Taylor & Francis
Taylor & Francis Group

Synthetic Communications

An International Journal for Rapid Communication of Synthetic Organic Chemistry

ISSN: 0039-7911 (Print) 1532-2432 (Online) Journal homepage: https://www.tandfonline.com/loi/lsyc20

Heterogeneous gold(I)-catalyzed cyclization between ynals and amidines: An efficient and practical synthesis of 2,4-disubstituted pyrimidines

Minhua Jiang, Quan Nie & Mingzhong Cai

To cite this article: Minhua Jiang, Quan Nie & Mingzhong Cai (2019): Heterogeneous gold(I)-catalyzed cyclization between ynals and amidines: An efficient and practical synthesis of 2,4-disubstituted pyrimidines, Synthetic Communications, DOI: 10.1080/00397911.2019.1631347

To link to this article: https://doi.org/10.1080/00397911.2019.1631347

Published online: 01 Jul 2019.

Submit your article to this journal

Article views: 18

View Crossmark data

Full Terms & Conditions of access and use can be found at
https://www.tandfonline.com/action/journalInformation?journalCode=lsyc20

SYNTHETIC COMMUNICATIONS®
https://doi.org/10.1080/00397911.2019.1631347

Taylor & Francis
Taylor & Francis Group

Check for updates

Heterogeneous gold(I)-catalyzed cyclization between ynals and amidines: An efficient and practical synthesis of 2,4-disubstituted pyrimidines

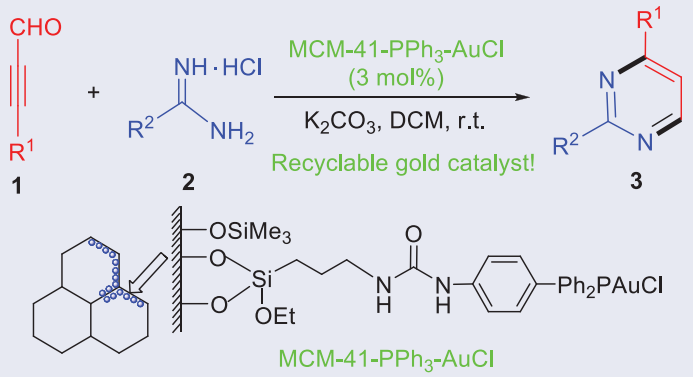
Minhua Jiang[a,b], Quan Nie[a], and Mingzhong Cai[a]

[a]Key Laboratory of Functional Small Organic Molecule, Ministry of Education and College of Chemistry and Chemical Engineering, Jiangxi Normal University, Nanchang, China; [b]School of New Energy Science and Engineering, Xinyu University, Xinyu, China

ABSTRACT

A novel and highly efficient heterogeneous gold(I)-catalyzed cyclization between ynals and amidines has been developed that proceeds smoothly under mild conditions and provides a general and practical method for the synthesis of a wide variety of 2,4-disubstituted pyrimidines with high atom-economy, good to high yield, and recyclability of the gold(I) catalyst. The present method is an attractive alternative to construct substituted pyrimidines.

GRAPHICAL ABSTRACT



ARTICLE HISTORY
Received 16 March 2019

KEYWORDS
Cyclization; gold; heterogeneous catalysis; pyrimidine; ynal

Introduction

Pyrimidine and its derivatives are ubiquitous in biologically active molecules, naturally products, and functional materials.[1] They exhibit a wide range of biological activities, including antibacterial, anticancer, antimycobacterial, anti-inflammatory, and antimalarial.[2] Besides, pyrimidines can be employed as potential candidates for light emitting

CONTACT Mingzhong Cai caimzhong@163.com Key Laboratory of Functional Small Organic Molecule, Ministry of Education and College of Chemistry and Chemical Engineering, Jiangxi Normal University, Nanchang 330022, China.

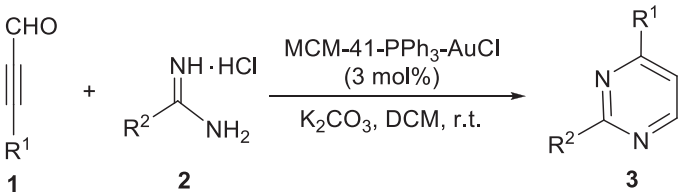
Supplemental data for this article can be accessed on the publisher's website.

Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/lsyc.

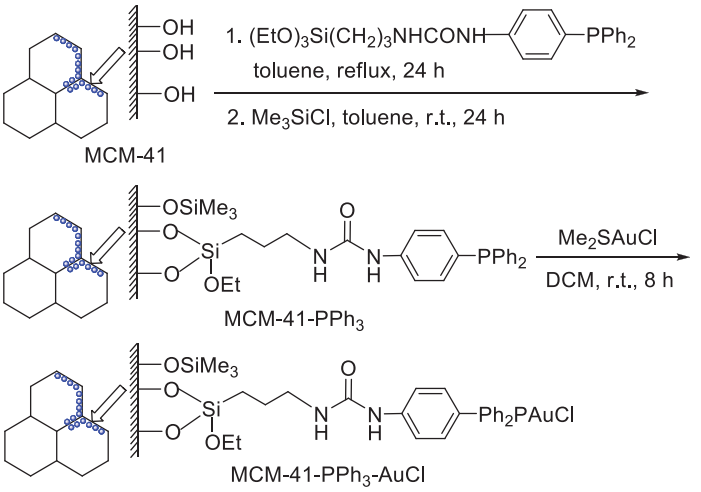
© 2019 Taylor & Francis Group, LLC

devices.[3] In view of their remarkable importance, the synthesis of pyrimidine derivatives has attracted considerable interest from chemists and pharmacologists. Traditionally, pyrimidines could be prepared by the condensation reactions of amidines or amidinium salts with 1,3-dicarbonyl compounds,[4] α,β-unsaturated ketones,[5] and ynones.[6] Recently, transition-metal-catalyzed multicomponent reactions have provided a powerful and useful alternative strategy for the construction of pyrimidines with various catalysts such as Ti,[7] Ir,[8] Mn,[9] Pd,[10] Zn,[11] and Cu.[12] In addition, various other synthetic approaches that do not employ transition metals have also been reported for the construction of pyrimidine derivatives.[13] However, the majority of these methods suffered from some drawbacks such as harsh reaction conditions (microwave irradiation, strong basic conditions), the use of expensive and moisture-sensitive reagents, starting materials that require multistep preparation, expensive catalysts, nonrecyclability of metal catalysts, and less atom efficiency. Therefore, development of an efficient, environmentally benign and atom-economic reaction for the acquisition of pyrimidines from readily available starting materials under mild conditions still represents a continuing challenge.

During the past two decades, homogeneous gold complexes-catalyzed organic reactions have become a highly useful and powerful tool in organic synthesis.[14] Recently, gold-catalyzed syntheses of *N*-heterocyclic compounds such as pyrroles,[15] indoles,[16] oxazoles,[17] and pyrimidines[18] have received much attention because of their high efficiency and mild reaction conditions, which strongly enriched the field of heterocyclic chemistry. However, application of these homogeneous gold complexes in large-scale synthesis or in industry remains a challenge because expensive gold catalysts are difficult to recover from the reaction mixture and are difficult to recycle. Recycling of homogeneous metal catalysts, especially expensive and/or toxic heavy metal complexes, is a task of great economic and environmental importance in the chemical and pharmaceutical industries. Immobilization of the existing homogeneous gold catalysts through covalent bond formation with functional groups on various supports appears to be an attractive solution to this problem.[19] Recently, we reported the synthesis of an MCM-41-immobilized phosphine gold(I) complex [MCM-41-PPh_3-AuCl] and its catalytic performance in the direct C_{sp2}–C_{sp} bond functionalization of arylalkynes through a nitrogenation process to amides.[20] In order to extend the application range of this heterogeneous gold(I) complex, herein we report an efficient heterogeneous gold(I)-catalyzed domino cyclization of ynals and amidines by using MCM-41-PPh_3-AuCl as a recyclable catalyst under mild conditions, providing 2,4-disubstituted pyrimidines in good to high yields (Scheme 1).



Scheme 1. Heterogeneous gold(I)-catalyzed synthesis of 2,4-disubstituted pyrimidines.



Scheme 2. Synthesis of the MCM-41-PPh_3-AuCl catalyst.

Results and discussion

The MCM-41-PPh_3-AuCl catalyst was easily synthesized by a simple procedure from readily available reagents as illustrated in Scheme 2.[20] First, mesoporous MCM-41 was reacted with 1-(4-(diphenylphosphino)phenyl)-3-(3-(triethoxysilyl)propyl)urea in toluene under reflux for 24 h, followed by the silylation with Me_3SiCl in toluene at room temperature for 24 h to give a triphenylphosphine-functionalized MCM-41 material [MCM-41-PPh_3]. Then, the latter underwent a coordination reaction with Me_2SAuCl in dichloromethane (DCM) under mild conditions to provide an MCM-41- immobilized phosphine gold(I) complex [MCM-41-PPh_3-AuCl] as a gray powder. The gold content of the heterogeneous catalyst was found to be 0.37 mmol g^{-1} by ICP-AES analysis.

The MCM-41-immobilized phosphine gold(I) complex [MCM-41-PPh_3-AuCl] was then employed as catalyst for the domino cyclization of ynals and amidines. Initial experiments with 3-phenylpropiolaldehyde **1a** and cyclopropanecarboximidamide **2a** were performed to optimize the reaction conditions, and the results are summarized in Table 1. At first, various bases were tested at 50 °C with DMF as solvent (entries 1–6). The use of Cs_2CO_3 and K_2CO_3 as bases afforded the desired product **3a** in 69% and 73% yields, respectively while NaOH and *t*-BuOK were ineffective, and organic bases such as DBU and Et_3N gave low yields. The reaction did not occur at all without a base (entry 7). We next examined the effect of solvents on the model reaction with K_2CO_3 as base (entries 8-14). When MeCN, DCM, dioxane and toluene were used as solvents, the desired **3a** were obtained in 71-83% yields and DCM was found to be the most efficient (entry 11), whilst other solvents such as DMSO, THF and EtOH were substantially less effective. The optimization of reaction temperature indicated that room temperature is optimal (entries 11, 15, and 16). In the absence of MCM-41-PPh_3-AuCl, the reaction proceeded very slowly and only a trace amount of **3a** was detected (entry 17). When a homogeneous Ph_3PAuCl was used as catalyst, the desired **3a** was also isolated in 86% yield, which indicates that the catalytic activity of MCM-41-PPh_3-AuCl was comparable to that of Ph_3PAuCl (entry 18). Finally, the amount of the catalyst was screened.

Table 1. Cyclization of 3-phenylpropiolaldehyde and cyclopropanecarboximidamide in different conditions.[a]

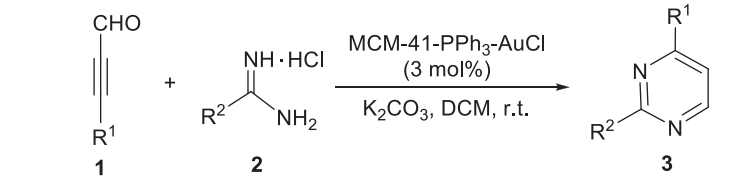
Entry	Base	Solvent	Temp. (°C)	Yield (%)[b]
1	Cs_2CO_3	DMF	50	69
2	K_2CO_3	DMF	50	73
3	NaOH	DMF	50	Trace
4	*t*-BuOK	DMF	50	0
5	DBU	DMF	50	25
6	Et_3N	DMF	50	21
7	–	DMF	50	0
8	K_2CO_3	DMSO	50	61
9	K_2CO_3	MeCN	50	76
10	K_2CO_3	THF	50	65
11	K_2CO_3	DCM	50	83
12	K_2CO_3	Dioxane	50	72
13	K_2CO_3	Toluene	50	71
14	K_2CO_3	EtOH	50	36
15	K_2CO_3	DCM	R.t.	85
16	K_2CO_3	DCM	80	51
17[c]	K_2CO_3	DCM	R.t.	Trace
18[d]	K_2CO_3	DCM	R.t.	86
19[e]	K_2CO_3	DCM	R.t.	59
20[f]	K_2CO_3	DCM	R.t.	86

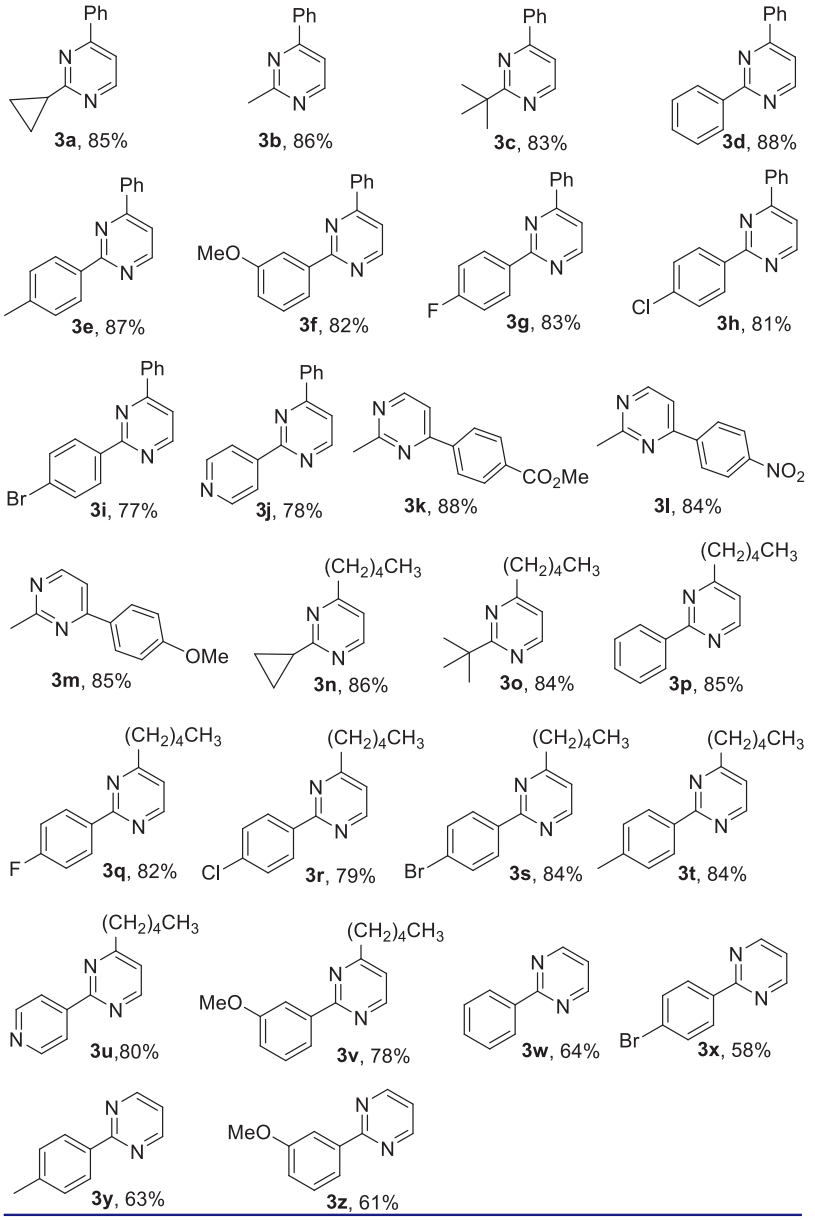
[a]Reaction conditions: **1a** (0.5 mmol), **2a** (0.6 mmol), MCM-41-PPh_3-AuCl (3 mol%), base (1.0 mmol), solvent (3 mL) under Ar for 3 h.
[b]Isolated yield.
[c]Without MCM-41-PPh_3-AuCl.
[d]Ph_3PAuCl (3 mol%) was used instead of 3 mol% of MCM-41-PPh_3-AuCl.
[e]1 mol% of MCM-41-PPh_3-AuCl was used for 12 h.
[f]5 mol% of MCM-41-PPh_3-AuCl was used for 2 h.

Reducing the amount of the catalyst to 1 mol% resulted in a decreased yield and required a longer reaction time (entry 19), whilst increasing the amount of the catalyst to 5 mol% did not enhance the yield significantly (entry 20). Therefore, the optimized reaction conditions for this transformation are the use of 3 mol% of MCM-41-PPh_3-AuCl with K_2CO_3 as base in DCM as solvent at room temperature for 3 h (Table 1, entry 15).

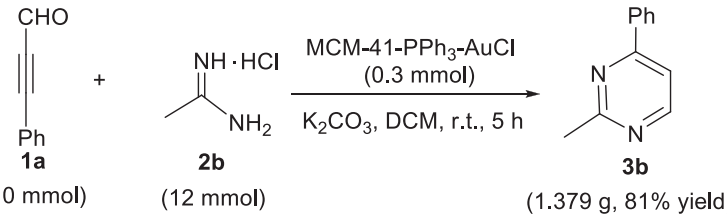
With the optimal reaction conditions in hand, we started to investigate the scope of this heterogeneous gold(I)-catalyzed domino cyclization reaction by using a variety of amidines and various ynals as substrates, and the results are summarized in Table 2. First, 3-phenylpropiolaldehyde **1a** was fixed as the substrate to examine various substituted amidines. Acetimidamide **2b** and pivalimidamide **2c** displayed a similar reactivity with **2a** and the reactions with **1a** proceeded effectively to afford the desired products **3b** and **3c** in 86% and 83% yields, respectively. In addition to alkyl-substituted amidines **2a–2c**, aryl-substituted amidines were also suitable substrates for this heterogeneous gold(I)-catalyzed domino process. For example, the reaction of benzimidamide **2d** with **1a** gave the expected product **3d** in 88% yield. Substituted benzimidamides bearing either an electron-donating or electron-withdrawing group **2e–2i** could also undergo

Table 2. Heterogeneous gold(I)-catalyzed synthesis of pyrimidines.[a,b]





[a]Reaction conditions: **1** (0.5 mmol), **2** (0.6 mmol), MCM-41-PPh_3-AuCl (3 mol%), K_2CO_3 (1.0 mmol), DCM (3 mL) at room temperature under Ar for 3 h.
[b]Isolated yield.

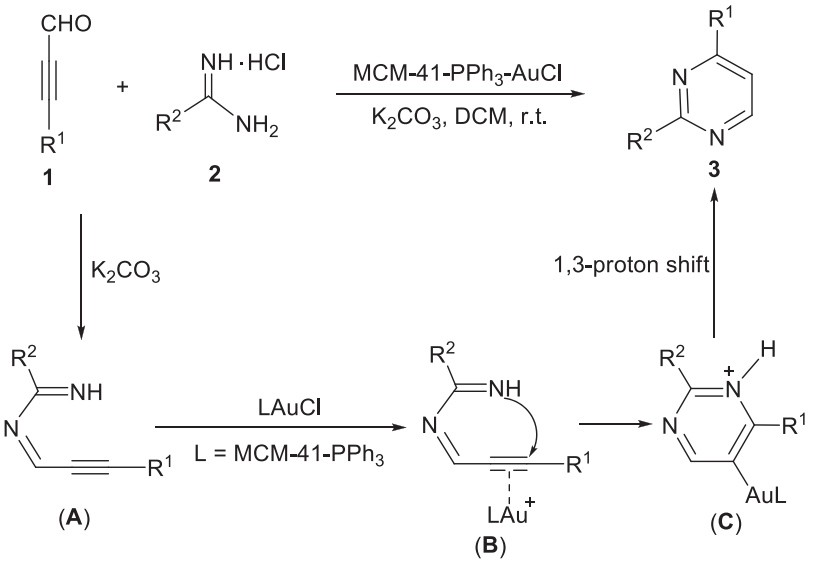


Scheme 3. Heterogeneous gold(I)-catalyzed gram-scale synthesis of 2-methyl-4-phenylpyrimidine (**3b**).

the domino cyclization with **1a** smoothly to provide the corresponding 2,4-disubstituted pyrimidines **3e**-**3i** in 77–87% yields. Notably, a heteroaryl-substituted amidine such as isonicotinimidamide **2j** was also compatible with the standard conditions and furnished the expected product **3j** in 78% yield. Subsequently, 3-arylpropiolaldehydes **1b–1d** and oct-2-ynal **1e** as the substrates were examined and the results are also listed in Table 2. As shown in Table 2, 3-phenylpropiolaldehydes **1b–1d** bearing a strongly electron-withdrawing or electron-donating group could undergo domino cyclization reaction with acetimidamide **2b** effectively to give the corresponding products **3k–3m** in high yields. The reactions of oct-2-ynal **1e** with various alkyl, aryl or heteroaryl-substituted amidines also proceeded smoothly to afford the corresponding 2,4-disubstituted pyrimidines **3n–3v** in 78–86% yields. A range of functional groups including methyl, methoxy, *tert*-butyl, cyclopropyl, fluoro, chloro, bromo, ester, nitro, and pyridyl was well tolerated. Interestingly, when 3-(trimethylsilyl)propiolaldehyde **1f** was employed as the substrate, the cyclization reaction with various aryl-substituted amidines also worked well, but the desilylation products **3w–3z** were obtained in 58–64% yields due to basic conditions. The present method provides a simple, general, and practical route to construct pyrimidine derivatives under mild conditions.

One of the concerns of polymer-bound catalysis reactions is large scale reproduction. In order to demonstrate synthetic utility of the developed methodology, we next attempted gram-scale synthesis of 2-methyl-4-phenylpyrimidine (**3b**) through this heterogeneous gold(I)-catalyzed domino process (Scheme 3). To our delight, the treatment of 3-phenylpropiolaldehyde **1a** (1.302 g, 10 mmol) with acetimidamide hydrochloride **2b** (1.134 g, 12 mmol) in the presence of MCM-41-PPh-AuCl (820 mg, 0.3 mmol) and K_2CO_3 (2.764 g, 20 mmol) in DCM (40 mL) at room temperature under Ar for 5 h afforded the desired **3b** (1.379 g) in 81% yield.

To confirm that the observed catalysis arises from the gold sites on the channel inner walls of MCM-41 and not from the leached gold species in the solution, we carried out the cyclization reaction of 3-phenylpropiolaldehyde **1a** and cyclopropanecarboximidamide **2a** and removed the catalyst from the reaction mixture by filtration at approximately 40% conversion of **1a**. After removal of the MCM-41-PPh_3-AuCl catalyst, the catalyst-free filtrate was again stirred with addition of K_2CO_3 (1.0 equiv.) at room temperature for 2 h. In this case, no significant increase in conversion of **1a** was observed, which demonstrates that leached Au species from the MCM-41-PPh_3-AuCl catalyst are not responsible for the observed conversion. It was also verified by ICP-AES analysis that no gold species could be detected in the filtrate (below 0.2 ppm). These results indicate that the actual catalytic activity should be attributed to MCM-41-PPh_3-AuCl and not to the leached Au species in the solution.



Scheme 4. Proposed catalytic cycle.

A plausible mechanism for the heterogeneous gold(I)-catalyzed cyclization reaction between ynals and amidines is shown in Scheme 4. First, K_2CO_3-promoted dehydration of ynals **1** with amidine hydrochlorides **2** occurs to produce imine intermediate **A**. The coordination of the MCM-41-PPh_3-AuCl catalyst to alkyne moiety in the imine intermediate **A** generates an MCM-41-immobilized alkyne-gold(I) complex intermediate **B**. Then, the latter undergoes an intramolecular nucleophilic attack of nitrogen toward alkyne moiety to give an MCM-41-immobilized vinylgold cation intermediate **C**. Finally, protonolysis of the Au–C bond in intermediate **C** via a 1,3-proton shift affords the target product **3** and regenerates the MCM-41-PPh_3-AuCl catalyst to complete the catalytic cycle.

For the practical application of a heterogeneous precious metal catalyst, it is important to examine its ease of separation, stability and reusability. The MCM-41-PPh_3-AuCl catalyst can be easily separated and recovered by a simple filtration of the product mixture. We next investigated the recycling of the catalyst in the cyclization reaction of 3-phenylpropiolaldehyde **1a** with benzimidamide **2d** under the standard conditions. After completion of the first reaction cycle, the catalyst was separated by a simple filtration and washed with distilled water and ethanol. After being air-dried, it can be reused directly without further purification. The recovered gold catalyst was reused for seven times, and the yield of **3d** in eight consecutive runs was found to be 88, 86, 87, 86, 85, 84, 84, and 83%. In addition, the gold content of the recovered catalyst after eight consecutive runs was determined to be 0.36 mmol g^{-1} by ICP-AES analysis, which revealed a negligible gold leaching.

Conclusions

In summary, we have developed a general, efficient and practical heterogeneous gold(I)-catalyzed intermolecular cyclization of ynals and amidines at room temperature leading to 2,4-disubstituted pyrimidines, which are broadly applicable for the synthesis of

bioactive molecules. The present method has some attractive advantages such as readily available starting materials, straightforward and simple procedure, mild reaction conditions, good yields, and easy recyclability of the catalyst, thereby providing an attractive alternative to construct pyrimidine derivatives.

Experimental

All reagents were obtained from commercial sources and used as received without further purification. All solvents were dried and distilled prior to use. All reactions were conducted under an atmosphere of argon. The products were purified by flash column chromatography on silica gel. A mixture of light petroleum ether and ethyl acetate was generally employed as eluent. ^{1}H NMR and 13C NMR spectra were recorded on a Bruker Avance 400 NMR spectrometer (400 MHz or 100 MHz, respectively) in $CDCl_3$ as solvent with TMS as internal reference. Melting points were determined on a Beijing Tech Instrument Co., LTD X-6 melting point apparatus and are uncorrected. HRMS spectra were recorded on a Q-Tof spectrometer with micromass MS software using electrospray ionization (ESI). Gold content was determined with inductively coupled plasma atom emission Atomscan16 (ICP-AES, TJA Corporation).

Preparation of MCM-41-PPh_3-AuCl[20]

A mixture of the mesoporous MCM-41 (2.1 g) and 1-(4-(diphenylphosphino)phenyl)-3-(3-(triethoxysilyl)propyl)urea (0.788 g, 1.5 mmol) in dry toluene (120 mL) was stirred at 110 °C for 24 h under Ar. The resulting solid product was filtered, washed with $CHCl_3$ (20 mL), and dried in vacuum at 140 °C for 3 h. The dried solid powder was then stirred with Me_3SiCl (3.0 g) in dry toluene (90 mL) at room temperature for 24 h. The resulting product was filtered, washed with acetone (3 × 20 mL), and dried in vacuum at 100 °C for 6 h to afford 2.621 g of triphenylphosphine-functionalized material MCM-41-PPh_3. The phosphine content was determined to be 0.47 mmol g^{-1} by elemental analysis.

In a 100 mL reaction tube, MCM-41-PPh_3 (1.20 g) was mixed with Me_2SAuCl (125 mg, 0.42 mmol) in dry CH_2Cl_2 (40 mL). The reaction mixture was stirred at room temperature for 8 h under Ar. The resulting solid product was filtered, washed with CH_2Cl_2 (2 × 10 mL), and dried at 80 °C in vacuum for 4 h to give 1.175 g of a gray gold(I) complex [MCM-41-PPh_3-AuCl]. The gold content was determined to be 0.37 mmol g^{-1} by ICP-AES.

General procedure for heterogeneous Au(I)-catalyzed synthesis of pyrimidines

A mixture of ynal **1** (0.5 mmol), amidine hydrochloride **2** (0.6 mmol), K_2CO_3 (1.0 mmol), and MCM-41-PPh_3-AuCl (41 mg, 0.015 mmol) in DCM (3 mL) was stirred at room temperature for 3 h (TLC monitored). The resulting mixture was then diluted with ethyl acetate (15 mL) and filtered. The gold catalyst was washed with distilled water (5 mL), and dry ethanol (2 × 5 mL) and reused in the next run. The filtrate was concentrated under reduced pressure and the residue was purified by chromatography on silica gel (eluent: petroleum ether/ethyl acetate) to afford the desired product **3**.

Full experimental detail, characterization data of all compounds. This material can be found via the "Supplementary Content" section of this article's webpage.

Funding

We thank the National Natural Science Foundation of China [No. 21462021], the Natural Science Foundation of Jiangxi Province of China [No. 20161BAB203086] and Key Laboratory of Functional Small Organic Molecule, Ministry of Education [No. KLFS-KF-201704] for financial support.

References

[1] (a) Lagoja, I. M. Pyrimidine as Constituent of Natural Biologically Active Compounds. *Chem. Biodiv.* **2005**, *2*, 1–50. DOI: 1chin.200945113/cbdv.200490173. (b) Walker, S. R.; Carter, E. J.; Huff, B. C.; Morris, J. C. Variolins and Related Alkaloids. *Chem. Rev.* **2009**, *109*, 3080–3098. DOI: 10.1021/cr900032s; (c) Michael, J. P. Quinoline, Quinazoline and Acridone Alkaloids. *Nat. Prod. Rep.* **2005**, *22*, 627–646. DOI: 1chin.200945113/chin.20001826. (d) Petrov, V. F. Pyrimidine as a Structural Fragment in Calamitic Liquid Crystals. *Mol. Cryst. Liq. Cryst.* **2006**, *457*, 121–149. DOI: 10.1080/15421400600598545. (e) Joshi, G.; Nayyar, H.; Kalra, S.; Sharma, P.; Munshi, A.; Singh, S.; Kumar, R. Pyrimidine Containing Epidermal Growth Factor Receptor Kinase Inhibitors: Synthesis and Biological Evaluation. *Chem. Biol. Drug Des.* **2017**, *90*, 995–1006. DOI: 10.1111/cbdd. 13027.

[2] (a) Parker, W. B. Enzymology of Purine and Pyrimidine Antimetabolites Used in the Treatment of Cancer. *Chem. Rev.* **2009**, *109*, 2880–2893. DOI: 10.1021/jm301475f. (b) Shao, H.; Shi, S.; Huang, S.; Hole, A. J.; Abbas, A. Y.; Baumli, S.; Liu, X.; Lam, F.; Foley, D. W.; Fischer, P. M.; et al. Substituted 4-(Thiazol-5-yl)-2-(Phenylamino)Pyrimidines Are Highly Active CDK9 Inhibitors: Synthesis, X-Ray Crystal Structures, Structure–Activity Relationship, and Anticancer Activities. *J. Med. Chem.* **2013**, *56*, 640–659. doi:1chin.200945113/chin.200946269. (c) El-Gazzar, A. R. B. A.; Hafez, H. N. Synthesis of 4-Substituted Pyrido[2,3- *d*]Pyrimidin-4(1H)-One as Analgesic and anti-Inflammatory Agents. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3392–3397. DOI: 10.1016/j.bmcl.2009.05.044. (d) Narayana, B. I.; Rao, A. R. R.; Rao, P. S. Synthesis of New 2-Substituted Pyrido[2,3-*d*]Pyrimidin-4(1)-Ones and Their Antibacterial Activity. *Eur. J. Med. Chem.* **2009**, *44*, 1369–1376. DOI: 10.1016/j.ejmech.2008.05.025. (e) Shipe, W. D.; Sharik, S. S.; Barrow, J. C.; McGaughey, G. B.; Theberge, C. R.; Uslaner, J. M.; Yan, Y.; Renger, J. J.; Smith, S. M.; Coleman, P. J.; Cox, C. D. Discovery and Optimization of a Series of Pyrimidine-Based Phosphodiesterase 10A (PDE10A) Inhibitors through Fragment Screening, Structure-Based Design, and Parallel Synthesis. *J. Med. Chem.* **2015**, *58*, 7888–7894. DOI: 10.1021/acs. jmedchem.5b00983. (f) Lee, S.; Lim, D.; Lee, E.; Lee, N.; Lee, H.; Cechetto, J.; Liuzzi, M.; Freitas-Junior, L. H.; Song, J. S.; Bae, M. A.; et al. Discovery of Carbohybrid-Based 2-Aminopyrimidine Analogues as a New Class of Rapid-Acting Antimalarial Agents Using Image-Based Cytological Profiling Assay. *J. Med. Chem.* **2014**, *57*, 7425–7434. DOI: 10.1021/jm5009693.

[3] (a) Itami, K.; Yamazaki, D.; Yoshida, J. Pyrimidine-Core Extended Pi-Systems: General Synthesis and Interesting Fluorescent Properties. *J. Am. Chem. Soc.* **2004**, *126*, 15396–15397. DOI: 1chin.200945113/chin.200514162. (b) Wong, K.-T.; Hung, T. S.; Lin, Y.; Wu, C.-C.; Lee, G.-H.; Peng, S.-M.; Chou, C.-H.; Su, Y. O. Suzuki Coupling Approach for the Synthesis of Phenylene-Pyrimidine Alternating Oligomers for Blue Light-Emitting Material. *Org. Lett.* **2002**, *4*, 513–516. DOI: 10.1021/ol017066z.

[4] (a) Erian, A. W. The Chemistry of β-Enamino Nitriles as Versatile Reagents in Heterocyclic Synthesis. *Chem. Rev.* **1993**, *93*, 1991–2005. DOI: 1chin.200945113/chin.199403289.

(b) Porcheddu, A.; Giacomelli, G.; De Luca, L.; Ruda, A. M. A "Catch and Release" Strategy for the Parallel Synthesis of 2,4,5-Trisubstituted Pyrimidines. *J. Comb. Chem.* **2004**, *6*, 105–111. DOI: 10.1021/cc034024o.

[5] (a) Vadagaonkar, K. S.; Kalmode, H. P.; Prakash, S.; Chaskar, A. C. Greener [3 + 3] Tandem Annulation-Oxidation Approach towards the Synthesis of Substituted Pyrimidines. *New J. Chem.* **2015**, *39*, 3639–3645. DOI: 10.1039/C4NJ02345E. (b) Guo, W. Base Mediated Direct C-H Amination for Pyrimidines Synthesis from Amidines and Cinnamaldehydes Using Oxygen as Green Oxidants. *Chin. Chem. Lett* **2016**, *27*, 47–50. DOI: 10.1016/j.cclet.2015.09.012.

[6] Bagley, M. C.; Hughes, D. D.; Taylor, P. H. Highly Efficient Synthesis of Pyrimidines under Microwave-Assisted Conditions. *Synlett* **2003**, *2*, 259–261. DOI: 10.1055/s-2003-36781.

[7] Odom, A. L.; McDaniel, T. J. Titanium-Catalyzed Multicomponent Couplings: Efficient One-Pot Syntheses of Nitrogen Heterocycles. *Acc. Chem. Res.* **2015**, *48*, 2822–2833. DOI: 1chin.200945113/chin.201603210.

[8] Deibl, N.; Ament, K.; Kempe, R. A Sustainable Multi-Component Pyrimidine Synthesis. *J. Am. Chem. Soc.* **2015**, *137*, 12804–12807. DOI: 10.1021/jacs. 5b09510.

[9] Deibl, N.; Kempe, R. Manganese-Catalyzed Multicomponent Synthesis of Pyrimidines from Alcohols and Amidines. *Angew. Chem. Int. Ed.* **2017**, *56*, 1663–1666. DOI: 1chin.200945113/anie.201611318.

[10] (a) Guo, W.; Liao, J.; Liu, D.; Li, J.; Ji, F.; Wu, W.; Jiang, H. A Four-Component Reaction Strategy for Pyrimidine Carboxamide Synthesis. *Angew. Chem. Int. Ed.* **2017**, *56*, 1289–1293. DOI: 1chin.200945113/anie.201608433. (b) Karpov, A. S.; Merkul, E.; Rominger, F.; Muller, T. J. J. Concise Syntheses of Meridianins by Carbonylative Alkynylation and a Four-Component Pyrimidine Synthesis. *Angew. Chem. Int. Ed* **2005**, *44*, 6951–6956. DOI: 1chin.200945113/anie. 200501703.

[11] Raj, T.; Sharma, H.; Singh, A.; Aree, T.; Kaur, N.; Singh, N.; Jang, D. O. "Solvent-Less" Mechanochemical Approach to the Synthesis of Pyrimidine Derivatives. *ACS Sustainable Chem. Eng.* **2017**, *5*, 1468–1475. DOI: 10.1021/acssuschemeng.6b02030.

[12] (a) Jalani, H. B.; Cai, W.; Lu, H. Copper-Catalyzed One-Pot Synthesis of Pyrimidines from Amides, N,N′-Dimethylformamide Dimethylacetal, and Enamines. *Adv. Synth. Catal.* **2017**, *359*, 2509–2513. DOI: 1chin.200945113/adsc. 201700234. (b) Su, L.; Sun, K.; Pan, N.; Liu, L.; Sun, M.; Dong, J.; Zhou, Y.; Yin, S.-F. Cyclization of Ketones with Nitriles under Base: A General and Economical Synthesis of Pyrimidines. *Org. Lett.* **2018**, *20*, 3399–3402. DOI: 10.1021/acs.orglett.8b01324.

[13] (a) Anderson, E. D.; Boger, D. L. Inverse Electron Demand Diels-Alder Reactions of 1,2,3-Triazines: pronounced Substituent Effects on Reactivity and Cycloaddition Scope. *J. Am. Chem. Soc.* **2011**, *133*, 12285–12292. DOI: 1chin.200945113/chin.201202150. (b) Wang, R.; Guan, W.; Han, Z.-B.; Liang, F.; Suga, T.; Bi, X.; Nishide, H. Ambient-Light-Promoted Three-Component Annulation: Synthesis of Perfluoroalkylated Pyrimidines. *Org. Lett.* **2017**, *19*, 2358–2361. DOI: 10.1021/acs.orglett.7b00894. (c) Liu, D.; Guo, W.; Wu, W.; Jiang, H. Base-Mediated Three-Component Tandem Reactions for the Synthesis of Multi-Substituted Pyrimidines. *J. Org. Chem.* **2017**, *82*, 13609–13616. DOI: 10.1021/acs.joc. 7b02113. (d) Guo, W.; Li, C.; Liao, J.; Ji, F.; Liu, D.; Wu, W.; Jiang, H. Transition Metal Free Intermolecular Direct Oxidative C–N Bond Formation to Polysubstituted Pyrimidines Using Molecular Oxygen as the Sole Oxidant. *J. Org. Chem.* **2016**, *81*, 5538–5546. DOI: 1chin.200945113/chin.201647185. (e) Kakiya, H.; Yagi, K.; Shinokubo, H. ; Oshima, K. Reaction of Alpha,Alpha- Dibromo Oxime Ethers with Grignard Reagents: Alkylative Annulation Providing a Pyrimidine Core. *J. Am. Chem. Soc.* **2002**, *124*, 9032–9033. DOI: 10.1021/ja 0269284. (f) Movassaghi, M.; Hill, M. D. Synthesis of Substituted Pyridine Derivatives via the Ruthenium-Catalyzed Cycloisomerization of 3-Azadienynes. *J. Am. Chem. Soc.* **2006**, *28*, 14254–14255. DOI: 10.1021/ja060626a. (g) Javorskis, T.; Orentas, E. Chemoselective Deprotection of Sulfonamides under Acidic Conditions: Scope, Sulfonyl Group Migration, and Synthetic Applications. *J. Org. Chem.*

2017, *82*, 13423–13439. DOI: 10.1021/acs.joc.7b02507. (h) Karpov, A. S.; Müller, T. J. J. Straightforward Novel One-Pot Enaminone and Pyrimidine Synthesis by Coupling-Addition-Cycloconden- Sation Sequences. *Synthesis* **2003**, *18*, 2815–2826. DOI: 10.1055/s-2003-42480.

[14] (a) Hashmi, A. S. K.; Hutchings, G. J. Gold Catalysis. *Angew. Chem. Int. Ed.* **2006**, *45*, 7896–7936. DOI: 1chin.200945113/anie.200602454. (b) Hashmi, A. S. K. Gold-Catalyzed Organic Reactions. *Chem. Rev.* **2007**, *107*, 3180–3211. (c) Gorin, D. J.; Sherry, B. D.; Toste, F. D. Ligand Effects in Homogeneous Au Catalysis. *Chem. Rev.* **2008**, *108*, 3351–3378. DOI: 10.1021/cr068430g. (d) Wegner, H. A.; Auzias, M. Gold for C-C Coupling Reactions: A Swiss-Army-Knife Catalyst?. *Angew. Chem. Int. Ed.* **2011**, *50*, 8236–8247. DOI: 1chin.200945113/anie.201101603. (e) Corma, A.; Leyva-Pérez, A.; Sabater, M. J. Gold-Catalyzed Carbon-Heteroatom Bond-Forming Reactions. *J. Chem. Rev.* **2011**, *111*, 1657–1712. DOI: 10.1021/cr100414u. (f) Dorel, R.; Echavarren, A. M. Gold(I)-Catalyzed Activation of Alkynes for the Construction of Molecular Complexity. *Chem. Rev.* **2015**, *115*, 9028–9072. DOI: 1chin.200945113/chin.201545264. (g) Huple, D. B.; Ghorpade, S.; Liu, R. S. Recent Advances in Gold-Catalyzed N- and O-Functionalizations of Alkynes with Nitrones, Nitroso, Nitro and Nitroxy Species. *Adv. Synth. Catal.* **2016**, *58*, 1348–1367. DOI: 1chin.200945113/chin.201627254. (h) Asiri, A. M.; Hashmi, A. S. K. Gold-Catalysed Reactions of Diynes. *Chem. Soc. Rev.* **2016**, *45*, 4471–4503. DOI: 10.1039/C6CS00023A.

[15] (a) Davies, P. W.; Martin, N. Counterion Effects in a Gold-Catalyzed Synthesis of Pyrroles from Alkynyl Aziridines. *Org. Lett.* **2009**, *11*, 2293–2296. DOI: 1chin.200945113/chin.200945113. (b) Ueda, H.; Yamaguchi, M.; Kameya, H.; Sugimoto, K.; Tokuyama, H. Autotandem Catalysis: synthesis of Pyrroles by Gold-Catalyzed Cascade Reaction. *Org. Lett.* **2014**, *16*, 4948–4951. DOI: 10.1002/chin.201512159. (c) Zhu, L.; Yu, Y.; Mao, Z.; Huang, X. Gold-Catalyzed Intermolecular Nitrene Transfer from 2H-Azirines to Ynamides: A Direct Approach to Polysubstituted Pyrroles. *Org. Lett.* **2015**, *17*, 30–33. DOI: 10.1021/ol503172h. (d) Li, X, Chen, M.; Xie, X.; Sun, N.; Li, S.; Liu, Y. Gold-Catalyzed Intermolecular Nitrene Transfer from 2H-Azirines to Ynamides: A Direct Approach to Polysubstituted Pyrroles. *Org Lett.* **2015**, *17*, 2984–2987. DOI: 10.1021/ol503172h. (e) Tokimizu, Y.; Wieteck, M.; Rudolph, M.; Oishi, S.; Fujii, N.; Hashmi, A. S. K.; Ohno, H. H. Dual Gold Catalysis: A Novel Synthesis of Bicyclic and Tricyclic Pyrroles from N-Propargyl Ynamides. *Org. Lett.* **2015**, *17*, 604–607. DOI: 10.1021/ol503623m. (f) Hashmi, A. S. K.; Salathe, R.; Frey, W. Gold Catalysis: Selectivity Problems in Hydroarylations with Pyrroles. *Eur. J. Org. Chem.* **2007**, 1648–1652. DOI: 10.1002/ejoc.200601062.

[16] (a) Shen, C. H.; Li, L.; Zhang, W.; Liu, S.; Shu, S.; Xie, Y. E.; Yu, Y. F.; Ye, L. W. Gold-Catalyzed Tandem Cycloisomerization/Functionalization of in Situ Generated α-Oxo Gold Carbenes in Water. *J. Org. Chem.* **2014**, *79*, 9313–9318. DOI: 10.1021/jo501872h. (b) Matuda, Y.; Naoe, S.; Oishi, S.; Fujii, N.; Ohno, H. Formal [4 + 2] Reaction between 1,3-Diynes and Pyrroles: Gold(I)-Catalyzed Indole Synthesis by Double Hydroarylation. *Chem. Eur. J.* **2015**, *21*, 1463–1467. DOI: 10.1002/chem.201405903. (c) Jin, H.; Huang, L.; Xie, J.; Rudolph, M.; Rominger, F.; Hashmi, A. S. K. Gold-Catalyzed Synthesis of Quinolines from Propargyl Silyl Ethers and Anthranils through the Umpolung of a Gold Carbene Carbon. *Angew. Chem. Int. Ed.* **2016**, *55*, 794–797. 10.1002/anie.201606043. (d) Kaldas, S. J.; Cannillo, A.; McCallum, T.; Barriault, L. Indole Functionalization via Photoredox Gold Catalysis. *Org. Lett.* **2015**, *17*, 2864–2866. DOI: 10.1021/acs.orglett.5b01260. (e) Wang, T.; Shi, S.; Pflästerer, D.; Rettenmeier, E.; Rudolph, M.; Rominger, F.; Hashmi, A. S. K. Synthesis of Polycyclic Indole Skeletons by a Gold(I)-Catalyzed Cascade Reaction. *Chem. Eur. J.* **2014**, *20*, 292–296. DOI: 10.1002/chem.201303539. (f) Hashmi, A. S. K.; Yang, W.; Rominger, F. Gold(I)-Catalyzed Rearrangement of 3-Silyloxy-1,5-Enynes: An Efficient Synthesis of Benzo[b]Thiophenes, Dibenzothiophenes, Dibenzofurans, and Indole Derivatives. *Chem. Eur. J.* **2012**, *18*, 6576–6580. DOI: 10.1002/chem. 201200314.

[17] (a) He, W.; Li, C. W.; Zhang, L. An Efficient [2 + 2 + 1] Synthesis of 2,5-Disubstituted Oxazoles via Gold-Catalyzed Intermolecular Alkyne Oxidation. *J. Am. Chem. Soc.* **2011**, *133*, 8482–8485. DOI: 10.1021/ja2029188. (b) Davies, P. W.; Cremonesi, A.; Dumitrescu, L. Intermolecular and Selective Synthesis of 2,4,5-Trisubstituted Oxazoles by a Gold-Catalyzed Formal [3 + 2] Cycloaddition. *Angew. Chem. Int. Ed.* **2011**, *50*, 8931–8935. DOI: 10.1002/anie.201103563. (c) Luo, Y.; Ji, K.; Li, Y.; Zhang, L. Tempering the Reactivities of Postulated α-Oxo Gold Carbenes Using Bidentate Ligands: Implication of Tricoordinated Gold Intermediates and the Development of an Expedient Bimolecular Assembly of 2,4-Disubstituted Oxazoles. *J. Am. Chem. Soc.* **2012**, *134*, 17412–17415. DOI: 10.1021/ja307948m. (d) Peng, H.; Akhmedov, N. G.; Liang, Y.-F.; Jiao, N.; Shi, X. Synergistic Gold and Iron Dual Catalysis: Preferred Radical Addition toward Vinyl–Gold Intermediate over Alkene. *J. Am. Chem. Soc.* **2015**, *137*, 8912–8915. DOI: 10.1021/jacs.5b05415. (e) Hashmi, A. S. K.; Weyrauch, J. P.; Frey, W.; Bats, J. W. Gold Catalysis: mild Conditions for the Synthesis of Oxazoles from N-Propargylcarboxamides and Mechanistic Aspects. *Org. Lett.* **2004**, *6*, 4391–4394. DOI: 10.1002/chin.200510125. (f) Mai, S.; Rao, C.; Chen, M.; Su, T.; Du, J.; Song, Q. Merging Gold Catalysis, Organocatalytic Oxidation, and Lewis Acid Catalysis for Chemodivergent Synthesis of Functionalized Oxazoles from *N*-Propargylamides. *Chem. Commun.* **2017**, *53*, 10366–10369. DOI: 10.1039/c7cc05746f. (g) Weyrauch, J. P.; Hashmi, A. S. K.; Schuster, A.; Hengst, T.; Schetter, S.; Littmann, A.; Rudolph, M.; Hamzic, M.; Visus, J.; Rominger, F.; et al. Cyclization of Propargylic Amides: Mild Access to Oxazole Derivatives. *Chem. Eur. J.* **2010**, *16*, 956–963. DOI: 10.1002/chem.200902472. (h) Querard, P.; Girard, S. A.; Uhlig, N.; Li, C. J. Gold-Catalyzed Tandem Reactions of Amide-Aldehyde-Alkyne Coupling and Cyclization-Synthesis of 2,4,5-Trisubstituted Oxazoles. *Chem. Sci.* **2015**, *6*, 7332–7335. DOI: 10.1039/c5sc02933c. (i) Reddy, R. J.; Ball-Jones, M. P.; Davies, P. W. Alkynyl Thioethers in Gold-Catalysed Annulations to Form Oxazoles. *Angew. Chem. Int. Ed.* **2017**, *56*, 13310–13313. DOI: 10.1002/anie.201706850. (j) Hashmi, A. S. K.; Blanco Jaimes, M. C.; Schuster, A. M.; Rominger, F. From Propargylic Amides to Functionalized Oxazoles: Domino Gold Catalysis/Oxidation by Dioxygen. *J. Org. Chem.* **2012**, *77*, 6394–6409. DOI: 10.1002/chin.201250130. (k) Bay, S.; Baumeister, T.; Hashmi, A. S. K.; Roder, T. Safe and Fast Flow Synthesis of Functionalized Oxazoles with Molecular Oxygen in a Microstructured Reactor. *Org. Process Res. Dev.* **2016**, *20*, 1297–1304. DOI: 10.1021/acs.oprd.6b00118. (l) Nalivela, K. S.; Rudolph, M.; Baeissa, E. S.; Alhogbi, B. G.; Mkhalid, I. A. I.; Hashmi, A. S. K. Sequential Au/Cu Catalysis: A Two Catalyst One-Pot Protocol for the Enantioselective Synthesis of Oxazole α-Hydroxy Esters viaIntramolecular Cyclization/Intermolecular Alder-Ene Reaction. *Adv. Synth. Catal.* **2018**, *360*, 2183–2190. DOI: 10.1002/adsc. 201800246.

[18] (a) Karad, S. N.; Liu, R.-S. Regiocontrolled Gold-Catalyzed [2 + 2 + 2] Cycloadditions of Ynamides with Two Discrete Nitriles to Construct 4-Aminopyrimidine Cores. *Angew. Chem. Int. Ed.* **2014**, *53*, 9072–9076. DOI: 10.1002/anie.201405312. (b) Zhan, H.; Chen, L.; Tan, J.; Cao, H. Au(I)-Catalyzed Domino Intramolecular Cyclization for the Synthesis of 2,4-Disubstituted Pyrimidines. *Catal. Commun.* **2016**, *73*, 109–112. DOI: 10.1016/j.catcom.2015.10.017.

[19] (a) Corma, A.; Gonzalez-Arellano, C.; Iglesias, M.; Navarro, M. T.; Sanchez, F. Synthesis of Bifunctional Au–Sn Organic–Inorganic Catalysts for Acid-Free Hydroamination Reactions. *Chem. Commun.* **2008**, *2008*, 6218–6220. DOI: 10.1039/b810310k. (b) Corma, A.; Gutierrez-Puebla, E.; Iglesias, M.; Monge, A.; Perez-Ferreras, S.; Sanchez, F. New Heterogenized Gold(I)-Heterocyclic Carbene Complexes as Reusable Catalysts in Hydrogenation and Cross-Coupling Reactions. *Adv. Synth. Catal.* **2006**, *348*, 1899–1907. DOI: 10.1002/adsc.200606163. (c) Villaverde, G.; Corma, A.; Iglesias, M.; Sanchez, F. Heterogenized Gold Complexes: Recoverable Catalysts for Multicomponent Reactions of Aldehydes, Terminal Alkynes, and Amines. *ACS Catal.* **2012**, *2*, 399–406. DOI: 10.1021/cs200601w. (d) Tsupova, S.; Cadu, A.; Carabineiro, S. A. C.; Rudolph, M.; Hashmi, A. S. K. Solid-Supported Nitrogen Acyclic Carbene (SNAC) Complexes of

Gold: Preparation and Catalytic Activity. *J. Catal.* **2017**, *350*, 97–102. DOI: 10.1016/j.jcat.2017.03.013. (e) Carrettin, S.; Blanco, M. C.; Corma, A.; Hashmi, A. S. K. Heterogeneous Gold-Catalysed Synthesis of Phenols. *Adv. Synth. Catal.* **2006**, *348*, 1283–1288. DOI: 10.1002/adsc. 200606099.

[20] Nie, Q.; Yi, F.; Huang, B.; Cai, M. Efficient Heterogeneous Gold(I)-Catalyzed Direct $C(sp^2)$–C(sp) Bond Functionalization of Arylalkynes through a Nitrogenation Process to Amides. *Adv. Synth. Catal.* **2017**, *359*, 3968–3976. DOI: 10.1002/adsc.201700783.