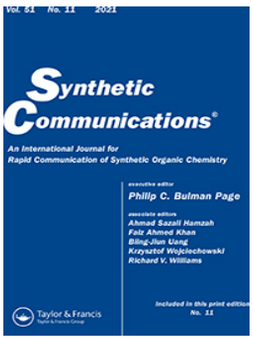

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Heterogeneous gold(I)-catalyzed hydroamination of allenamides with arylamines toward allylamino *E*-enamides

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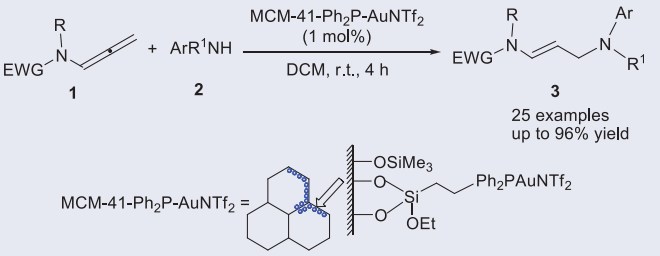
ABSTRACT

A novel and highly efficient heterogeneous gold(I)-catalyzed hydroamination of allenamides with arylamines has been developed that proceeds effectively under mild conditions and offers a general and practical route for the synthesis of allylamino *E*-enamides with good to excellent yields and high stereoselectivity. The supported gold(I) catalyst can be reused at least seven times without any apparent decrease in the catalytic activity.

GRAPHICAL ABSTRACT



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KEYWORDS
Gold; hydroamination; enamide; allenamide; heterogeneous catalysis

Introduction

The enamide moiety, especially the *E*-enamide framework, appears in many natural products[1] and pharmaceuticals with antitumor, antibiotic, anthelmintic, cytotoxic, and antifungal activities.[2] Enamides are also important synthetic intermediates in the construction of heterocycles and amines,[3] and serve as useful substrates in various organic transformations including cycloaddition,[4] cross-coupling/Heck reaction,[5] enantioselective addition,[6] asymmetric hydrogenation/halogenation,[7] and C–H functionalization.[8] The traditional routes to enamides involve the addition of amides to alkynes,[9] condensation of carbonyl groups with amides,[10] acylation of imines,[11] or Curtius rearrangement.[12] These approaches generally lack regioselectivity and/or *E/Z* stereoselectivity and usually require harsh reaction conditions. In recent years, transition metal-catalyzed syntheses of enamides have been well developed including the addition

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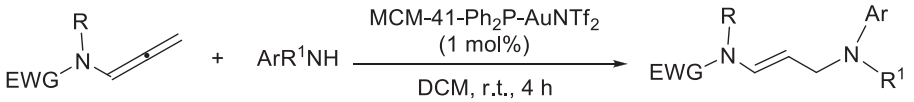


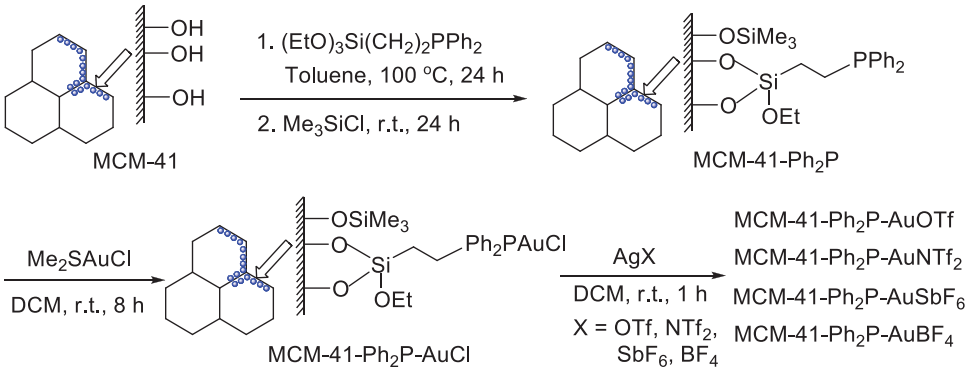
Scheme 1. Heterogeneous gold(I)-catalyzed hydroamination of allenamides with arylamines.

of amides to alkynes,[13] the isomerization of *N*-allylamides,[14] the cross-coupling of amides with vinyl compounds,[15] and the semihydrogenation of ynamides,[16] but problems with functional group tolerance and non-recyclability of metals have persisted.

Gold catalysts have been widely employed in organic synthesis for their unique ability to activate carbon–carbon π bonds, thereby allowing the construction of carbon–carbon and carbon–heteroatom bonds by nucleophilic attack on these activated multiple bonds.[17] Allenamides represent a fascinating and versatile functional group and have been widely applied to various organic reactions including radical cyclizations,[18a] cyclopropanations,[18b] tandem epoxidation/cycloadditions,[18c,d] [4 + 2] and [4 + 3] cycloadditions,[18e–g] Pauson-Khand cyclizations,[18h] palladium-mediated transformations,[18i] acid-catalyzed cyclization/rearrangements,[18j] and base-catalyzed CO_2 capture.[18k] Recently, Kimber *et al.* reported gold(I)-catalyzed nucleophilic addition of electron-rich aromatics or heteroaromatics to allenamides leading to *E*-enamides and hydroamination of allenamides with arylamines toward allylamino *E*-enamides.[19] However, homogeneous gold catalysis suffers from the high cost and non-recyclability of gold catalysts as well as the decay of cationic gold, which restrict their applications in large-scale synthesis and in industry.[20] Recycling of transition metal catalysts, especially expensive and/or toxic heavy metal complexes, still remains an important challenge in the chemical and pharmaceutical industries. Anchoring homogeneous gold complexes through covalent bond formation onto various solid supports appears to be an effective way to solve this problem.[21] Xu and coworkers reported the synthesis of *Z*-enamides through heterogeneous Au/TiO_2-catalyzed stereoselective hydrogenation of ynamides.[22] Recently, we report the synthesis of an MCM-41-anchored diphenylphosphine gold(I) complex [MCM-41-Ph_2P-AuNTf_2] and its successful application to oxidative ring expansion of 2-alkynyl-1,2-dihydropyridines or -quinolines leading to functionalized azepine derivatives under mild conditions.[23] To further expand application range of this heterogeneous gold(I) catalyst, herein, we wish to report an efficient heterogeneous gold(I)-catalyzed intermolecular hydroamination of allenamides with arylamines using the MCM-41-Ph_2P-AuNTf_2 complex as the catalyst toward allylamino *E*-enamides stereoselectively and in good to excellent yields (Scheme 1).

Results and discussion

Several ethyldiphenylphosphine-functionalized MCM-41-anchored gold(I) complexes [MCM-41-Ph_2P-AuX, X = Cl, OTf, NTf_2, SbF_6, and BF_4] were facilely prepared by a simple procedure from commercially available starting materials as depicted in Scheme 2.[23] First, the condensation of mesoporous MCM-41 with commercially available 2-(diphenylphosphino)ethyltriethoxysilane in toluene at reflux, followed by silylation with Me_3SiCl at room temperature generated ethyldiphenylphosphine-functionalized MCM-41 material (MCM-41-Ph_2P). The MCM-41-Ph_2P was then reacted



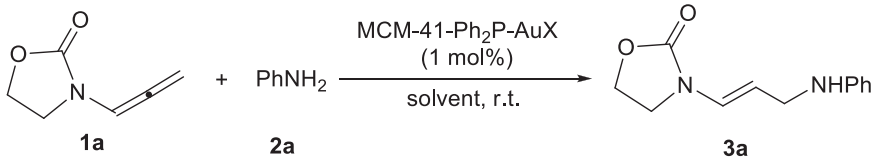
Scheme 2. Preparation of the MCM-41-Ph_2P-AuX complexes.

with Me_2SAuCl in dichloromethane (DCM) at room temperature to provide MCM-41-Ph_2P-AuCl, which was subsequently treated with various silver salts (AgX = AgOTf, $AgNTf_2$, $AgSbF_6$ and $AgBF_4$) in DCM at room temperature to give the ethyldiphenylphosphine-functionalized MCM-41-anchored gold(I) complexes [MCM-41-Ph_2P-AuX, X = OTf, NTf_2, SbF_6 and BF_4] as gray powders.

Initial experiments with 3-(propa-1,2-dienyl)oxazolidin-2-one (**1a**) and aniline (**2a**) were conducted to optimize the reaction conditions, and the results are given in Table 1. At first, various supported gold(I) complexes were used as catalysts at room temperature in 1,2-dichloroethane (DCE) to evaluate their catalytic efficiency (entries 1–5). When MCM-41-Ph_2P-AuCl was used as the catalyst, only a trace of the product **3a** was detected (entry 1). However, changing the counterion (Cl^-) on the gold catalyst to OTf^-, NTf_2^-, SbF_6^-, or BF_4^- has an important influence on the reaction course, as the desired **3a** was obtained in 32–85% yields (entries 2–5) and MCM-41-Ph_2P-$AuNTf_2$ gave the best result (entry 3). The reaction did not occur in the absence of any catalyst (entry 6). Also, the use of $AgNTf_2$ alone as the catalyst did not deliver the desired **3a** (entry 7), which revealing the unique catalytic role of gold catalyst. We next examined the effect of solvents on the model reaction (entries 8–13). Replacement of DCE with MeCN, dichloromethane (DCM), or toluene afforded the desired **3a** in 65–86% yields and DCM was found to be the best option (entry 9), while other solvents such as dioxane, DMF and DMSO were substantially less effective (entries 11–13). Reducing the amount of MCM-41-Ph_2P-$AuNTf_2$ to 0.5 mol% resulted in a slight decrease in the yield of **3a**, but a long reaction time was required (entry 14). When the amount of MCM-41-Ph_2P-$AuNTf_2$ was increased to 3 mol%, the reaction was completed within 2 h, but no improvement in the yield was observed (entry 15). The use of homogeneous $Ph_3PAuNTf_2$ (1 mol%) as the catalyst also delivered the desired **3a** in 86% yield (entry 16), which indicating that the catalytic efficiency of heterogeneous MCM-41-Ph_2P-$AuNTf_2$ was similar to that of homogeneous $Ph_3PAuNTf_2$. Thus, the optimized reaction conditions for this transformation were the use of MCM-41-Ph_2P-$AuNTf_2$ (1 mol%) in DCM as solvent at room temperature for 4 h (entry 9).

For an immobilized precious metal catalyst, it is important to evaluate its ease of separation, stability and recyclability. The MCM-41-Ph_2P-$AuNTf_2$ catalyst can be readily separated and recovered through a simple filtration process. We next examined the

Table 1. Optimization of reaction conditions.[a].



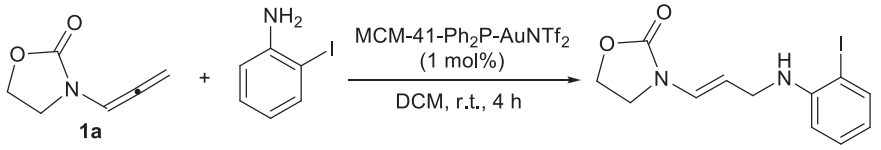
Entry	Catalyst	Solvent	Time (h)	Yield (%)[b]
1	MCM-41-Ph_2P-AuCl	DCE	12	trace
2	MCM-41-Ph_2P-AuOTf	DCE	8	83
3	MCM-41-Ph_2P-$AuNTf_2$	DCE	4	85
4	MCM-41-Ph_2P-$AuSbF_6$	DCE	12	62
5	MCM-41-Ph_2P-$AuBF_4$	DCE	12	32
6	–	DCE	12	0
7	$AgNTf_2$ (5 mol%)	DCE	12	0
8	MCM-41-Ph_2P-$AuNTf_2$	MeCN	5	76
9	MCM-41-Ph_2P-$AuNTf_2$	DCM	4	86
10	MCM-41-Ph_2P-$AuNTf_2$	toluene	8	65
11	MCM-41-Ph_2P-$AuNTf_2$	dioxane	8	54
12	MCM-41-Ph_2P-$AuNTf_2$	DMF	12	18
13	MCM-41-Ph_2P-$AuNTf_2$	DMSO	12	13
14[c]	MCM-41-Ph_2P-$AuNTf_2$	DCM	10	81
15[d]	MCM-41-Ph_2P-$AuNTf_2$	DCM	2	85
16	$Ph_3PAuNTf_2$ (1 mol%)	DCM	4	86

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (0.55 mmol), solvent (3.0 mL), and room temperature.
[b]Isolated yield.
[c]The gold catalyst (0.5 mol%) was used.
[d]The gold catalyst (3 mol%) was used.

recycling of the gold(I) catalyst in the hydroamination reaction of 3-(propa-1,2-dienyl)oxazolidin-2-one (**1a**) with 2-iodoaniline and the results are provided in Table 2. After completion of the hydroamination reaction, the gold(I) catalyst was recovered by filtration of the reaction solution, followed by washing with acetone. After being air-dried, the recovered catalyst can be reused directly without further purification. The recovered gold catalyst was used in the next cycle, and almost the same yield was obtained for eight consecutive runs. In addition, the gold content of the recovered catalyst after eight consecutive cycles was measured to be 0.36 mmol g^{-1} by ICP-AES analysis, which showing almost the consistent gold content as the fresh one (0.37 mmol g^{-1}). Compared with previously reported approach,[19b] the current method has significant advantages of easy separation from the product and excellent recyclability of the heterogeneous gold(I) catalyst.

Having established the optimum reaction conditions, we started to explore the scope of this heterogeneous gold(I)-catalyzed intermolecular hydroamination by using a variety of arylamines and various allenamides as substrates, and the results are listed in Table 3. *para*- or *meta*-Substituted anilines **2b–2f** bearing either electron-withdrawing or electron-donating groups successfully added to allenamide **1a** to give the corresponding *E*-enamides **3b–3f** in 61–95% yields. The results indicated that the electronic nature of substituents on anilines has a limited influence on the heterogeneous gold(I)-catalyzed hydroamination reaction. Sterically hindered *ortho*-substituted anilines **2g–2j** also participated in the hydroamination reaction effectively to afford the desired *E*-enamides **3g–3j** in 82–96% yields. Notably, a heteroarylamine **2k** was compatible in the reaction,

Table 2. Recycle of the MCM-41-Ph_2P-$AuNTf_2$ catalyst.[a].



1a

Entry	Gold catalyst	Yield[b] (%)	Entry	Gold catalyst	Yield[b] (%)
1	Fresh	96	5	Recycle 4	95
2	Recycle 1	95	6	Recycle 5	93
3	Recycle 2	95	7	Recycle 6	94
4	Recycle 3	94	8	Recycle 7	93

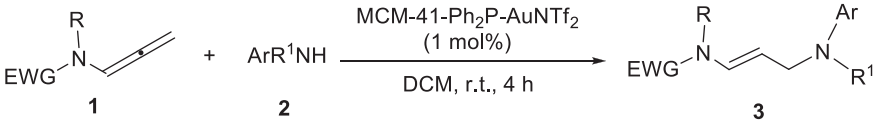
[a]Reaction conditions: **1a** (0.5 mmol), 2-iodoaniline (0.55 mmol), MCM-41-Ph_2P-$AuNTf_2$ (1 mol%), DCM (3.0 mL), room temperature, 4 h.
[b]Isolated yield.

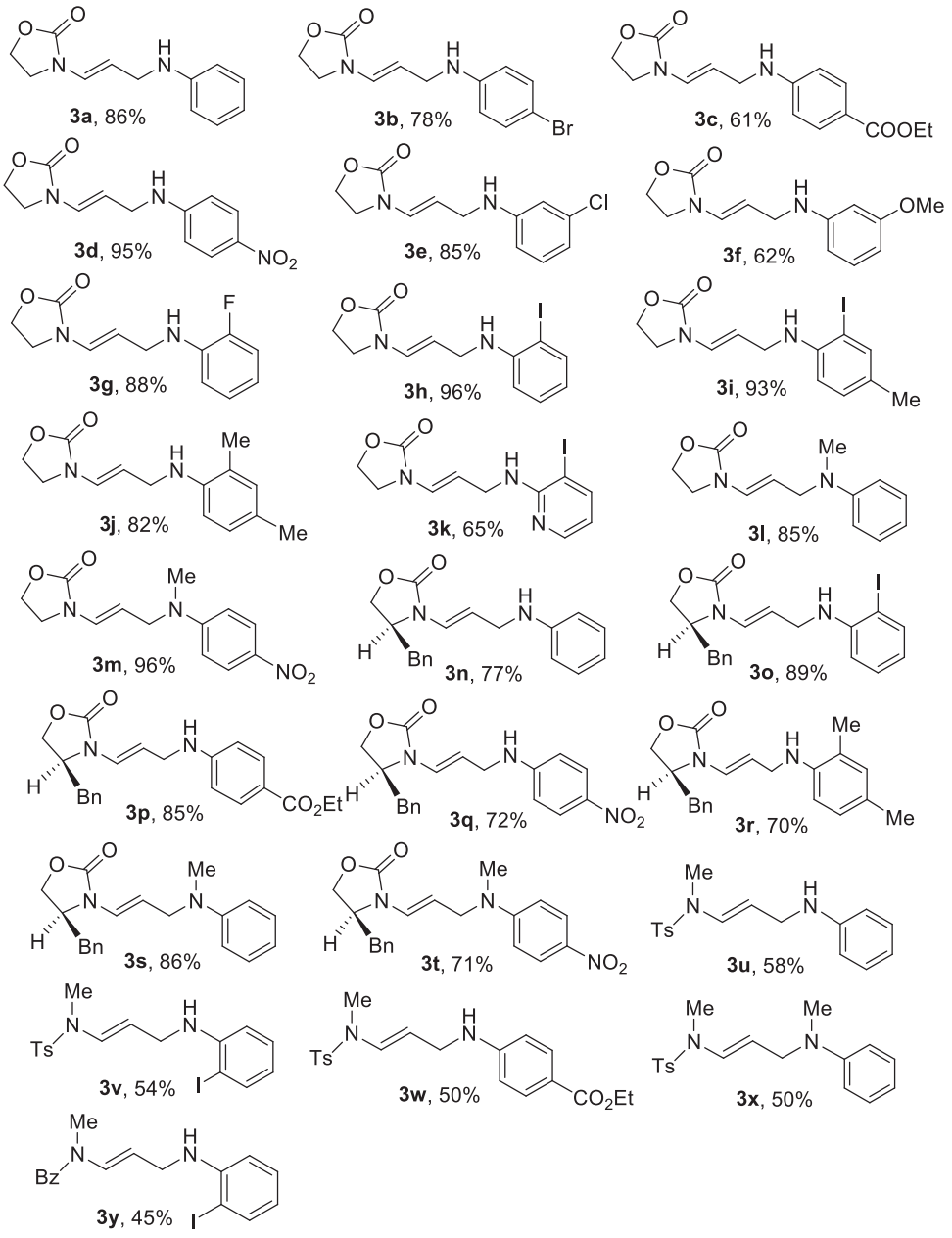
thereby providing the expected product **3k** in a moderate yield of 65%. When *N*-methylanilines **2l–2m** were used as substrates, the reaction proceeded smoothly to give the corresponding *N*-methylenamides **3l–3m** in 85–96% yields. A wide range of functional groups such as methyl, methoxy, fluoro, chloro, bromo, iodo, nitro and ester were tolerated well.

We next performed the hydroamination reaction with chiral and acyclic allenamides as substrates under the optimized conditions, and the results are also summarized in Table 3. Chiral allenamide **1b** could undergo hydroamination with electron-nuetral, electron-deficient or electron-rich anilines smoothly giving the corresponding chiral enamides **3n–3r** in 70–89% yields. Besides, the reaction of chiral allenamide **1b** with *N*-methylanilines also worked well to deliver the expected chiral *N*-methylenamides **3s–3t** in good yields. Finally, acyclic allenamides **1c** and **1d** also readily participated in the hydroamination reaction with various arylamines, but the desired enamides **3u–3y** were obtained in only moderate yields of 45–58% due to their poorer stability. The stereochemistry of the *E*-enamide double bond was confirmed by their ^{1}H NMR spectra, in which vinyl proton shows a coupling constant of 14.0–14.4 Hz. In order to dismiss the possibility of isomerization from *cis* to *trans*, we also conducted NMR studies of all the products prior to workup, which indicating that no *cis*-isomers were observed in all cases.

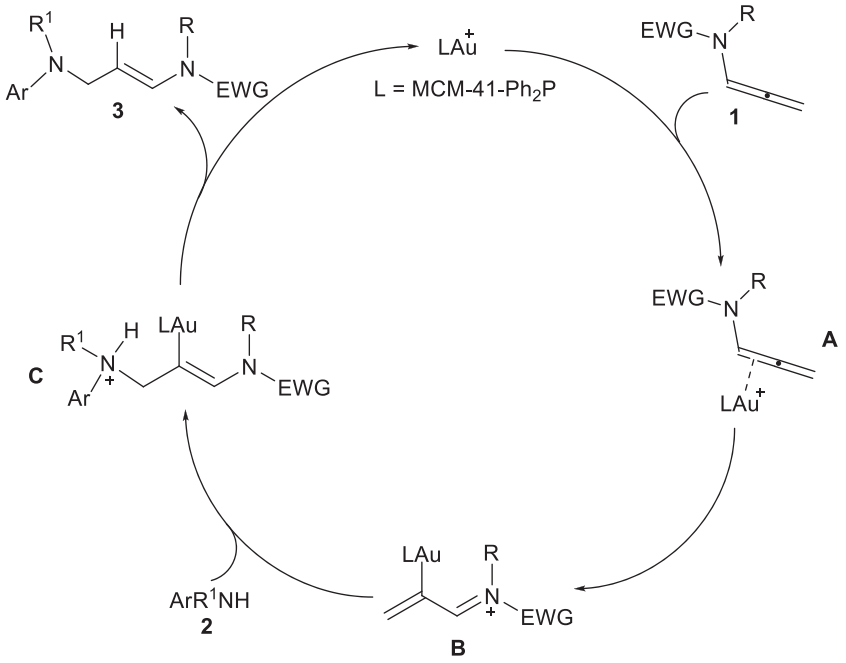
To verify whether the observed hydroamination was due to the heterogeneous MCM-41-Ph_2P-$AuNTf_2$ catalyst or to a soluble gold species leached from this catalyst, we focused on the hydroamination reaction of 3-(propa-1,2-dienyl)oxazolidin-2-one (**1a**) with aniline (**2a**). We filtered off the MCM-41-Ph_2P-$AuNTf_2$ catalyst after 2 h and allowed the catalyst-free filtrate to react further at room temperature for 2 h. It was found that, after removal of the Au catalyst, no increase in the conversion of **1a** was observed, revealing that leached gold species from the catalyst (if any) should not be responsible for the observed transformation. Besides, no gold species could be detected in the clear filtrate based on ICP-AES analysis. These results indicate that the MCM-41-Ph_2P-$AuNTf_2$ complex was stable during the hydroamination and the observed reaction was intrinsically heterogeneous.

Table 3. Heterogeneous gold(I)-catalyzed hydroamination of allenamides with arylamines.[a,b].





[a]Reaction conditions: **1** (0.5 mmol), **2** (0.55 mmol), MCM-41-Ph_2P-$AuNTf_2$ (1 mol%), DCM (3.0 mL), room temperature, 4 h.
[b]Isolated yield.



Scheme 3. Proposed catalytic cycle.

A possible mechanism for this heterogeneous gold(I)-catalyzed hydroamination reaction of allenamides with arylamines is shown in Scheme 3.[19b] First, coordination of the MCM-41-Ph_2P-$AuNTf_2$ complex to allene moiety in allenamides **1** produces an MCM-41-bound gold(I)–allene–π complex intermediate **A**, which is further converted into an MCM-41-bound conjugated vinylgold(I) intermediate **B**. Then intermediate **B** undergoes 1,2-addition with the aniline derivatives **2** to provide intermediate **C**. Finally, the protodeauration of intermediate **C** occurs to afford the desired *E*-enamide **3** and regenerate the gold(I) complex to complete the catalytic cycle.

Conclusions

In summary, we have developed an efficient and practical heterogeneous gold(I)-catalyzed hydroamination of allenamides with arylamines by using the MCM-41-Ph_2P-$AuNTf_2$ complex as the catalyst leading to allylamino *E*-enamides which have the potential to be important building blocks in organic synthesis since they have two valuable functionalities, allyl amines and enamides, within one framework. The current method has some attractive advantages including readily available starting materials, simple procedure, mild reaction conditions, high yields, excellent stereoselectivity, and easy recycle of the gold catalyst, thus offering an attractive alternative to synthesize *E*-enamides.

Experimental

All chemicals were reagent grade and used as purchased. Dichloromethane (DCM) was dried over P_2O_5 and distilled before use. The MCM-41-Ph_2P-$AuNTf_2$ complex was

prepared from commercially easily available materials according to our previous procedure,[23] the gold content was determined to be 0.37 mmol g^{-1} according to the ICP-AES analysis. Cyclic allenamides[24] and acyclic allenamides[25] were prepared by referring to literature methods. The products were purified by flash chromatography on silica gel. Mixture of petroleum ether and EtOAc was generally used as eluent. ^{1}H NMR spectra were recorded on a Bruker Avance 400 MHz spectrometer with TMS as an internal standard in $CDCl_3$ as solvent. ^{13}C NMR spectra (100 MHz) were recorded on a Bruker Avance 400 MHz spectrometer in $CDCl_3$ as solvent. 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).

General procedure for heterogeneous gold(I)-catalyzed hydroamination reaction of allenamides with arylamines

A mixture of allenamide **1** (0.5 mmol), arylamine **2** (0.55 mmol), and MCM-41-Ph_2P-$AuNTf_2$ (14 mg, 0.005 mmol) in DCM (3 mL) was stirred at room temperature for 4 h (TLC monitored). The reaction mixture was diluted with ethyl acetate (5 mL) and filtered. The gold catalyst was washed with acetone (2 × 5 mL), air-dried and reused directly in the next run. The filtrate was concentrated under reduced pressure and purified by flash column chromatography on silica gel (petroleum ether: ethyl acetate = 20:1) to afford the desired *E*-enamide **3**.

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

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