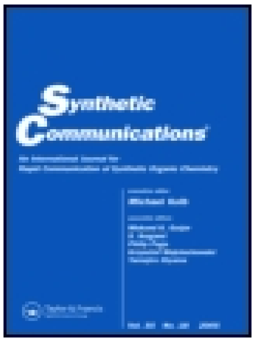

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Heterogeneous gold(I)-catalyzed three-component reaction of aldehydes, alkynes, and orthoformates toward propargyl ethers

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ABSTRACT

A novel and efficient heterogeneous gold(I)-catalyzed three-component reaction of aldehydes, alkynes, and orthoformates has been developed that proceeds smoothly in dichloroethane (DCE) at 83 °C in the presence of 5 mol% magnetic nanoparticles-anchored phosphine gold(I) complex ($Fe_3O_4@SiO_2$-P-AuOTf) and offers a general and practical approach for the preparation of a variety of propargyl ethers with good yields. This heterogeneous gold(I) catalyst can be facilely recovered by simply applying an external magnetic field and recycled at least eight times without any apparent decrease in the catalytic efficiency.

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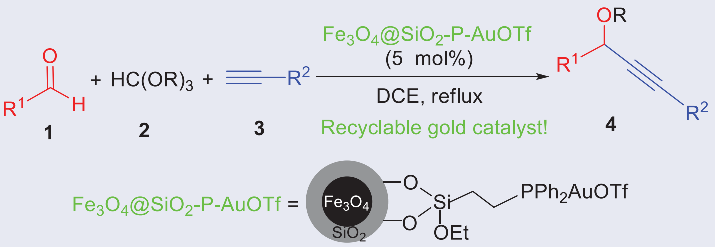
Gold; heterogeneous catalysis; magnetic nanoparticles; propargyl ether; three-component reaction

GRAPHICAL ABSTRACT



Introduction

Development of catalytic carbon–carbon bond-forming reactions by additions to C=O or C=N is of great importance in modern organic synthesis. In this context, metal alkynilides are a class of versatile nucleophiles that can react with a wide range of electrophiles.[1] The traditional methods for the generation of metal alkynilides involve the reaction of terminal alkynes with organolithium or organomagnesium reagents.[2] The alkyne deprotonation for the formation of metal alkynilides must be carried out as a separate step owing to the strong nucleophilicity of organolithium or organomagnesium reagents. Therefore, development of catalytic processes that can lead to the generation of reactive transition-metal alkynilides from the corresponding terminal alkynes in situ

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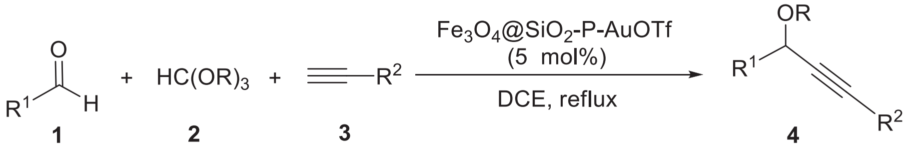
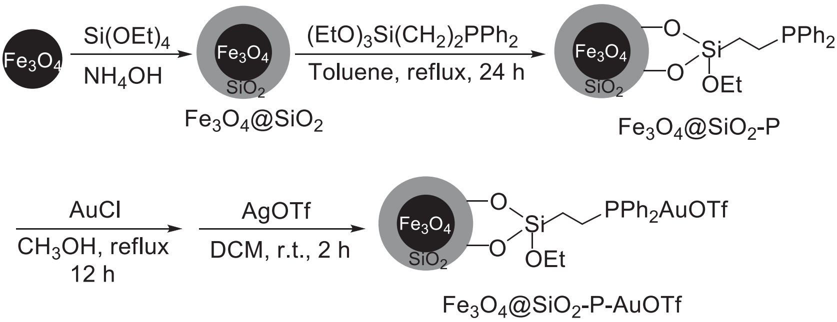
under conditions that are compatible with electrophiles are highly desirable. Carreira et al. reported an efficient addition of terminal alkynes to nitrones in the presence of 10 mol% $Zn(OTf)_2$ and 25 mol% i-Pr_2NEt which involving a catalytic in situ generation of Zn(II)-alkynilides intermediates.[3] Subsequently, a variety of addition reactions of terminal alkynes to various electrophiles have been reported with In,[4] Ru,[5] Rh,[6] Ir,[7] Cu,[8] Fe,[9] Ag,[10] and Hg[11] complexes as catalysts. Recently, gold-catalyzed A^3 coupling reaction of aldehydes, alkynes, and amines has provided a convenient and efficient route to propargylamines.[12] In almost all the reactions, metalated terminal alkynes are considered as reactive intermediates.

In the past decades, homogeneous Au(I) or Au(III) complexes have proven to be highly efficient catalysts for a wide variety of organic transformations involving alkynes, allenes, and alkenes.[13] The majority of these reactions are based on the propensity of gold to serve as a soft and carbophilic Lewis acid in the activation of carbon–carbon π bonds,[14] thus allowing for the construction of carbon–carbon and carbon–heteroatom bonds by nucleophilic attack on these activated multiple bonds. In contrast, the reactions involving gold-alkyne species as nucleophiles have received less attention. Li et al. have developed a gold(I)-catalyzed cascade addition/cyclization of terminal alkynes with *ortho*-alkynylaryl aldehydes leading to 1-alkynyl-1*H*-isochromenes. A gold alkynilide species is suggested as the reactive intermediate which adds to C=O bond of aldehyde.[15] Wang et al. reported a $AuCl_3$/CuBr-catalyzed three-component reaction of aldehydes, alkynes, and amines toward quinoline derivatives through a sequential catalytic process, which involving initial formation of propargylamine via nucleophilic addition of gold acetylide species to C=N bond.[16] Zhang and coworkers reported a Au(III)-catalyzed acyl migration of propargylic esters in which the intramolecular attack of nuceleophilic Au(III)–C(sp^2) to C=O bond is proposed as the key step.[17] These results demonstrate that the nucleophilicity of Au–C bond can be utilized in the construction of C–C bond. In addition, gold-catalyzed reaction of terminal alkynes with benzyl trichloroacetimidates and the three-component reaction of aldehydes, alkynes, and triethyl orthoformate have been reported by Wang and coworkers.[18]

However, in almost all cases, homogeneous gold(I) or gold(III) catalysts were used in the reactions involving gold-alkyne species. The non-recyclability of expensive homogeneous gold catalysts and the decay of cationic gold greatly restrict their application in large-scale synthesis.[19] Therefore, development of highly efficient and recyclable heterogeneous gold catalysts for use in such transformations is highly desirable. In this regard, magnetic nanoparticles-supported catalysts are a better choice because of their facile magnetic separation which efficiently prevents loss of the catalyst and improves the reusability.[20] Recently, we reported the synthesis of a magnetic nanoparticles-anchored phosphine gold(I) complex [Fe_3O_4@SiO_2-P-AuOTf] and its successful application to ring expansion of unactivated alkynylcyclo-propanes.[21] In order to expand the application range of this heterogeneous gold(I) catalyst, herein, we wish to report an efficient heterogeneous gold(I)-catalyzed three-component reaction of aldehydes, alkynes, and orthoformates using the Fe_3O_4@SiO_2-P-AuOTf complex as a recyclable gold(I) catalyst (Scheme 1), providing a novel and practical route to propargyl ethers which are important structural motifs that can serve as intermediates in many organic transformations.[22]



Scheme 1. Heterogeneous gold(I)-catalyzed three-component reaction of aldehydes, alkynes, and orthoformates.



Scheme 2. Preparation of the $Fe_3O_4@SiO_2$-P-AuOTf catalyst.

Results and discussion

The $Fe_3O_4@SiO_2$-P-AuOTf catalyst was easily prepared by a simple procedure from commercially easily available starting materials according to our previously reported method,[21] as illustrated in Scheme 2. The content of gold was found to be 0.38 mmol g^{-1} based on ICP-AES analysis. The oxidation states of gold in the fresh $Fe_3O_4@SiO_2$-P-AuOTf complex and the used catalyst were determined by X-ray photoelectron spectroscopy (XPS). The XPS of the fresh $Fe_3O_4@SiO_2$-P-AuOTf (Figure 1a) showed that the pair at 85.0 and 88.7 eV can be assigned as the spin orbit coupling of Au $4f^{7/2}$ and Au $4f^{5/2}$, respectively, of Au(I).[23]

The magnetically separable nanocomposite $Fe_3O_4@SiO_2$-P-AuOTf was then used as catalyst for the three-component reaction of aldehydes, alkynes, and orthoformates. Initial experiments with benzaldehyde (**1a**), triethyl orthoformate (**2a**) and phenylacetylene (**3a**) were performed to optimize the reaction conditions, and the results are summarized in Table 1. At first, the effect of reaction temperature on the model reaction was examined in the presence of 5 mol% $Fe_3O_4@SiO_2$-P-AuOTf with DCE as the solvent (entries 1–5). The reaction did not occur at room temperature or 40 °C. When the reaction was carried out at reflux temperature, the desired product **4a** was isolated in 85% yield (entry 4), whilst other temperatures such as 65 or 100 °C were substantially less effective. The use of $Fe_3O_4@SiO_2$-P-AuCl as catalyst did not give the desired **4a**, which indicating the important role of the counterion ($^{-}$OTf) (entry 6). When homogeneous Ph_3PAuCl/AgOTf system was used as catalyst, the desired product **4a** was also isolated in 87% yield (entry 7), while the use of AgOTf alone as catalyst was ineffective (entry 8). These results indicated that the catalytic efficiency of $Fe_3O_4@SiO_2$-P-AuOTf was comparable to that of Ph_3PAuCl/AgOTf system. We next checked the effect of solvents on the reaction (entries 9–12). When the reaction was performed in benzene or toluene, the product **4a** was also obtained in good yields (entries 9 and 10), however,

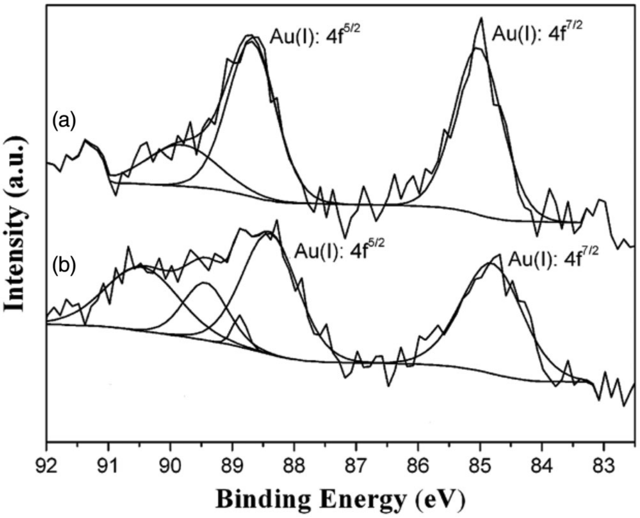
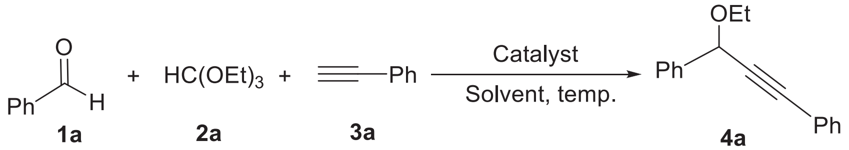


Figure 1. XPS of the fresh $Fe_3O_4@SiO_2$-P-AuOTf complex (a) and the recovered gold catalyst after the 8th run (b).

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

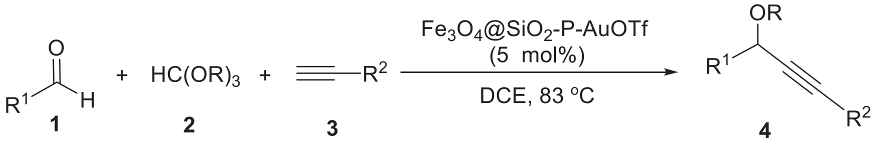


Entry	Catalyst (mol%)	Solvent	Temp (°C)	Time (h)	Yield (%)[b]
1	$Fe_3O_4@SiO_2$-P-AuOTf (5)	DCE	25	24	0
2	$Fe_3O_4@SiO_2$-P-AuOTf (5)	DCE	40	24	Trace
3	$Fe_3O_4@SiO_2$-P-AuOTf (5)	DCE	65	24	46
4	$Fe_3O_4@SiO_2$-P-AuOTf (5)	DCE	83	12	85
5	$Fe_3O_4@SiO_2$-P-AuOTf (5)	DCE	100	12	73
6	$Fe_3O_4@SiO_2$-P-AuCl (5)	DCE	83	24	0
7	Ph_3PAuCl (5)/AgOTf (5)	DCE	83	12	87
8	AgOTf (5)	DCE	83	24	Trace
9	$Fe_3O_4@SiO_2$-P-AuOTf (5)	Benzene	80	12	82
10	$Fe_3O_4@SiO_2$-P-AuOTf (5)	Toluene	83	12	78
11	$Fe_3O_4@SiO_2$-P-AuOTf (5)	MeCN	80	24	56
12	$Fe_3O_4@SiO_2$-P-AuOTf (5)	THF	65	24	52
13	$Fe_3O_4@SiO_2$-P-AuOTf (5)	H_2O	83	24	0
14	$Fe_3O_4@SiO_2$-P-AuOTf (2)	DCE	83	24	61
15	$Fe_3O_4@SiO_2$-P-AuOTf (10)	DCE	83	6	86
16[c]	$Fe_3O_4@SiO_2$-P-AuOTf (5)	DCE	83	12	80

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.6 mmol), **3a** (0.6 mmol) and solvent (3 mL) under Ar. [b] Isolated yield. [c] The reaction was carried out under air.

replacement of DCE with MeCN or THF resulted in lower yields (entries 11 and 12). The reaction in water did not occur at all (entry 13). Reducing the amount of the catalyst to 2 mol% led to a decreased yield and required a longer reaction time (entry 14), while increasing the amount of the catalyst to 10 mol% did not improve the yield significantly (entry 15). When the reaction was carried out under air, the desired **4a** was produced in a slightly lower yield of 80% (entry 16). Hence, the optimal reaction

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



Entry	R^1	R	R^2	*t* (h)	Yield (%)	TON	TOF (h^{-1})
1	C_6H_5 (**1a**)	Et (**2a**)	C_6H_5 (**3a**)	12	**4a**, 85	17.0	1.4
2	C_6H_5 (**1a**)	Me (**2b**)	C_6H_5 (**3a**)	12	**4b**, 87	17.4	1.5
3	4-MeC_6H_4 (**1b**)	Et (**2a**)	C_6H_5 (**3a**)	12	**4c**, 81	16.2	1.4
4	4-$MeOC_6H_4$ (**1c**)	Me (**2b**)	C_6H_5 (**3a**)	18	**4d**, 48	9.6	0.5
5	3-$MeOC_6H_4$ (**1d**)	Et (**2a**)	C_6H_5 (**3a**)	18	**4e**, 83	16.6	0.9
6	3,4-$CH_2O_2C_6H_3$ (**1e**)	Me (**2b**)	C_6H_5 (**3a**)	18	**4f**, 79	15.8	0.9
7	4-ClC_6H_4 (**1f**)	Me (**2b**)	C_6H_5 (**3a**)	12	**4g**, 86	17.2	1.4
8	4-ClC_6H_4 (**1f**)	Et (**2a**)	C_6H_5 (**3a**)	12	**4h**, 84	16.8	1.4
9	4-BrC_6H_4 (**1g**)	Me (**2b**)	C_6H_5 (**3a**)	12	**4i**, 87	17.4	1.5
10	4-BrC_6H_4 (**1g**)	Et (**2a**)	C_6H_5 (**3a**)	12	**4j**, 83	16.6	1.4
11	3-BrC_6H_4 (**1h**)	Me (**2b**)	C_6H_5 (**3a**)	12	**4k**, 82	16.4	1.4
12	3-BrC_6H_4 (**1h**)	Et (**2a**)	C_6H_5 (**3a**)	12	**4l**, 79	15.8	1.3
13	4-$CF_3C_6H_4$ (**1i**)	Et (**2a**)	C_6H_5 (**3a**)	12	**4m**, 77	15.4	1.3
14	2-BrC_6H_4 (**1j**)	Me (**2b**)	C_6H_5 (**3a**)	18	**4n**, 79	15.8	0.9
15	2-MeC_6H_4 (**1k**)	Et (**2a**)	C_6H_5 (**3a**)	18	**4o**, 88	17.6	1.0
16	1-Naphthyl (**1l**)	Me (**2b**)	C_6H_5 (**3a**)	18	**4p**, 82	16.4	0.9
17	2-Naphthyl (**1m**)	Me (**2b**)	C_6H_5 (**3a**)	24	**4q**, 78	15.6	0.7
18	2-Naphthyl (**1m**)	Et (**2a**)	C_6H_5 (**3a**)	24	**4r**, 74	14.8	0.6
19	C_6H_5 (**1a**)	Me (**2b**)	4-ClC_6H_4 (**3b**)	12	**4s**, 75	15.0	1.3
20	C_6H_5 (**1a**)	Et (**2a**)	4-ClC_6H_4 (**3b**)	12	**4t**, 72	14.4	1.2
21	C_6H_5 (**1a**)	Et (**2a**)	4-$MeOC_6H_4$ (**3c**)	12	**4u**, 67	13.4	1.1
22	4-BrC_6H_4 (**1g**)	Me (**2b**)	4-MeC_6H_4 (**3d**)	12	**4v**, 78	15.6	1.3
23	4-BrC_6H_4 (**1g**)	Et (**2a**)	4-ClC_6H_4 (**3b**)	12	**4w**, 82	16.4	1.4
24	C_6H_{11} (**1n**)	Me (**2b**)	4-ClC_6H_4 (**3b**)	24	**4x**, 60	12.0	0.5
25	C_6H_{11} (**1n**)	Et (**2a**)	4-ClC_6H_4 (**3b**)	24	**4y**, 56	11.2	0.5

[a] Reaction conditions: **1** (0.5 mmol), **2** (0.6 mmol), **3** (0.6 mmol), Fe_3O_4@SiO_2-P-AuOTf (5 mol%), and DCE (3 mL) at 83 °C under Ar. [b] Isolated yield.

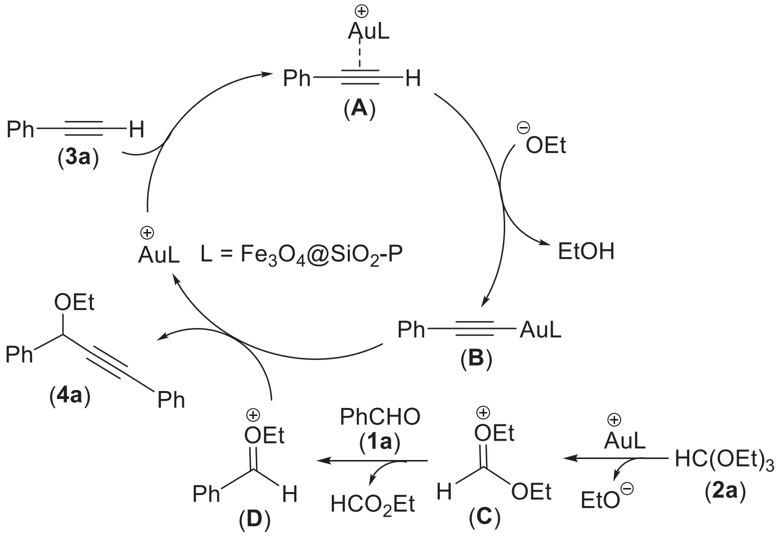
conditions for this transformation are the use of 5 mol% Fe_3O_4@SiO_2-P-AuOTf in DCE as solvent at 83 °C under Ar for 12 h (entry 4).

With the optimal reaction conditions in hand, we started to examine the scope of this heterogeneous gold(I)-catalyzed three-component reaction by using a series of aldehydes and terminal alkynes as substrates. The results are summarized in Table 2. For a wide range of 3- or 4-substituted benzaldehydes bearing either electron-donating or electron-withdrawing groups **1b** and **1d–i**, the reactions with phenylacetylene **3a** and orthoformates **2a** or **2b** proceeded smoothly to give the corres-ponding propargylation products **4c** and **4e–m** in good to high yields (entries 3 and 5–13). In the case of 4-methoxybenzaldehyde **1c** as substrate, the desired product **4d** was obtained in only 48% yield and 1,5-diphenyl-3-(4-methoxyphenyl)pent-1,4-diyne as by-product was also isolated in 39% yield (entry 4). When aromatic aldehydes with a strong electron-withdrawing group such as 4-nitrobenzaldehyde and 4-cyanobenzaldehyde were used as substrates, the formation of a complex mixture was observed. The sterically hindered 2-substituted benzaldehydes **1j** and **1k** were also suitable substrates and afforded the desired addition products **4n** and **4o** in 79 and 88% yield, respectively (entries 14 and 15). Besides, bulky 1-naphthaldehyde **1l** and 2-naphthaldehyde **1m** were compatible with the standard conditions and gave the expected products **4p–r** in 74–82% yields (entries 16–18). However, when aliphatic aldehydes such as butyraldehyde and heptanal were used as substrates, no desired addition products were detected. We also checked the possibility of reaction using ketones as substrates, but ketones such as acetone and acetophenone were not reactive in this transformation, and the reaction did not occur at all. In addition to phenylacetylene, electron-deficient or electron-rich arylacetylenes **3b–d** also proven to be good substrates and underwent the three-component reaction effectively with various aromatic aldehydes and orthoformates to furnish the corresponding propargylation products **4s–w** in good yields (entries 19–23). Unfortunately, aliphatic terminal alkynes such as 1-hexyne and ethynylcyclohexane were not suitable substrates and no reaction was observed. Notably, secondary cyclohexanecarbaldehyde **1n** could react with 4-chlorophenylacetylene **3b** effectively and afforded the expected products **4x–y** in 56–60% yields (entries 24 and 25).

To verify that the high activity of $Fe_3O_4@SiO_2$-P-AuOTf results from the gold sites on the surface of the magnetic nanoparticles and not from the soluble Pd species leached from $Fe_3O_4@SiO_2$-P-AuOTf, the heterogeneity of the catalyst was confirmed by hot filtration test. For this, the three-component reaction of benzaldehyde (**1a**), triethyl orthoformate (**2a**) and phenylacetylene (**3a**) was carried out until an approximately 40% conversion of **1a**. Then the $Fe_3O_4@SiO_2$-P-AuOTf catalyst was separated magnetically from the solution at 83 °C and the solution was transferred to another reaction tube and stirred again at 83 °C for 12 h. It was found that no increase in conversion of benzaldehyde (**1a**) was observed in the clear solution, demonstrating that the observed high activity was not related to the soluble Au species leached from $Fe_3O_4@SiO_2$-P-AuOTf. Besides, no Au species could be detected in the clear solution based on ICP-AES analysis. The above results confirm the fact that the $Fe_3O_4@SiO_2$-P-AuOTf catalyst is stable during the reaction and supports heterogeneous nature of the three-component reaction.

A possible mechanism for this heterogeneous gold(I)-catalyzed three-component reaction of aldehydes, alkynes, and orthoformates is illustrated in Scheme 3.[18b] First, coordination of the $Fe_3O_4@SiO_2$-P-AuOTf complex to phenylacetylene **3a** produces an $Fe_3O_4@SiO_2$-bound gold(I)–alkyne–π complex intermediate **A**, which is further transformed into an $Fe_3O_4@SiO_2$-bound gold(I)–alkynilide intermediate **B** with the aid of a base. Under the catalysis of $Fe_3O_4@SiO_2$-P-AuOTf as a Lewis acid, triethyl orthoformate **2a** can form a reactive intermediate **C**, which reacts with benzaldehyde **1a** to generate the oxocarbenium ion intermediate **D**. Subsequent nucleophilic addition of gold(I)–alkynilide intermediate **B** to the C=O bond of oxocarbenium ion intermediate **D** affords the desired product **4a** and regenerates the gold(I) catalyst to complete the catalytic cycle.

For investigation on the reusability of the catalyst, it was recovered by magnetic separation, washed with ethyl acetate and ethanol, dried in air and reused in the next cycle. More than 99% of the catalyst could be recovered by simply fixing a magnetic field near to the reaction tube. For the reaction of 2-methylbenzaldehyde **1k** with phenylacetylene **3a** and triethyl orthoformate **2a**, the supported gold catalyst $Fe_3O_4@SiO_2$-P-AuOTf could be recycled up to eight times without apparent loss of activity, and the yield of **4o** in eight consecutive runs was found to be 88, 87, 85, 86, 85, 85, 84, and



Scheme 3. Proposed catalytic cycle.

83%, respectively. In addition, the content of gold for the recovered gold catalyst after eight consecutive cycles was determined to be 0.37 mmol g^{-1} based on ICP-AES analysis. After the first cycle, the amount of residual gold species in the crude reaction product **4o** was also measured to be 0.4 ppm by ICP-AES analysis, compared with 14.5 ppm for $Ph_3PAuCl/AgOTf$ catalytic system. Thus, gold species leaching into the crude product was not completely eliminated, but appeared to be negligible. Figure 1b shows the XPS of the recycled gold catalyst. The binding energies of Au $4f^{7/2}$ and Au $4f^{5/2}$ of the recovered $Fe_3O_4@SiO_2$-P-AuOTf (after 8th run) are 84.8 and 88.4 eV, respectively, indicating that the oxidation state of gold in the recovered catalyst is still Au(I).

Conclusions

In summary, we have developed an efficient and practical heterogeneous gold(I)-catalyzed three-component reaction of aldehydes, terminal alkynes, and orthoformates leading to propargyl ethers which are important building blocks in organic synthesis. The developed methodology has some attractive advantages such as easily available starting materials, straightforward and simple procedure, mild reaction conditions, good yields, and easy recyclability of the expensive gold catalyst, thus providing an attractive alternative to prepare propargyl ethers.

Experimental

All chemicals were obtained from different commercial sources and used as received without further purification. All solvents were dried and distilled before use. $Fe_3O_4@SiO_2$-P-AuOTf was prepared according to our previously reported method.[21] The products were purified by flash column chromatography on silica gel with a mixture of light petroleum ether and ethyl acetate as eluent. ^1H NMR and ^{13}C 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. 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 Fe_3O_4@SiO_2-P-AuOTf [21]

A mixture of Fe_3O_4@SiO_2 (0.75 g) and 2-(diphenylphosphino)ethyltriethoxysilane (0.57 g) in 40 mL of dry toluene was stirred at reflux under Ar for 24 h. Then the resulting nanoparticles were magnetically separated, washed repeatedly with toluene and CH_2Cl_2 and dried at 90 °C in vacuo for 6 h to give 0.85 g of the diphenyl-phosphine-modified Fe_3O_4@SiO_2 (Fe_3O_4@SiO_2-P) as brown nanoparticles. The content of phosphorus was determined to be 0.44 mmol g^{-1} by elemental analysis.

A mixture of AuCl (80 mg, 0.34 mmol) and 0.82 g of Fe_3O_4@SiO_2-P in MeOH (50 mL) was stirred at 65 °C under Ar for 12 h. The solid product was magnetically separated, washed with MeOH, and dried in vacuo at 80 °C for 3 h. The resulting Fe_3O_4@SiO_2-P-AuCl catalyst was then reacted with AgOTf (0.4 mmol) in DCM (50 mL) at room temperature for 2 h. The product was magnetically separated, washed with DCM, and dried in vacuo at 80 °C for 2 h to provide 0.86 g of Fe_3O_4@SiO_2-P-AuOTf as brown nanoparticles. The content of gold was determined to be 0.38 mmol g^{-1} by ICP-AES analysis.

General procedure for heterogeneous Au(I)-catalyzed three-component reaction of aldehydes, alkynes, and orthoformates

A mixture of aldehyde **1** (0.5 mmol), $HC(OR)_3$ **2** (0.6 mmol), terminal alkyne **3** (0.6 mmol), and Fe_3O_4@SiO_2-P-AuOTf (66 mg, 0.025 mmol) in DCE (3 mL) was stirred at 83 °C under Ar for 12–24 h (TLC monitored). After the reaction mixture was cooled to room temperature, the gold catalyst was magnetically separated and the reaction mixture was concentrated under reduced pressure and then purified by flash column chromatography on silica gel (petroleum ether: ethyl acetate = 100:1) to afford the corresponding propargyl ether **4**. The recovered gold catalyst was washed with DCE (2 × 2 mL), air-dried, and reused directly in the next run.

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

Funding

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