synthesis of 1,2,3-triazoles **13** and **15**.

the fourth cycle, the catalytic activity was decreased, as determined by percent conversion to the final product **10**.

1,2,3-Triazoles are important heterocyclic structures that may be found in a variety of compounds and have a wide range of therapeutic uses [38]. In 2013, Muthusubramanian and coworkers used AuNPs supported on nanoporous titania for the synthesis of 1,2,3-triazoles **13** and **15** in an aqueous medium [39]. [3+2] Cycloaddition reaction was accomplished by reacting substituted phenacyl azides **11** with acetylenes **12** in water or in a *tert*-BuOH/H_2O mixture with the omnipresence of Au/TiO_2, yielding 1,4-disubstituted 1,2,3-triazoles **13** as the only regioisomer (Scheme **4**). In this reaction, the utilization of symmetrical internal alkynes **14** was also investigated. In contrast to the noncatalytic process, it was discovered that the omnipresence of the Au/TiO_2 catalyst resulted in good yields of products **15** in a short reaction time. This improvement in product yield can be ascribed to the gold alkynophilic property, which activates the internal alkyne, resulting in a faster reaction rate. The porous architecture of the Au/TiO_2 nanospheres, generated by the aggregation of TiO_2 nanoparticles of roughly 10 nm, is clearly visible in the TEM picture. The HRTEM images of the Au/TiO_2 nanospheres demonstrate the dispersion of Au nanoparticles with a size of 5 nm on the porous TiO_2 surface. The EDAX spectra verified that Au was present in the porous TiO_2 matrix.

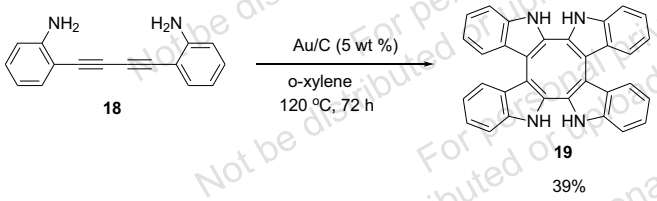
In 2013, Lopez-Sanchez, Helaja, and coworkers reported the synthesis of indoles **17** in good yields by the cycloisomerization process of 2-alkynylanilines **16** in the presence of carbon supported AuNPs as catalyst (Scheme **5**) [40]. Substrate molecules with different substituent on the alkynes and/or aryl rings performed the cycloisomerization process in good to excellent yields under the optimal reaction conditions. The presence of an electron-withdrawing substituent R^1 in the starting molecules **16** reduced reactivity and catalytic efficiency, whereas the presence of an electron-donor *p*-methoxyphenyl group as R^1 enhanced reactivity and catalytic

efficiency. The employment of an aliphatic alkyne, on the other hand, resulted in low yields of the desired product and had a negative impact on catalytic activity. The catalytic activity on anilines **16** was shown to be enhanced by the presence of a chlorine substituent (R^2) at the C-4 or C-5 atoms. Except for 2-alkynyl-4-nitroanilines, the majority of the substrates produced good yields of the expected product **17**.



Scheme 5. AuNPs catalyzed synthesis of functionalized indoles **17**.

Furthermore, employing 2,2'-(1,3-butadiyne-1,4-diyl)-bisaniline (**18**) as a starting material, an unusual synthesis of cyclooctatetraene condensed with four indole rings **19** was performed. In comparison to the afore-mentioned cycloisomerization reaction of 2-alkynylanilines **16**, this reaction needed high catalyst loading (5 wt%) and a higher temperature to complete (Scheme **6**).



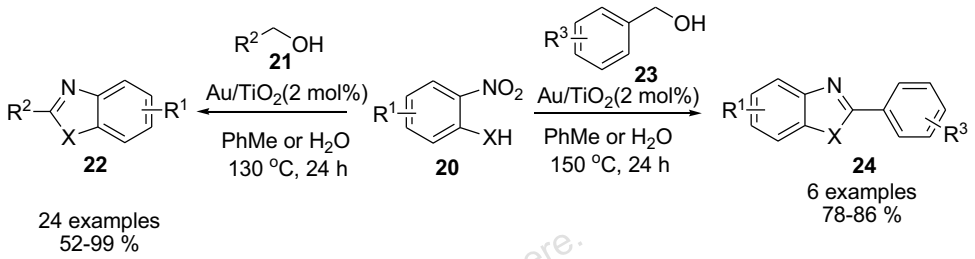
Scheme 6. AuNPs catalyzed synthesis of cyclooctatetraene condensed indole **19**.

In many commercialized medicines and therapeutic prospects, benzoxazole and benzimidazole cores are frequent structural components [41, 42]. Wang and coworkers demonstrated a very nice synthesis of benzoxazoles **22** and benzimidazoles **24** containing substituents at 2-position [43]. 2-Substituted benzoxazoles **22** were selectively synthesized using Au/TiO_2 as a catalyst in the reaction of 2-nitrophenols **20** (X = O) and alcohols **21** (Scheme **7**). Substituted benzylic alcohols **21** provide good yields of the required products **22** under the optimized reaction conditions. The reaction rate is slowed by the steric hindrance of the substituents in the *ortho* position of the benzene ring. The benzene ring was replaced with a naphthalene ring, resulting in high yields of the desired product. On the phenyl ring of nitrophenol **20** (X = O), the presence of either electron-donating or electron-withdrawing groups was well tolerated. *O*-nitroanilines **20** (X = N) and benzyl alcohols **23** were transformed into 2-arylbenzimidazoles **24** in high to good yields under identical reaction conditions employing toluene or water as a solvent. Surprisingly, using *N*-methyl-*o*-nitroaniline as a substrate increased product yield. The authors studied the reusability of the catalyst and found that the activity of the Au/TiO_2 catalyst was reduced after the completion of six catalytic cycles. The merits of this protocol are that in this reaction, no additional additives, oxidants, or reductants are required.

Because of their presence in a variety of natural products and drug-like compounds, spiroindolines have generated a lot of attention. Under microflow conditions, Van der Eycken and coworkers demonstrated an efficient synthesis of spiroindolines **26** catalyzed by supported AuNPs through cycloisomerization and the construction of C-C bond [44]. In their protocol, a ball-milling technique was used to make the heterogeneous gold catalyst Au@Al-SBA15. In a microreactor filled with Au@Al-SBA15, the sterically restricted Ugi-adducts **25** were cyclized to spiroindolines **26** at 120°C in an aqueous EtOH solvent, with hexafluoroisopropyl alcohol (HFIP) as a proton transporter (Scheme **8**). Substrates **25** with aliphatic and aromatic substituents gave good to excellent yields of the respective spiroindolines **26** under the optimized reaction conditions. As R^2 substituents, *p*-methoxybenzyl and other aliphatic moieties were tolerated well. The inclusion of a *tert*-Bu or a Cy group as an R^3 substituent results in high product yields. The impact of water on the reaction selectivity was also studied, with results suggesting that the presence of water speeds up the proto-decoordination of the AuNPs, promoting the synthesis of spiroindolines **26** by enhancing the catalytic process. The authors found that after extended usage, catalyst deactivation was observed. The Au@AlSBA15 catalytic bed did not exhibit any obvious leaching. Their findings suggest that the catalyst species is deactivated by two additional mechanisms: first, the oxidation of Au(0) to Au(III), and second, the agglomeration of gold nanoparticles.

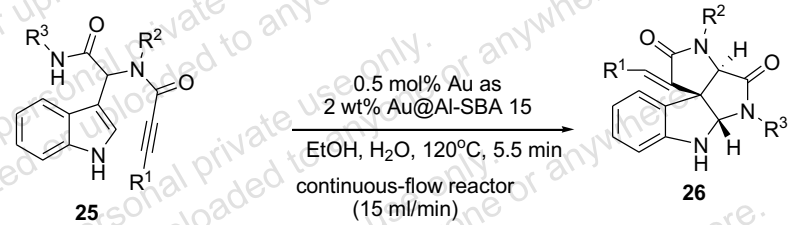
The three-component coupling process of phenylacetylene (**27**), dichloromethane (DCM, **28**), and cyclic amines **29** was described for the synthesis of propargylamines **30** using AuNPs supported ceria-catalyzed AHA (Alkyne-Halomethane-Amine) coupling (Scheme **9**) [45]. However, only a small number of substrates were examined for AHA coupling, with the catalyst being recycled just three times and yields ranging from 30 to 53%. From a mechanistic standpoint, DCM (**28**) reacts with amine **29** to produce a Mannich base, which then forms chloromethanamine *via* the removal of HCl. Propargylamines **30** are formed when the Mannich base reacts with arylacetylene **27** adsorbed on the catalyst surface. TEM, DRX, and DR-UV visible spectroscopy were used to investigate the catalyst species, and consistent distribution of 2-4 nm-sized gold particles was found on the ceria.

The synthesis of quinolines and pyridocoumarins from propargylamines by AuNPs supported on TiO_2 was documented by Litinas and coworkers [46]. As a consequence of treating 6-propargylaminocoumarins **31** in 1,2-dichloroethane (DCE) with $Au\text{-}TiO_2$ at 70°C for 48 h, good yields of the desired products **32** were obtained. 6-*Endo-dig* cyclization and a 1,3-H shift were used to interpret the reaction. The use of water as a solvent resulted in reduced product yields. In addition, the reaction may be carried out on various supported AuNPs, such as $Au\text{-}Al_2O_3$, which was equally effective. On the other hand, the reaction of *N*-propargylanilines with $Au\text{-}TiO_2$ for 3 days resulted in modest yields of the expected products as well as considerable quantities of dimerized products (Scheme **10**). The commercially available 1% gold on TiO_2 and 1% gold on Al_2O_3 nano-catalyst were used in this protocol.



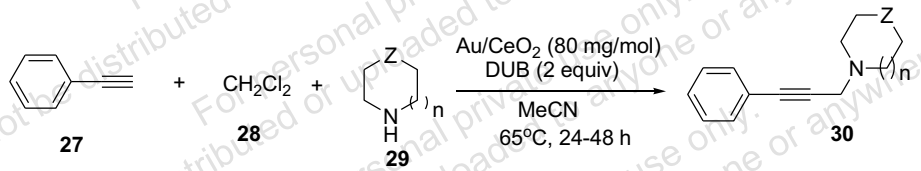
22, X = O; R^1 = H, 4-Me, 5-Me,4-OMe, 5-F, 4-Cl
R^2 = Me, t-Bu, n-Pent, Cy, Ph, 2-MeC_6H_4, 3-MeC_6H_4, 4-MeC_6H_4, 3-FC_6H_4, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-$CF_3C_6H_4$, 1-Naphth
24, X = NH, NMe; R^1 = H
R^3 = H,4-MeC_6H_4, 4-$MeOC_6H_4$, 4-FC_6H_4, 4-ClC_6H_4

Scheme 7. AuNPs catalyzed synthesis of benzoxazoles **22** and benzimidazoles **24**.



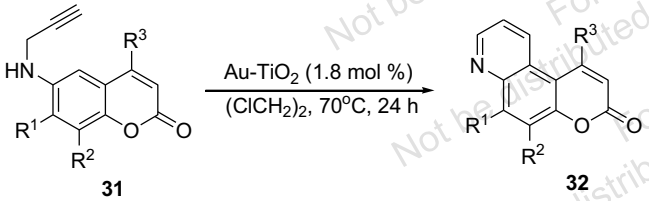
R^1 = Ph, Me, Et, PMP,Cy
R^2 = PMP, Cy, n-C_5H_{11}, Bn, i-Pr, n-Bu
R^3 = t-Bu, Cy, Bn, $C(Me)_2CH_2CMe_3$

Scheme 8. AuNPs catalyzed synthesis of spiroindolines **26**.



Z = CH_2, O
n = 0, 1

Scheme 9. AuNPs catalyzed synthesis of propargylamines **30**.



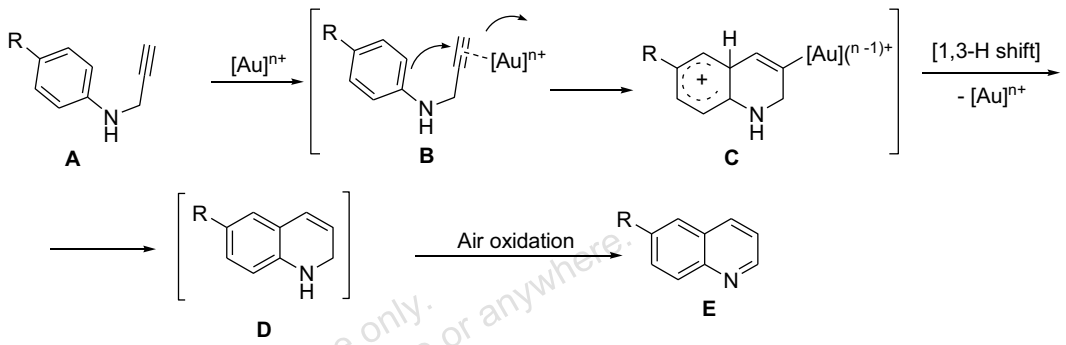
R^1 = R^2 = H, alkyl, fused ring
R^3 = H, COOMe

Scheme 10. AuNPs catalyzed synthesis of pyridocoumarins **32**.

Scheme **11** depicts a mechanistic scenario for the hydroarylation of alkynes by Friedele-Crafts catalysed by cationic Au^I or Au^{III} species present in Au/TiO_2 to produce fused pyridocoumarins or quinolines from N-propargylanilines. Through a 6-endo-dig cyclization, the activated alkyne-Au-π-complex B's electrophilic aromatic substitution by the electron-rich arene produced the vinyl-Au intermediate C. Under catalyst regeneration, the dihydroquinoline derivative D was produced *via* a 1,3-H shift. The products E were produced solely by the air-oxidation of D.

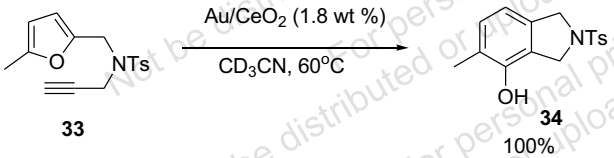
Hashmi and coworkers compared homogeneous and heterogeneous gold catalysts for the cyclization of ω-alkynylfurans as compound **33** to phenols [47]. The Au/CeO_2 catalyst showed significant activity, yielding approximately 100% phenol **34** after 20 h. However, using $CDCl_3$ as a solvent resulted in gold leaching. As a result, CD_3CN was selected as the solvent to retain the reaction heterogeneity and to provide the required product **34** in 100% yield (Scheme **12**). Despite this, leaching analysis revealed a gold concentration in the solution of about 25 ppm. The turnover number (TON) was, on the other hand, comparable to that of homogeneous gold catalyzed processes [48]. The surface Au(III) of AuNPs is thought to be responsible for their activity, which is comparable to that of homogeneous gold catalysts in which Au(III) is the active catalytic component.

In 2014, Jonnalagadda and co-workers reported a gold nanoparticle catalysed one-pot, four-component reactions



Scheme 11. Mechanism of AuNPs catalyzed synthesis of quinolines.

involving malononitrile **35**, ammonium acetate **36**, ketones **37** and different benzaldehydes **38**, an effective route to highly substituted pyridines (Scheme **13**) [49]. In this protocol, MgO-supported Au nanoparticles were used as a catalyst. The advantages of this strategy are quick reaction times, excellent yields, and simple workups. Additionally, Au/MgO catalysts may be employed again for six successive cycles without significantly losing their catalytic activity. Scanning electron microscopy (SEM) was used to characterise the morphology of the synthesised Au/MgO catalyst. Mesoporous entities were identified as particles of uniform size and shape with typical morphology.



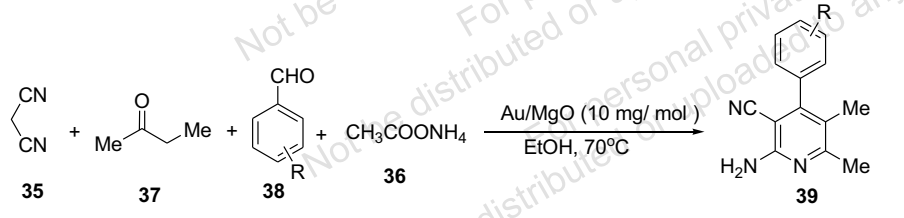
Scheme 12. AuNPs catalyzed synthesis of phenol **34**.

By directly reducing $HAuCl_4 \cdot 3H_2O$, Tran and co-workers prepared gold nanocrystals in a variety of shapes, including nanospheres, nanostars, and nanorods, which they then used as catalysts in a one-pot, three-component Biginelli reaction [50]. Among them, the gold nanorod solution showed excellent catalytic performance. With the use of ethyl acetoacetate, benzaldehyde derivatives, and urea, Au nanorod colloids catalyzed the reaction for the synthesis of 3,4-dihydropyrimidin-2 (1H)-ones with good yields in short reaction times (Scheme **14**). This catalytic system worked well with benzaldehyde derivatives that have both electron-donating and electron-withdrawing groups. Although in their study, the authors did not comment on the probable mechanism, they did mention the recyclability and reusability of the catalytic system.

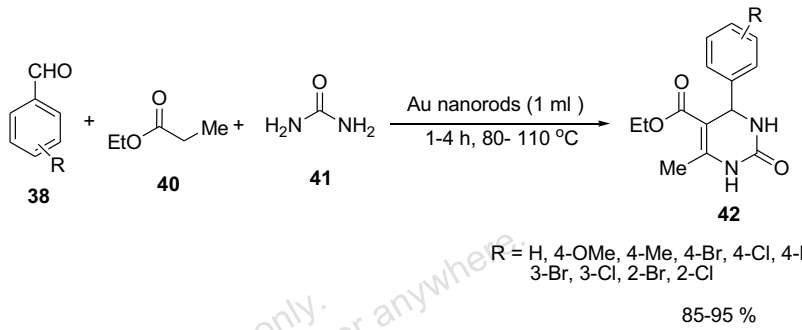
Organic processes assisted by microwaves have higher yields, less byproducts, faster reaction, and occasionally altered selectivity. In fact, microwaves may be used to execute novel reactions and conditions that are not possible with normal heating. Gold catalyzed organic transformations under microwave irradiation were one of the growing fields in organic synthesis, since various important molecules were successfully prepared with good efficiency in less time [51]. Very recently, Librando and co-workers have reported the microwave-assisted TiO_2 supported gold nanoparticle catalyzed one-pot three-component (alkyne **43**, organohalide **44**, and sodium azide) reactions to yield the corresponding triazoles **45** (Scheme **15**) in moderate yields, after 15 minutes, using a mixture of water and acetonitrile at MW (30 W, 150°C) and 1 mol% of catalyst loading [52]. The catalyst was recovered and reused up to five consecutive cycles, although with a loss of activity due to the increase of gold nanoparticle size. In view of the advantages, the current method displays several merits, including the utilisation of inexpensive and readily available materials, mild reaction conditions, easy operation, and the recyclability of the catalyst.

4. SYNTHESIS OF OXYGEN-HETEROCYCLES

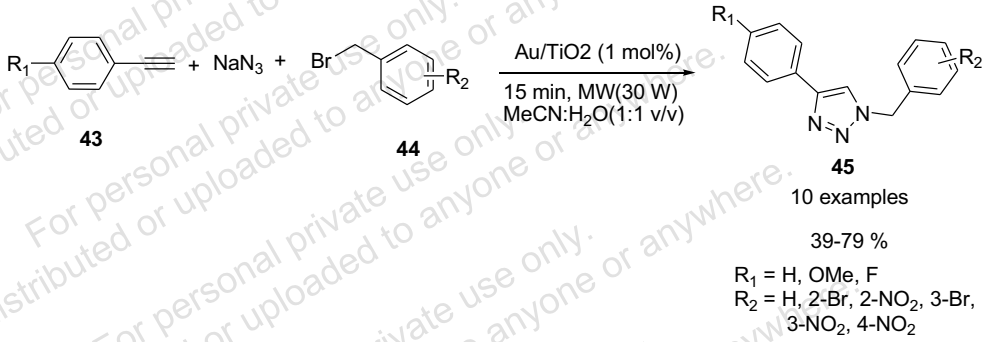
Many naturally occurring, therapeutically active compounds contain oxygen-based heterocycles as common structural elements. Then there are five- and six-membered oxacycles like tetrahydropyrans, dihydropyrans, tetrahydrofurans,



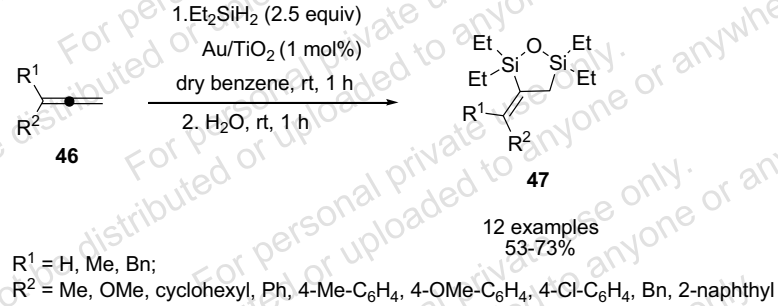
Scheme 13. AuNPs catalyzed synthesis of pyridines **39**.



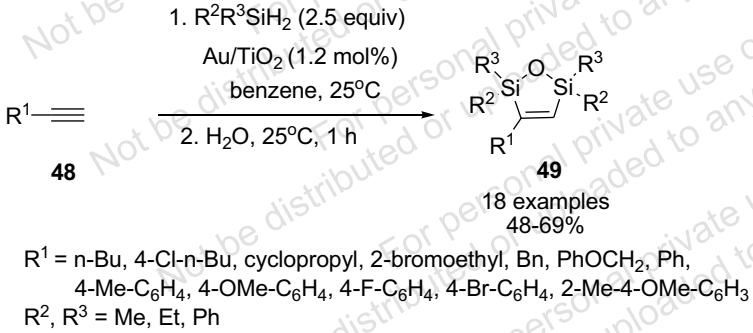
Scheme 14. AuNPs catalyzed synthesis of 3,4-dihydropyrimidin-2 (1H)-ones **42**.



Scheme 15. AuNPs catalyzed synthesis of triazoles **45**.

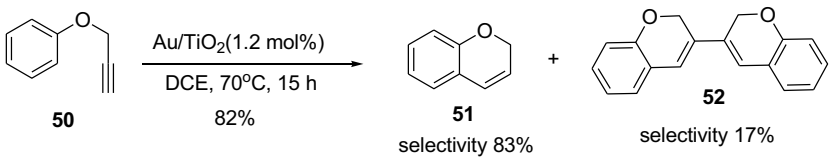


Scheme 16. AuNPs catalyzed synthesis of 3-alkylidene-1-oxa-2,5-disilacyclopentanes **47**.

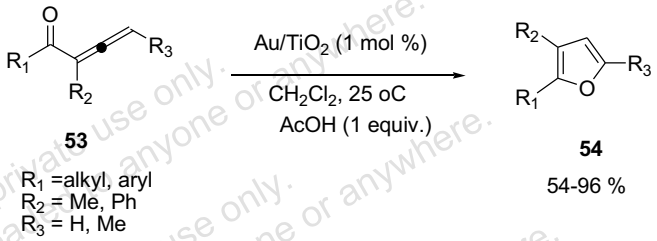


Scheme 17. AuNPs catalyzed synthesis of 2,5-dihydro-1,2,5-oxadisiloles **49**.

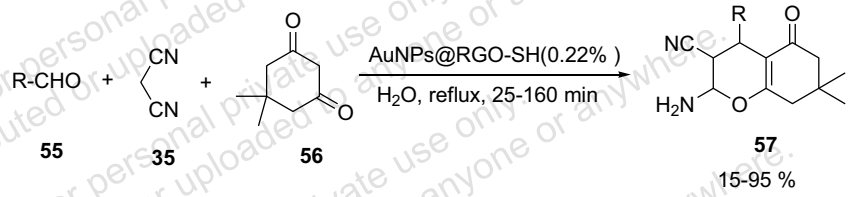
or various forms of γ- and δ-lactones that have a high occurrence in medically and biologically significant natural and non-natural products. The one-pot synthesis of new 3-alkylidene-1-oxa-2,5-disilacyclopentanes **47** from allenes **46** and diethylsilane using AuNPs supported TiO_2 (Au/TiO_2) catalyzed regioselective dehydrogenative 1,2-disilylation was described (Scheme **16**) [53]. Its application in C-C bond-forming Hiyama-type reactions for the synthesis of arylolefins was also described by Stratakis and co-workers. They also reported utilising Au/TiO_2 as a catalyst in the *cis*-1,2-dehydrogenative disilylation of alkynes for the synthesis of 2,5-dihydro-1,2,5-oxadisiloles **49** (Scheme **17**) from alkynes **48** and disubstituted silanes in benzene solvent at 25°C followed by catalyzed hydrolysis with water [54].



Scheme 18. AuNPs catalyzed synthesis of benzopyrans **51** and **52**.



Scheme 19. AuNPs catalyzed synthesis of furan **54**.



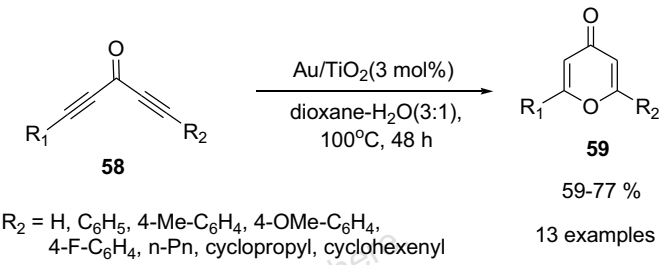
Scheme 20. AuNPs catalyzed synthesis of tetrahydro-4H-chromenes **57**.

Cyclic ethers are a prevalent type of oxygen-containing heterocyclic molecule and are found in a wide range of naturally occurring biologically and medicinally active chemicals [55]. Cyclic ethers are important components for the development of prospective medicinal molecules, as seen by a large number of FDA-approved cyclic ethers, including medicinal compounds. Additionally, they are commonly found as important structural components in synthetic agrochemicals and drugs. Thus many methods are available in the literature for the synthesis of ethers, including dehydration of alcohols [56], metathesis [57], red-ox strategy [58] and employing organometallic chemistry [59]. In 2011, Stratakis and coworkers reported utilizing gold supported on TiO_2 to cycloisomerize or oxidative dimerize propargyl ethers [60]. The reaction of phenyl propargyl ether (**50**) with Au/TiO_2 in DCE at 70°C resulted in an 82% yield of two products, with the bicyclic product **51** being the main product (83%) and the dimerized product **52** being produced at a low yield (17%) (Scheme **18**). The suggested mechanism entails the formation of an auric-monocyclic intermediate to yield a cyclized product. On the other hand, the auric-monocyclic intermediate can combine with another molecule of propargyl ether to yield a diorganogold intermediate, which then leads to a dimerized product.

Recently, Zorba and co-workers have reported a ligandless gold nanoparticle catalyzed cycloisomerization of conjugated allenones **53** for the synthesis of functionalized furans **54** in excellent yields (Scheme **19**) under mild reaction conditions [61]. In this protocol, 1% gold nanoparticles supported on TiO_2 were used in the presence of one equivalent of acetic acid. The acid accelerated the rate of the reaction (from 1 hour to 10 minutes). Mechanistic studies with CD_3COOD revealed that, unlike cationic Au(I) or Au(III) catalysis, the acid does not participate in the protodeauriation steps, indicating that gold and proton exchange occurs very quickly in the chemisorbed gold nanoparticles cyclized intermediate. This catalytic process finds that the catalyst is completely heterogeneous, recyclable, and reusable for several runs.

In 2018, Naeimi and co-workers demonstrated a sustainable and efficient method for the synthesis of tetrahydro-4H-chromenes using gold nanoparticles supported on thiol-functionalized reduced graphene oxide (AuNPs@RGO-SH) as a suitable catalyst for the reaction of substituted benzaldehyde and malononitrile in an aqueous medium under reflux conditions (Scheme **20**) [62]. Atomic force microscopy (AFM), field emission scanning electron microscopy (FE-SEM), FT-IR spectroscopy, thermal gravimetric analysis (TGA), and XRD were used to analyse the self-developed catalysts. The authors also found that the catalyst can be reused up to six times without significant loss of catalytic activity.

Conjugated ynones are a special type of structural motif that possesses impressive chemical versatility [63]. They are significant Michael species and exhibit high reactivity in cycloaddition as well as cyclocondensation reactions with a variety of nucleophiles. Many crucial organic functional groups and scaffolds may be formed from conjugated



Scheme 21. AuNPs catalyzed synthesis of γ-pyrones **59**.

ynones. Stratakis and co-workers have reported an elegant method for the synthesis of γ-pyrones **59** from skipped diynones **58** in the presence of gold nanoparticles supported on TiO_2 as a suitable catalyst in aqueous dioxane solvent (Scheme **21**) [64]. The reaction proceeds through Au/TiO_2 catalyzed activation of the triple bond followed by hydration and 6-endo cyclization. Interestingly, these results differed from the homogeneous gold(I) catalyzed hydration of diynones, which results in isomeric 3(2H)-furanones *via* 5-exo cyclization [65]. This may be due to following the reactions into two different mechanistic pathways with Au (I) and Au NPs catalysts.

CONCLUSION

The synthesis of heterocyclic compounds by AuNPs was summarized using various protocols. Fast and green synthetic techniques exploiting microflow conditions have revealed significant possibilities for the preparation of heterocycles employing NPs as a suitable catalyst. The soft carbophilic characteristic of gold, which triggers alkyne for subsequent reactions, makes homogeneous gold catalysis significant. On the other hand, in the case of alkyne activation, the heterogeneous gold catalysis appears to be underestimated due to a debate on active gold species in AuNPs. The AuNPs catalyzed heterocyclic compound synthesis techniques are environmentally benign and offer numerous benefits, including fasterreaction rates, greater yields, a simplified workup procedure, and catalyst recyclability. It is quite confident that NPs catalyzed reactions have enormous potential for the synthesis of various heterocycles and will attract organic chemists' interest. In the near future, rapid growth in NPs catalyzed reactions is highly desirable.

LIST OF ABBREVIATIONS

AFM	=	Atomic Force Microscopy
AuNPs	=	Gold Nanoparticles
DCM	=	Dichloromethane
EDX	=	Energy-dispersive X-ray
FFT	=	Fast-Fourier Transform
HFIP	=	Hexafluoroisopropyl Alcohol
MNPs	=	Metal Nanoparticles
SEM	=	Scanning Electron Microscopy
TEM	=	Transmission Electron Microscopy
TON	=	Turnover Number

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

Dr. B. Panda is the Associate Editorial Board Member of Letters in Organic Chemistry.

ACKNOWLEDGEMENTS

I am thankful to City College, Kolkata, for constant help and support. I would like to convey my sincere thanks to Dr. Bhaskar Paul, Dr. Totan Mondal, Mr. Aranya Sarkar, Barnali Roy and Dr. Sujay Nandi for their incessant help.

REFERENCES

[1] Panda, B. *ChemistrySelect,* **2019**, *4*(31), 9143-9164. http://dx.doi.org/10.1002/slct.201900779
[2] Panda, B. *ARKIVOC,* **2019**, *2019*(1), 293-303. http://dx.doi.org/10.24820/ark.5550190.p010.966
[3] Panda, B.; Gooyee, A.K. *Lett. Org. Chem.,* **2021**, *18*(7), 507-512. http://dx.doi.org/10.2174/1570178617999200909114431
[4] Panda, B. *J. Indian Chem. Soc.,* **2019**, *96*, 231-238.
[5] Panda, B.; Sarkar, T.K. *J. Org. Chem.,* **2013**, *78*(6), 2413-2421. http://dx.doi.org/10.1021/jo302545n PMID: 23428314
[6] Thomas, J.M.; Thomas, W.J. *Principles and Practice of Heterogeneous Catalysis,* 2nd ed; Wiley-VCH: Weinheim, **2014**.
[7] Li, L.; Hu, J.; Yang, W.; Alivisatos, A.P. *Nano Lett.,* **2001**, *1*(7), 349-351. http://dx.doi.org/10.1021/nl015559r
[8] Jin, R. *Nanotechnol. Rev.,* **2012**, *1*(1), 31-56. http://dx.doi.org/10.1515/ntrev-2011-0003
[9] Daniel, M.C.; Astruc, D. *Chem. Rev.,* **2004**, *104*(1), 293-346. http://dx.doi.org/10.1021/cr030698+ PMID: 14719978
[10] Rosi, N.L.; Mirkin, C.A. *Chem. Rev.,* **2005**, *105*(4), 1547-1562. http://dx.doi.org/10.1021/cr030067f PMID: 15826019
[11] Isomura, Y.; Narushima, T.; Kawasaki, H.; Yonezawa, T.; Obora, Y. *Chem. Commun. (Camb.),* **2012**, *48*(31), 3784-3786. http://dx.doi.org/10.1039/c2cc30975k PMID: 22430058
[12] Corma, A.; Leyva-Pérez, A.; Sabater, M.J. *Chem. Rev,* **2011**, *111*, 1657-1712.
[13] Hashmi, A.S.K. *Acc. Chem. Res.,* **2014**, *47*, 864-867.
[14] Hashmi, A.S.K. *Chem. Rev.,* **2007**, *107*(7), 3180-3211. http://dx.doi.org/10.1021/cr000436x PMID: 17580975
[15] Pflästerer, D.; Hashmi, A.S.K. *Chem. Soc. Rev.,* **2016**, *45*(5), 1331-1367. http://dx.doi.org/10.1039/C5CS00721F PMID: 26673389
[16] Fürstner, A. *Chem. Soc. Rev.,* **2009**, *38*(11), 3208-3221. http://dx.doi.org/10.1039/b816696j PMID: 19847352
[17] Panda, B.; Sarkar, T.K. *Synthesis,* **2013**, *45*, 817-829. http://dx.doi.org/10.1055/s-0032-1318119

[18] Panda, B.; Sarkar, T.K. *Chem. Commun. (Camb.),* **2010**, *46*(18), 3131-3133. http://dx.doi.org/10.1039/c001277g PMID: 20361097

[19] Panda, B.; Sarkar, T.K. *Tetrahedron Lett.,* **2010**, *51*(2), 301-305. http://dx.doi.org/10.1016/j.tetlet.2009.11.003

[20] Kaur, R.; Bariwal, J.; Voskressensky, L.G.; Van der Eycken, E.V. *Chem. Heterocycl. Compd.,* **2018**, *54*(3), 241-248. http://dx.doi.org/10.1007/s10593-018-2259-1

[21] Dhameliya, T.M.; Donga, H.A.; Vaghela, P.V.; Panchal, B.G.; Sureja, D.K.; Bodiwala, K.B.; Chhabria, M.T. *RSC Advances,* **2020**, *10*, 32740-32820. http://dx.doi.org/10.1039/D0RA02272A PMID: 35516511

[22] Takale, B.S.; Bao, M.; Yamamoto, Y. *Org. Biomol. Chem.,* **2014**, *12*(13), 2005-2027. http://dx.doi.org/10.1039/c3ob42207k PMID: 24525525

[23] Thompson, D.T. *Nano Today,* **2007**, *2*(4), 40-43. http://dx.doi.org/10.1016/S1748-0132(07)70116-0

[24] Ren, D.; He, L.; Yu, L.; Ding, R.S.; Liu, Y.M.; Cao, Y.; He, H.Y.; Fan, K.N. *J. Am. Chem. Soc.,* **2012**, *134*(42), 17592-17598. http://dx.doi.org/10.1021/ja3066978 PMID: 23020578

[25] Climent, M.J.; Corma, A.; Iborra, S.; Martínez-Silvestre, S. *ChemCatChem,* **2013**, *5*(12), 3866-3874. http://dx.doi.org/10.1002/cctc.201300416

[26] Kumar, S.; Sharma, S.; Das, P. *Adv. Synth. Catal.,* **2016**, *358*(18), 2889-2894. http://dx.doi.org/10.1002/adsc.201600199

[27] Vilhanová, B.; van Bokhoven, J.A.; Ranocchiari, M. *Adv. Synth. Catal.,* **2017**, *359*(4), 677-686. http://dx.doi.org/10.1002/adsc.201601147

[28] Ye, R.; Zhukhovitskiy, A.V.; Kazantsev, R.V.; Fakra, S.C.; Wickemeyer, B.B.; Toste, F.D.; Somorjai, G.A. *J. Am. Chem. Soc.,* **2018**, *140*(11), 4144-4149. http://dx.doi.org/10.1021/jacs.8b01017 PMID: 29506380

[29] Panda, B.; Albano, G. *Molecules,* **2021**, *26*(24), 7544. http://dx.doi.org/10.3390/molecules26247544 PMID: 34946630

[30] Lal, S.; Snape, T.J. *Curr. Med. Chem.,* **2012**, *19*(28), 4828-4837. http://dx.doi.org/10.2174/092986712803341449 PMID: 22830349

[31] Sharma, V.; Kumar, P.; Pathak, D. *J. Heterocycl. Chem.,* **2010**, *47*, 491-502.

[32] Yamane, Y.; Liu, X.; Hamasaki, A.; Ishida, T.; Haruta, M.; Yokoyama, T.; Tokunaga, M. *Org. Lett.,* **2009**, *11*, 5162-5165. http://dx.doi.org/10.1021/ol902061j PMID: 19905025

[33] Panda, B.; Basak, S.; Hazra, A.; Sarkar, T.K. *J. Chem. Res.,* **2010**, *34*(2), 109-113. http://dx.doi.org/10.3184/030823410X12659067482702

[34] Panda, B.; Bhadra, J.; Sarkar, T.K. *Synlett,* **2011**, 689-693.

[35] Panda, B.; Sarkar, T.K. *Synthesis,* **2013**, *45*, 1227-1234. http://dx.doi.org/10.1055/s-0032-1318454

[36] So, M.H.; Liu, Y.; Ho, C.M.; Lam, K.Y.; Che, C.M. *ChemCatChem,* **2011**, *3*(2), 386-393. http://dx.doi.org/10.1002/cctc.201000312

[37] Climent, M.J.; Corma, A.; Hernández, J.C.; Hungría, A.B.; Iborra, S.; Martínez-Silvestre, S. *J. Catal.,* **2012**, *292*, 118-129. http://dx.doi.org/10.1016/j.jcat.2012.05.002

[38] Bonandi, E.; Christodoulou, M.S.; Fumagalli, G.; Perdicchia, D.; Rastelli, G.; Passarella, D. *Drug Discov. Today,* **2017**, *22*, 1572-1581. http://dx.doi.org/10.1016/j.drudis.2017.05.014 PMID: 28676407

[39] Boominathan, M.; Pugazhenthiran, N.; Nagaraj, M.; Muthusubramanian, S.; Murugesan, S.; Bhuvanesh, N. *ACS Sustain. Chem.& Eng.,* **2013**, *1*, 1405-1411. http://dx.doi.org/10.1021/sc400147r

[40] Perea-Buceta, J.E.; Wirtanen, T.; Laukkanen, O.-V.; Mäkelä, M.K.; Nieger, M.; Melchionna, M.; Huittinen, N.; Lopez-Sanchez, J.A.; Helaja, J. *Angew. Chem. Int. Ed.,* **2013**, *52*, 11835-11839. http://dx.doi.org/10.1002/anie.201305579

[41] Shah, K.; Chhabra, S.; Shrivastava, S.K.; Mishra, P. *Med. Chem. Res.,* **2013**, *22*(11), 5077-5104. http://dx.doi.org/10.1007/s00044-013-0476-9

[42] Jain, A.K.; Paul, A.; Maji, B.; Muniyappa, K.; Bhattacharya, S. *J. Med. Chem.,* **2012**, *55*(7), 2981-2993. http://dx.doi.org/10.1021/jm200860b PMID: 22452380

[43] Tang, L.; Guo, X.; Yang, Y.; Zha, Z.; Wang, Z. *Chem. Commun. (Camb.),* **2014**, *50*(46), 6145-6148. http://dx.doi.org/10.1039/c4cc01822b PMID: 24776805

[44] Schröder, F.; Erdmann, N.; Noël, T.; Luque, R.; Van der Eycken, E.V. *Adv. Synth. Catal.,* **2015**, *357*(14-15), 3141-3147. http://dx.doi.org/10.1002/adsc.201500628

[45] Berrichi, A.; Bachir, R.; Benabdallah, M.; Choukchou-Braham, N. *Tetrahedron Lett.,* **2015**, *56*(11), 1302-1306. http://dx.doi.org/10.1016/j.tetlet.2015.01.132

[46] Symeonidis, T.S.; Lykakis, I.N.; Litinas, K.E. *Tetrahedron,* **2013**, *69*(23), 4612-4616. http://dx.doi.org/10.1016/j.tet.2013.04.026

[47] Carrettin, S.; Blanco, M.C.; Corma, A.; Hashmi, A.S.K. *Adv. Synth. Catal.,* **2006**, *348*(10-11), 1283-1288. http://dx.doi.org/10.1002/adsc.200606099

[48] Hashmi, A.S.K.; Rudolph, M.; Weyrauch, J.P.; Wölfle, M.; Frey, W.; Bats, J.W. *Angew. Chem. Int. Ed.,* **2005**, *44*(18), 2798-2801. http://dx.doi.org/10.1002/anie.200462672

[49] Pagadala, R.; Maddila, S.; Moodley, V.; van Zyl, W.E.; Jonnalagadda, S.B. *Tetrahedron Lett.,* **2014**, *55*(29), 4006-4010. http://dx.doi.org/10.1016/j.tetlet.2014.05.089

[50] Nguyen, N.H.T.; Tran, P.H.; Nguyen, H.T.; Hansen, P.E.; Le, T.N. *ChemistrySelect,* **2017**, *2*(1), 571-575. http://dx.doi.org/10.1002/slct.201601681

[51] Kidonakis, M.; Kotzabasaki, V.; Vasilikogiannaki, E.; Stratakis, M. *Chemistry,* **2019**, *25*(39), 9170-9173. http://dx.doi.org/10.1002/chem.201901408 PMID: 31106923

[52] Panda, B. *Curr. Microw. Chem.,* **2020**, *7*(3), 166-182. http://dx.doi.org/10.2174/2213335607999200811130113

[53] Librando, I.L.; Mahmoud, A.G.; Carabineiro, S.A.C.; Guedes da Silva, M.F.C.; Maldonado-Hódar, F.J.; Geraldes, C.F.G.C.; Pombeiro, A.J.L. *Catalysts,* **2022**, *12*, 45.

[54] Saridakis, I.; Kidonakis, M.; Stratakis, M. *ChemCatChem,* **2018**, *10*(5), 980-983. http://dx.doi.org/10.1002/cctc.201701526

[55] Lu, Q.; Harmalkar, D.S.; Choi, Y.; Lee, K. *Molecules,* **2019**, *24*(20), 3778. http://dx.doi.org/10.3390/molecules24203778

[56] Zheng, T.; Narayan, R.S.; Schomaker, J.M. *J. Am. Chem. Soc.,* **2005**, *127*, 6946-6947. http://dx.doi.org/10.1021/ja043002i PMID: 15884926

[57] Panda, B. *Asian J. Org. Chem.,* **2018**, *7*(12), 2386-2396. http://dx.doi.org/10.1002/ajoc.201800515

[58] Panda, B. *Tetrahedron Lett.,* **2008**, *49*, 6701-6703. http://dx.doi.org/10.1016/j.tetlet.2008.09.046

[59] Panda, B. *J. Indian Chem. Soc.,* **2018**, *95*, 981-985.

[60] Efe, C.; Lykakis, I.N.; Stratakis, M. *Chem. Commun. (Camb.),* **2011**, *47*(2), 803-805. http://dx.doi.org/10.1039/C0CC03353G PMID: 21069226

[61] Zorba, L.; Kidonakis, M.; Saridakis, I.; Stratakis, M. *Org. Lett.,* **2019**, *21*(14), 5552-5555. http://dx.doi.org/10.1021/acs.orglett.9b01869 PMID: 31283240

[62] Naeimi, H.; Farahnak Zarabi, M. *Appl. Organomet. Chem.,* **2018**, *32*(4), e4225. http://dx.doi.org/10.1002/aoc.4225

[63] Nájera, C.; Sydnes, L.K.; Yus, M. *Chem. Rev.,* **2019**, *119*(20), 11110-11244. http://dx.doi.org/10.1021/acs.chemrev.9b00277 PMID: 31640347

[64] Zantioti-Chatzouda, E.-M.; Kotzabasaki, V.; Stratakis, M. *J. Org. Chem.,* (Article ASAP).

[65] Solas, M.; Muñoz, M.A.; Suárez-Pantiga, S.; Sanz, R. *Org. Lett.,* **2020**, *22*(19), 7681-7687. http://dx.doi.org/10.1021/acs.orglett.0c02892 PMID: 32915582