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An efficient heterogeneous gold(I)-catalyzed intermolecular cycloaddition of 2-aminoaryl carbonyls and internal alkynes leading to polyfunctionalized quinolines

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ABSTRACT

The first heterogeneous intermolecular cycloaddition of 2-aminoaryl carbonyls and internal alkynes was realized in DMF at 100°C by using a triphenylphosphine-functionalized MCM-41-supported gold(I) complex [MCM-41-PPh₃-AuCI] and AgOTf as catalysts, yielding a variety of polyfunctionalized quinolines in good to excellent yields. This heterogeneous gold(I) complex could easily be prepared via a simple two-step procedure from commercially available reagents and recovered by filtration of the reaction mixture. The recovered catalyst could be reused at least seven times with almost consistent activity without addition of AgOTf as a cocatalyst.

GRAPHICAL ABSTRACT



KEYWORDS

Cycloaddition; gold; heterogeneous catalysis; internal alkynes; quinoline



Introduction

Quinolines, existing in many biologically active compounds and pharmaceuticals,^[1] are a significant class of annulated six-membered nitrogen heterocycles. Quinoline-containing natural products have many interesting biological activities and are widely used as antibacterial,^[2] antifungal,^[3] antimalarial,^[4] anti-inflammatory,^[5] antiepileptic,^[6]

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analgesic,^[7] and antitumor drugs.^[8] Based on the high importance of quinoline and its derivatives, the development of various methods for their synthesis has attracted great interest. Consequently, many named reactions have been developed, including Skraup,^[9] Doebner-von Miller,^[10] Conrad-Limpach,^[11] Pfitzinger,^[12] and Friedlander concentration syntheses.^[13] However, these classical methods suffer from some drawbacks such as harsh reaction conditions, hazardous reagents in stoichiometric amounts, a limited substrate scope, and poor functional tolerance. Recently, transition metal-catalyzed construction of quinolines was extensively investigated and a variety of transition metals, including Pd,^[14] Rh,^[15] Ru,^[16] Ag,^[17] In,^[18] Co,^[19] Cu,^[20] Fe,^[21] and Ni^[22] salts have been used as catalysts for quinoline synthesis. Besides, metal-free coupling/cyclization strategy has also emerged as one of the most powerful tools for the construction of quinoline framework.^[23] Although significant progress has been achieved for the synthesis of quinoline derivatives, most of these known methods are confined for the lack of generality, the use of non-readily available starting materials, and limited functional group tolerance, especially for the construction of multisubstituted quinolines. Therefore, the development of versatile and efficient methodologies to construct multisubstituted quinoline derivatives from readily available starting materials still remains a demanding goal due to their high significance.

During the past two decades, homogeneous gold-catalyzed organic reactions have become a powerful tool for the preparation of valuable building blocks.^[24] Recently, gold-catalyzed synthesis of heterocyclic compounds, including furans,^[25] pyrroles,^[26] indoles,^[27] oxazoles,^[28] and quinolines^[29] has received much attention because of their high efficiency and mild reaction conditions, which greatly enriched the synthetic methodologies of heterocyclic compounds. However, applications of these homogeneous gold complexes in large-scale synthesis or multistep syntheses remain a challenge because expensive gold catalysts are difficult to separate and are difficult to recycle. In homogeneous catalysis, this problem in part can be avoided by highly active catalysts, which need only low catalyst loadings.^[30] Recycling of homogeneous metal catalysts, especially expensive and/or toxic heavy metal complexes, is a task of great economic and environmental significance in the chemical and pharmaceutical industries. This is achieved for hydroformylation (18 megatonnes yearly volume) for an Rh catalyst on the bulk chemical scale, the same applies to the Karstedt's catalyst (Platinum) for the homogeneous hydrosilylation to form different silicones for technical applications on large scale, too. Both are very efficiently recycled from homogeneous catalysis reactors with minimum loss of metal. Immobilization of the existing homogeneous gold catalysts on various supports appears to be an attractive solution to this problem.^[31] Very recently, we reported the synthesis of a triphenylphosphine-functionalized MCM-41-supported gold(I) complex [MCM-41-PPh₃-AuCl] and found that it is a highly efficient and recyclable catalyst for the direct C_{sp2} - C_{sp} bond functionalization of aryl alkynes through a nitrogenation process to amides with TMSN₃ as a nitrogen source.^[32] In order to further expand the application of this heterogeneous gold(I) catalyst in organic synthesis, herein we report an efficient, heterogeneous Au(I)-catalyzed intermolecular cycloaddition of 2-aminoaryl carbonyls and internal alkynes by using MCM-41-PPh₃-AuCl and AgOTf as catalysts, providing polyfunctionalized quinolines in good to excellent yields (Scheme 1).



Scheme 1. Heterogeneous gold(I)-catalyzed synthesis of polysubstituted quinolines.



Scheme 2. Preparation of MCM-41-PPh₃-AuCl complex.

Results and discussion

The MCM-41-PPh₃-AuCl complex was prepared by a simple two-step procedure from readily available reagents as shown in Scheme 2.^[32] The condensation of mesoporous MCM-41 with 1-(4-(diphenylphosphino)phenyl)-3-(3-(triethoxysilyl)propyl)urea in toluene at 110 °C for 24 h, followed by silylation with Me₃SiCl in toluene at room temperature for 24 h generated a triphenylphosphine-functionalized MCM-41 [MCM-41-PPh₃]. The latter was then reacted with Me₂SAuCl in dichloromethane (DCM) at room temperature for 8 h to afford the MCM-41-supported phosphine gold(I) complex [MCM-41-PPh₃-AuCl] as a gray powder. The gold content of the complex was determined to be 0.39 mmol g⁻¹ by ICP-AES analysis.

The MCM-41-supported phosphine gold(I) complex [MCM-41-PPh₃-AuCl] was then used as a catalyst for the intermolecular cycloaddition of 2-aminoaryl carbonyls and internal alkynes. Initial experiments with 2-aminobenzaldehyde **1a** and ethyl 3-phenylpropiolate **2a** were performed to optimize the reaction conditions, and the results are summarized in Table 1. At first, various heterogeneous gold(I) complexes as catalysts were tested at 100 °C in DMF as solvent (entries 1–6). When MCM-41-PPh₃-AuCl was used as a catalyst, the desired product **3a** was not detected (entry 1). Silver salts as additives have been known to complement gold catalysts by increasing the electrophilicity of the gold center through halide abstraction. When various silver salts such as AgNO₃, AgOTf, AgNTf₂, AgBF₄, and Ag₂CO₃ were used as co-catalysts, AgOTf was the best choice and the desired **3a** was obtained in 86% isolated yield (entry 3), while other silver salts were less effective and Ag₂CO₃ was not effective (entries 2 and 4–6).

	0 H + Ph-	OM	M-41-PPh ₃ -AuCl (10 mol%)	OEt	
	NH ₂	OEt silve	er salt, solvent, temp.	N	Ph
	1a	2a		3a	
Entry	Silver salt (mol%)	Solvent	Temp. (°C)	Time (h)	Yield (%) ^b
1	_	DMF	100	12	0
2	AgNO ₃ (10)	DMF	100	12	8
3	AgOTf (10)	DMF	100	4	86
4	AgNTf ₂ (10)	DMF	100	6	75
5	AgBF ₄ (10)	DMF	100	8	47
6	Ag_2CO_3 (10)	DMF	100	12	0
7 ^c	AgOTf (10)	DMF	100	12	0
8 ^d	_	DMF	100	4	87
9	AgOTf (10)	MeCN	80	12	56
10	AgOTf (10)	THF	67	12	45
11	AgOTf (10)	CH ₂ Cl ₂	45	24	11
12	AgOTf (10)	DMAc	100	12	64
13	AgOTf (10)	DMF	80	8	77
14	AgOTf (10)	DMF	60	12	63
15	AgOTf (10)	DMF	110	3	84
16	AgOTf (5)	DMF	100	12	81
17	AgOTf (20)	DMF	100	2	85
18 ^e	AgOTf (10)	DMF	100	3	87

Table 1. Cycloaddition of 2-aminobenzaldehyde and ethyl 3-phenylpropiolate in different conditions. $^{\rm a}$

^aReaction conditions: 1a (0.5 mmol), 2a (0.75 mmol), MCM-41-PPh₃-AuCl (10 mol%), silver salt (10 mol%), solvent (5 mL), under Ar.

^bIsolated yield.

^cWithout MCM-41-PPh₃-AuCl.

^d10 mol% of MCM-41-PPh₃-AuOTf was used as a catalyst.

^ePh₃PAuCl (10 mol%) was used instead of 10 mol% of MCM-41-PPh₃-AuCl.

When AgOTf alone was used as the catalyst, no reaction was observed (entry 7). These results indicated that the real catalyst for this transformation was MCM-41-PPh₃-AuOTf, generated in situ from MCM-41-PPh₃-AuCl and AgOTf. In order to further confirm that the supported AuOTf is the real catalyst, we prepared MCM-41-PPh₃-AuOTf by the reaction of MCM-41-PPh₃-AuCl with AgOTf in DCM at 25 °C for 0.5 h and employed it as the catalyst, the desired product 3a was isolated in 87% yield after 4 h (entry 8). Our next studies focused on the effect of solvent on the model reaction and a significant solvent effect was observed (entries 9-12). Replacement of DMF with other solvents such as MeCN, THF, and DMAc resulted in decreased yields, and CH_2Cl_2 was less effective, so DMF as a solvent was the most efficient (entry 3). When reaction temperature was reduced to 80 or 60 °C, lower yields were obtained and longer reaction times were required (entries 13 and 14). Raising the temperature to 110 °C also resulted in a slightly decreased yield (entry 15), thus, the reaction temperature was fixed at 100 °C. Finally, the gold catalyst and silver additive loadings were screened. When the loadings were decreased to 5 mol%, a slightly decreased yield of 81% was observed and the reaction time was prolonged to 12 h (entry 16). The increase of the loadings to 20 mol% could shorten the reaction time but did not improve the yield (entry 17). When a homogeneous Ph₃PAuCl (10 mol%)/AgOTf (10 mol%) catalytic system was used, the desired 3a was also isolated in 87% yield (entry 18), indicating that the



 Table 2. Heterogeneous gold(I)-catalyzed cycloaddition of ethyl 3-phenylpropiolate and various 2-aminoaryl carbonyls.^{a,b}

^aReaction conditions: 1 (0.5 mmol), 2a (0.75 mmol), MCM-41-PPh₃-AuCl (10 mol%), AgOTf (10 mol%) in DMF (5 mL) at 100 °C under Ar for 4 h. ^bIsolated yield.

catalytic activity of MCM-41-PPh₃-AuOTf was comparable to that of Ph₃PAuOTf. Therefore, the optimized reaction conditions for this transformation are the use of 10 mol% of MCM-41-PPh₃-AuCl/AgOTf in DMF as solvent at 100 °C for 4h (Table 1, entry 3).

With the optimal reaction conditions (10 mol% of MCM-41-PPh₃-AuCl/AgOTf in DMF at 100 °C for 4 h) in hand, we started to investigate the scope of this heterogeneous gold(I)-catalyzed cycloaddition reaction by using a variety of 2-aminoaryl carbonyls and internal alkynes as substrates. First, the scope of 2-aminoaryl carbonyls was examined with ethyl 3-phenyl propiolate 2a as a substrate. As shown in Table 2, the reaction of 2'-aminoacetophenone 1b with 2a proceeded smoothly under the standard conditions to give the desired product 3b in 91% yield. 2-Aminobenzophenone 1c displayed a similar reactivity with 2'-aminoacetophenone 1b and afforded the target product 3c in 90% yield. 4'-Methyl- or 4'-chloro-substituted 2-amino benzophenones 1d and 1e were also suitable substrates and produced the corresponding products 3d and 3e in 81-87% yields. Notably, bulky (2-aminophenyl)(naphthalene-2-yl)methanone If also reacted well in this transformation, thus providing the expected product 3f in good yield. In addition, 5-halo-substituted 2-amino benzophenones 1 g and 1 h were compatible with the standard conditions and furnished the corresponding products **3g** and **3h** in slightly lower yields than 2-amino benzophenone 1c, presumably due to the presence of electron-withdrawing halo groups, which decreasing the nucleophilicity of amino group.





^aReaction conditions: 1a or 1b (0.5 mmol), 2 (0.75 mmol), MCM-41-PPh₃-AuCl (10 mol%), AgOTf (10 mol%) in DMF (5 mL) at 100 $^{\circ}$ C under Ar for 4 h. ^bIsolated yield.

Under the optimized reaction conditions, we next examined the scope of internal alkynes by using 2-amino benzaldehyde **1a** and 2'-aminoacetophenone **1b** as substrates and the results are summarized in Table 3. The reactions of 2-amino benzaldehyde **1a** with various substituted ethyl 3-phenylpropionates bearing either electron-donating or electron-withdrawing groups **2b-2e** proceeded smoothly under the optimized reaction conditions to give the corresponding quinolines **3i-3l** in 79–92% yields. The reactivity of ethyl 3-phenylpropiolates bearing electron-donating substituents was higher than that of ones bearing electron-withdrawing substituents, but the difference is less significant and good yield was acquired even for ethyl 3-(4-nitrophenyl)propiolate **2e**. Furthermore, bulky ethyl 3-(naphthalen-1-yl)propiolate **2f** also reacted well in this transformation, thus giving the desired product **3m** in 83% yield. In addition, alkyl alkynes displayed a similar reactivity with aryl alkynes. For example, the reaction of ethyl but-2-ynoate **2g** with **1a** gave the expected product **3n** in a high yield of 87%. Besides ethyl propiolates, 4-phenylbut-3-yn-2-one **2h** was also compatible with the

standard conditions and gave the target product **30** in good yield. Subsequently, the reactions of 2'-aminoacetophenone **1b** with various internal alkynes were carried out and the results are also listed in Table 3. As expected, the reactions of 2'-aminoacetophenone **1b** with various ethyl propiolates **2b** and **2d-2g** proceeded smoothly to provide the corresponding polysubstituted quinolines **3p-3t** in good to excellent yields. Notably, the reaction also worked well with alkyl- or cyclopropyl-substituted methyl propiolates **2i** and **2j**, producing the desired quinolines **3u** and **3v** in 88 and 80% yield, respectively. Although 4-phenylbut-3-yn-2-one **2h** and bulky ethyl 3-(naphthalen-1-yl)propiolate **2f** showed a slightly lower reactivity than ethyl 3-phenylpropiolate **2a**, the reactions with 2-amino benzophenone **1c** could proceeded effectively to give the desired products **3w** and **3x** in good yields. The present method provides a facile, general and practical procedure for the construction of polysubstituted quinoline derivatives.

It would be a concern if the leaching of active gold species into the solution is substantial. A hot-filtration experiment^[33] was performed to examine the leaching of gold species from MCM-41-PPh₃-AuOTf. For this, the intermolecular cycloaddition reaction of 2-amino benzaldehyde **1a** and ethyl 3-phenylpropiolate **2a** was carried out until a conversion of approximately 40%. Then the catalyst was removed from the reaction mixture by filtration at the reaction temperature (100 °C) and the catalyst-free solution was again stirred at 100 °C for 4 h. In this case, no significant increase in conversion of **1a** was observed, indicating that leached gold species from the catalyst (if any) are not responsible for the observed activity. It was further confirmed by ICP-AES analysis that no gold species could be detected in the clear solution. These results exclude any contribution to the observed activity from the leached gold species, indicating that MCM-41-PPh₃-AuOTf was stable during the cycloaddition reaction, and the observed catalysis was intrinsically heterogeneous.

A plausible reaction mechanism for this heterogeneous gold(I)-catalyzed intermolecular cycloaddition is shown in Scheme 3. Firstly, coordination of the MCM-41- PPh₃-AuOTf catalyst to internal alkyne 2 and subsequent hydroamination reaction with 2-aminoaryl carbonyl 1 generates an MCM-41-immobilized vinyl gold cation intermediate **A**. Then, intermediate **A** undergoes protonolysis of the Au–C bond via a 1,3-proton shift, followed by recoordination of the gold(I) catalyst to oxygen atom of the carbonyl to provide intermediate **B**. Subsequently, the intramolecular enamine addition of intermediate **B** occurs to produce intermediate **C**, which undergoes 1,5-proton shift to form intermediate **D** and regenerate the gold(I) catalyst. Finally, dehydration of intermediate **D** readily happens to afford the desired quinoline **3**.

From the green and sustainable chemistry point of view, the recyclability of MCM-41-PPh₃-AuOTf was evaluated in the reaction between 2-amino benzaldehyde **1a** and ethyl 3-(4-methoxyphenyl)propiolate **2c** under the optimized conditions. After the first reaction cycle, filtration of the reaction mixture followed by washing of the resulting solid with $NH_3 \cdot H_2O$, distilled water and acetone allowed the easy recovery of the gold(I) catalyst. The recovered catalyst could be recycled up to seven times, and almost the same yield of **3j** was observed (Fig. 1). It is noteworthy that the reaction catalyzed by the recovered catalyst didn't need the addition of AgOTf because the MCM-41-PPh₃-AuCl had been converted into the MCM-41-PPh₃-AuOTf after the first cycle.



Scheme 3. Proposed catalytic cycle.



Figure 1. Recycle of the MCM-41-PPh₃-AuOTf catalyst.

Conclusions

In summary, we have developed a highly efficient heterogeneous gold(I)-catalyzed intermolecular cycloaddition of 2-aminoaryl carbonyls and internal alkynes leading to polyfunctionalized quinolines, which are commonly found in many bioactive molecules. This heterogeneous intermolecular cycloaddition has many attractive features, such as: (1) the substrate scope is broad, and a wide range of 2-aminoaryl carbonyls and internal alkynes are allowed; (2) a variety of quinoline derivatives were obtained in good to excellent yields; (3) this intermolecular cyclization of internal alkynes allowed the efficient integration of more functional groups into quinolines; (4) the heterogeneous gold(I) catalyst can easily be prepared via a simple procedure from commercially available reagents and recovered by filtration of the reaction solution. The recovered catalyst [MCM-41-PPh₃-AuOTf] can be reused at least seven times with almost consistent activity. Our catalytic system not only solves the basic problems of catalyst recovery and recycle but also avoids the use of AgOTf as a co-catalyst in recycling process.

Experimental

All reagents were obtained from commercial sources without further purification, and commercially available solvents were purified by distillation. All reactions were conducted under an atmosphere of argon. The products were purified by flash chromatography on silica gel. Mixture of EtOAc and light petroleum ether was generally used as eluent. ¹H NMR and ¹³C NMR spectra were recorded on a Bruker Avance 400 MHz spectrometer with TMS as an internal standard in CDCl₃ as a 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).

Preparation of MCM-41-PPh₃-AuCl

To a suspension of the mesoporous MCM-41 (2.1 g) in dry toluene (120 mL) was added 1-(4-(diphenylphosphino)phenyl)-3-(3-(triethoxysilyl)propyl)urea (0.788 g, 1.5 mmol).^[32] The mixture was then stirred at 110 °C for 24 h under Ar. The resulting solid material was filtered, washed with CHCl₃ (20 mL), and dried in vacuum at 140 °C for 3 h. The dried solid powder was then soaked in a solution of Me₃SiCl (3.0 g) in dry toluene (90 mL) with stirring 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 hybrid material MCM-41-PPh₃. The phosphine content was found to be 0.47 mmol g⁻¹ by elemental analysis.

In a small Schlenk tube, MCM-41-PPh₃ (1.12 g) was mixed with Me₂SAuCl (125 mg, 0.42 mmol) in dry CH₂Cl₂ (40 mL). The reaction mixture was stirred at room temperature for 8 h under Ar. The resulting solid product was filtered, washed with CH₂Cl₂ (2 × 10 mL), and dried at 80 °C in vacuum for 5 h to afford 1.153 g of a gray gold(I) complex [MCM-41-PPh₃-AuCl]. The gold content was determined to be 0.39 mmol g⁻¹ by ICP-AES.

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

To a solution of 2-aminoaryl carbonyl 1 (0.5 mmol), MCM-41-PPh₃-AuCl (128 mg, 0.05 mmol), AgOTf (12.9 mg, 0.05 mmol) in DMF (5 mL) was added internal alkyne 2 (0.75 mmol) under Ar. The reaction mixture was stirred at 100 °C for 4 h (TLC monitored). The resulting mixture was then diluted with ethyl acetate (20 mL) and filtered. The gold catalyst was washed with $NH_3 \cdot H_2O$ (2 × 5 mL), distilled water (5 mL), and

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acetone $(2 \times 5 \text{ mL})$ and reused in the next run. The filtrate was washed with water $(2 \times 10 \text{ mL})$ and brine $(2 \times 10 \text{ mL})$, and the organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 15/1) to afford the desired product **3**.

The characterization data and copies of ¹H and ¹³C NMR spectra of products **3a-x** have been provided in supplementary material.

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