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Au(III) catalyst supported on a thermoresponsive hydrogel and its application to the A-3 coupling reaction in water

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ABSTRACT

Poly(NIPAM-co-4-VP), synthesized from N-isopropylacrylamide and 4-vinylpyridine with a 1:1 monomer ratio, exhibits a temperature-dependent phase transition in water with a low critical solution temperature (LCST) of 47 °C. Coordination of Au(III) with the polymer results in material with metal catalytic activity combined with the inverse solubility phenomenon of the polymer, which catalyzes the three-component coupling reaction of aldehydes, amines, and alkynes in water with excellent yields. The polymer not only functions as a supporter for Au(III) but also accelerates the catalysis by undergoing a coil-to-globule phase transition above the LCST. The catalyst is efficient, is stable in air, and tolerates a variety of substrates. Moreover, the recyclability of the catalyst makes it eco-friendly and economical to use.

1. Introduction

Gold catalysts support a wide spectrum of transformations, including a variety of organic reactions [1] and rearrangements [2]. One such reaction is the three-component one-pot reaction of an aldehyde, amine, and acetylene, designated as an A-3 coupling, which has a substantial role in the synthesis of heterocycles [3–5] as well as of biologically active compounds [6–8]. This transformation has received good deal of attention by researchers worldwide because of its high efficiency, excellent atom economy, mild reaction conditions, tolerance to a variety of functionalities, and the synthetic utility of the product propargylamines. Propargylamines are of interest not only as useful synthetic building blocks but also because they are an integral functionality found in natural products [9] and drugs [10].

A-3 coupling has been found to be catalyzed by different transition metals including Cu [11], Ag [12], Au [13], Ni [14], Co [15], Fe [16], and Zn [17], yet there is a need for improvements in the process. Gold catalysis has recently been advancing through the use of metallic nanoparticles [18,19] as well as in complexes or in salt form [20,21]. Gold-catalyzed A-3 coupling was first investigated by the Li group [22], who reported better activity with Au(III) salts than with Au(I) catalysts. Furthermore, water gave the best results among all the solvents investigated. While later reports utilizing supported catalysts addressed many of the shortcomings of typical homogeneous catalysis, such as difficult separation, poor recyclability, thermal instability, and the high cost of the catalyst [23], these procedures included harsh reaction conditions including reflux or elevated temperatures [24].

In other studies, several equivalents of an oxidative additive were sometimes required for efficient recyclability [25], or the reaction time was prolonged [26]. Therefore, there is a need for a heterogeneous catalyst that performs efficiently under mild conditions and recyclability.

Hence, we focused on the development of a Au(III) catalyst supported on a thermosensitive polymer. Our group has previously used poly(NIPAM-co-4-VP) as a support for palladium nanoparticles and their subsequent application to the Suzuki–Miyaura coupling reaction [27]. Thus, we focused on the development of a Au(III) catalyst supported on thermoresponsive poly(NIPAM-co-4-VP), as shown in Scheme 1. At temperatures higher than 47 °C, hydrogen bonds between the polymer and solvent molecules become weak, and the polymer coils around itself, shrinking in size as intramolecular hydrogen bonding of the polymer becomes significant. This mechanism is proposed for the coil-to-globule transition of polymer coils that takes place in hydrophilic solvents.

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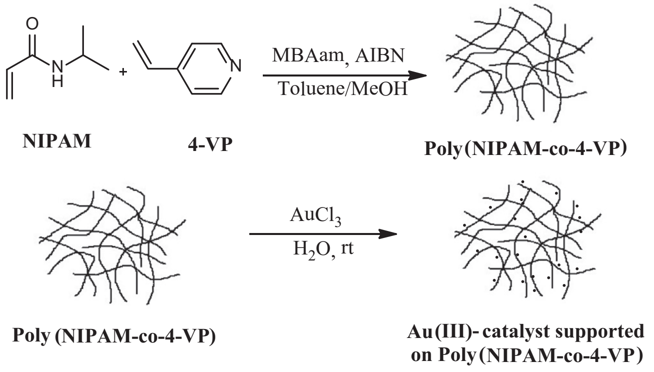


Scheme 1. Schematics of polymerization to synthesize poly(NIPAM-co-4-VP) and the subsequent coordination of Au (III) with poly(NIPAM-co-4-VP).

2. Experimental methods

2.1. Catalyst preparation

Poly(NIPAM-co-4-VP) copolymer hydrogels were prepared by free radical solution polymerization using NIPAM and 4-VP (1:1) in toluene according to the standard procedure [27].

To coordinate Au(III) with the polymer, 0.05 g of gold trichloride trihydrate, $AuCl_3{\cdot}3H_2O$, was added to 25 mL of aqueous solution containing 0.1 g poly(NIPAM-co-4-VP). The resulting mixture was sonicated for 1 min, followed by vigorous mechanical shaking at room temperature for 12 h. The catalyst was collected after filtration, washed with methanol, and dried in a vacuum oven at 60 °C.

2.2. General procedure for A-3 coupling reaction

All the chemicals were purchased from commercial sources (Aldrich & TCI) and used as received, among them aldehydes and solvents were used after distillation.

For a typical experiment, benzaldehyde (1.0 equiv., 2.0 mmol, 0.20 mL), pyrrolidine (1.2 equiv., 2.4 mmol, 0.20 mL), phenylacetylene (1.5 equiv., 3.0 mmol, 0.34 mL), and the catalyst (6.75 mol%, 0.135 mmol, 0.05 g) were added to water (2.0 mL) in a 10-mL round-bottom flask. The reaction mixture was subjected to vigorous stirring at 60 °C under argon. The reaction was monitored by thin layer chromatography (TLC). After completion, the reaction mixture was cooled to room temperature and filtered to recover the catalyst. The catalyst was washed with water and ethyl acetate (10 mL each), and then the organic layer was separated by extraction with three 10-mL portions of ethyl acetate. The combined organic layers were dried over $MgSO_4$ and filtered using Celite-545. The solvent was evaporated at reduced pressure, and the product was separated by flash column chromatography. The product was analyzed by ^1H NMR. Further confirmation of the novel compounds was carried out by analyses such as IR, ^1H NMR, ^{13}C NMR, and HRMS (spectra provided in the Supplementary Information).

2.3. Characterization and analysis

Scanning electron microscopy (SEM) and energy dispersive X-ray analysis (EDXA) measurements were performed on a JEOL high-resolution transmission electron microscope (HRTEM) at an acceleration of 300 kV. The loading value of Au(III) in the catalyst was estimated by ICP analysis with a JY Ultima2C. ICP also helped to check for leaching out after the recycle test. The lower critical solution temperature (LCST) of the synthesized hydrogel was characterized by differential scanning calorimetry (DSC) measurements (TA Instrument, DSC 2010). The phase transition takes place with the endothermic heat flow caused by the breakage of hydrogen bonds between water and polymer molecules [28]. Infrared spectroscopic data were obtained using an Alpha-E FT-IR spectrometer with a NaCl window for liquid samples. ^1H and ^{13}C NMR were recorded on a Bruker 400 MHz instrument using $CDCl_3$ solvent.

3. Results and discussion

3.1. Polymer and catalyst behavior

According to DSC data, the synthesized polymer shows inverse-temperature solubility behavior at 47 °C, as shown by the curve in Fig. 1. This analysis helped to make use of reaction temperatures higher than 47 °C for the catalysis, as we predicted strong interactions of the catalyst in the hydrophobic phase with organic reactants in water. Typically, organic reactions in water are predicted to be slow; however, in our system, above this transition temperature, known as the LCST, organic reactants are attracted to the inner hydrophobic part of a small globule of heterogeneous catalyst so that the reaction is accelerated.

Coordination of Au(III) with the polymer was efficiently performed at room temperature. The reaction was aided by the high solubility ($K_{sp} = 3.2 \times 10^{-25}$ at 25 °C) of gold trichloride in water at room temperature. Gold has a high affinity to carbon as well as other heteroatoms such as nitrogen, phosphorus, sulfur, and even O-donor ligands, such that it forms stable complexes [29]. Pyridine is one such ligand, whose coordination with gold is so strong that it can form complexes by ligand exchange [30]. Therefore, the developed catalyst has Au(III) strongly anchored by the pendent pyridine groups of the polymer support, which minimizes the opportunity for gold to leach out into the reaction mixture.

However, autoreduction of Au(III) species to metallic gold is possible in sonicated water [31]; there are some reports of the use of oxidative additives in A-3 coupling reactions for the regeneration of Au(III) species [25]. However, to verify that the Au(III) oxidation state was maintained, we analyzed the X-ray photoelectron spectrum (XPS) for fresh and recycled catalyst (XPS spectra provided in the Supplementary Information). Both fresh and recycled catalyst XPS spectra showed peaks for the $Au4f_{7/2}$ peaks with a binding energy around 84 eV [32] with no noticeable changes in the characteristic peaks, demonstrating the stability of our catalyst. Further quantitative analysis of Au(III) was accomplished by ICP analysis of the freshly prepared catalyst. The loading value of the catalyst was found to be promising (2.7 mmol Au/g of polymer).

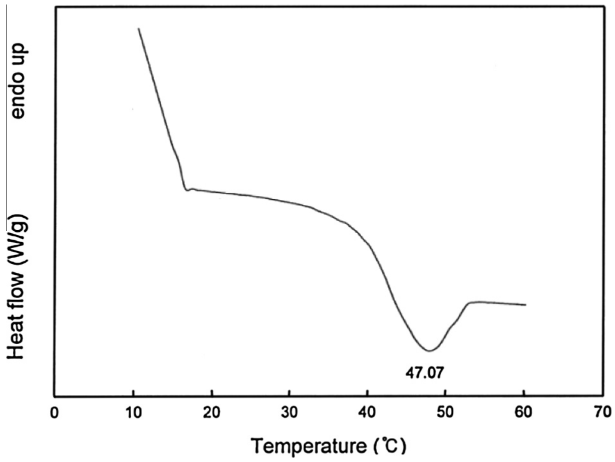


Fig. 1. Differential scanning calorimetry curve for poly(NIPAM-co-4-VP).

3.2. A-3 coupling reaction

The catalyst was tested for the three-component–one-pot A-3 coupling reaction. The reaction proceeded smoothly in water, a solvent that is in accordance with green chemistry. The reaction was carried out with varying amounts of the catalyst at various temperatures, as described in Table 1. Initially, using less than 6.75 mol% (0.05 g) of catalyst resulted in moderate yields of the product. Later, an increase in the catalyst loading to 6.75 mol% gave excellent results. Any further increase in the catalyst amount could only decrease the reaction time, as the catalyst efficiency stay almost the same, marked by comparable turnover frequencies (TOF). Thus, we preferred to use 6.75 mol% of catalyst. However, in the absence of catalyst, no product was observed. There are reports on gold catalysts with high TOF values, too, but they are applicable to relatively simpler reactions [33,34]. To thoroughly investigate the effect of temperature on catalytic efficiency, reactions were performed at temperatures below and above the LCST (RT, 40 °C, and 60 °C). As predicted, reactions performed at temperatures below the LCST did not give satisfactory results, in contrast to reactions performed at temperatures above the LCST. The result can be explained by the increased interactions of reactants with the hydrophobic catalyst at higher temperatures.

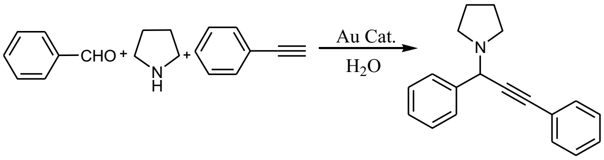
The reaction was also successfully scaled up 10 times under the mentioned conditions at 60 °C and 6.75 mol% of catalyst to obtain around 5 g (92%) of the product after 5 h.

Moreover, the morphology of the catalyst was determined by scanning electron microscopy (SEM) images that elaborated the absence of any changes in morphology before and after catalysis. The presence of Au in the catalyst was also confirmed by EDXA before and after coupling experiments. See Fig. 2.

3.3. Substrate scope

The scope of the reaction was also determined using a general protocol for the A-3 coupling reaction under the optimized conditions for our catalyst in water. The catalyst performed efficiently with both aryl and aliphatic aldehydes. Amines including pyrroli-

Table 1
The A-3 coupling reaction using Au(III) catalyst in water.[a]



Entry	Catalyst (mol%) (supported catalyst (g))	Temp. (°C)	Conv. (%)[b]	Time (h)	TON (mol/mol)[c]	TOF (h^{-1})[d]
1	6.75 (0.050)	25	35	5	5	1.03
2	6.75 (0.050)	40	64	5	9	1.89
3[e]	6.75 (0.050)	60	100	5	15	2.96
4	2.70 (0.020)	60	39	5	14	2.89
5	9.45 (0.070)	60	100	4	11	2.64
6	13.50 (0.100)	60	100	3	7	2.47

[a] Reaction conditions: benzaldehyde (1.0 equiv., 2.0 mmol), pyrrolidine (1.2 equiv., 2.4 mmol), phenylacetylene (1.5 equiv., 3.0 mmol).
[b] Determined by GC analysis using dodecane as an internal standard.
[c] Reactant moles converted/catalyst moles.
[d] (Reactant moles converted/catalyst moles)/reaction time.
[e] No reaction occurred in the absence of the catalyst.

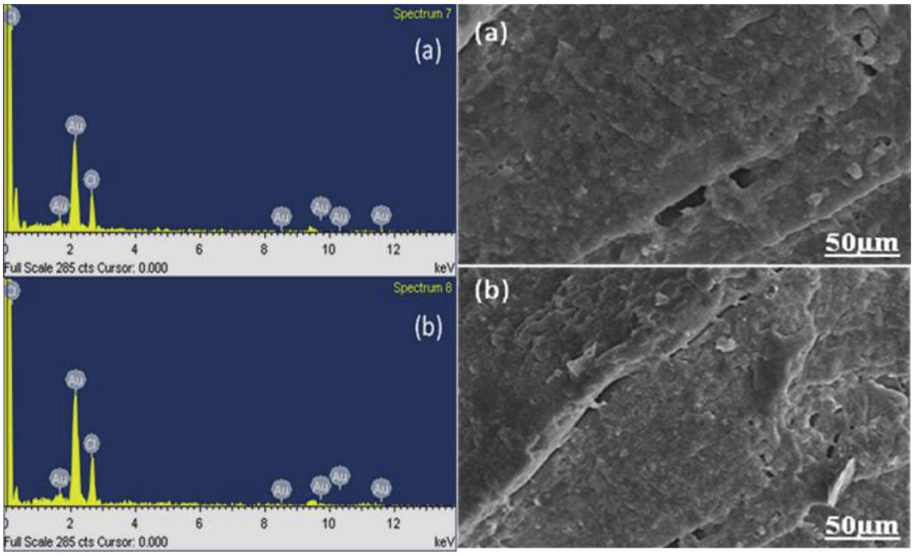
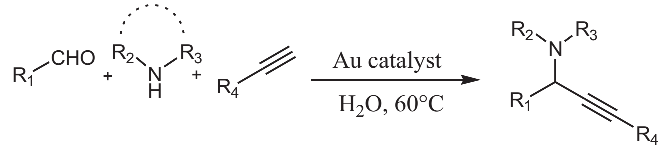


Fig. 2. EDXA measurements and SEM images of (a) fresh and (b) recycled catalyst.

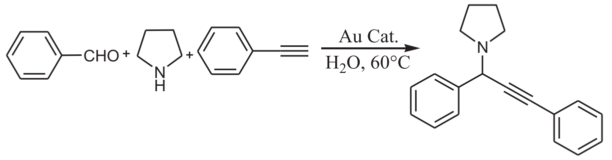
Table 2
Substrate scope of A-3 coupling reaction using Au-catalyst supported on poly(NIPAM-co-4-VP).[a]



Entry	R_1	R_2R_3NH	R_4	Time	Yield
1	Ph	Pyrrolidine	Ph	6	93
2	Ph	Piperidine	Ph	5	95
3	Ph	Morpholine	Ph	4	78
4	Ph	Dibenzylamine	Ph	3	96
5	2,4-diCl–C_6H_3	Pyrrolidine	Ph	7	80
6	*p*-Br–C_6H_4	Pyrrolidine	Ph	3	89
7	*p*-CH_3O–C_6H_4	Pyrrolidine	Ph	8	93
8	*p*-C_2H_5O–C_6H_4	Pyrrolidine	Ph	8	83
9	*p*-iPr–C_6H_4	Pyrrolidine	Ph	7	80
10	*o*-HO–C_6H_4	Pyrrolidine	Ph	5	85
11	$C_{10}H_7$	Pyrrolidine	Ph	15	91
12	$PhCH_2CH_2$	Pyrrolidine	Ph	10	81
13	$CH_3(CH_2)_4$	Pyrrolidine	Ph	5	100
14	*tert*-Bu	Pyrrolidine	Ph	8	96
15	Ph	Pyrrolidine	*p*-NH_2–C_6H_4	1	97
16	Ph	Pyrrolidine	3,4-diCl–C_6H_3	5	91
17	Ph	Pyrrolidine	*p*-^{n}Bu–C_6H_4	6	96

[a] Reaction conditions: aldehyde (1 equiv., 2.0 mmol), amine (1.2 equiv., 2.4 mmol), phenylacetylene (1.5 equiv., 3.0 mmol), 6.75 mol% Au catalyst.

Table 3
Catalyst recycling in the A-3 coupling reaction.[a]



Recycle	1	2	3	4	5	6	7	8	9	10
Yield (%)[b]	93	92	92	92	92	91	91	90	90	90

[a] Reaction conditions: benzaldehyde (1 equiv., 2.0 mmol), pyrrolidine (1.2 equiv., 2.4 mmol), phenylacetylene (1.5 equiv., 3 mmol), 6.75 mol% catalyst, reaction time 6 h.

[b] Isolated yield.

dine, piperidine, morpholine, and even bulky amines such as dibenzylamine participated well in the reaction. The broad substrate scope is evident by the tolerance of different functional groups on the substrates, as shown in Table 2.

3.4. Recyclability

Recyclability of the catalyst was determined by 10 repetitions, demonstrating an output of 90–93% after ten recycle tests, as shown in Table 3. The filtrate from these reactions was collected after the recycling experiments and was analyzed by ICP to determine the amount of Au(III) leached into the water. Fortunately, very insignificant leaching was observed (Au < 10 ppm).

4. Conclusions

In conclusion, we have developed a heterogeneous gold catalyst for the three-component coupling reaction of aldehydes, amines, and acetylenes that works efficiently in water. Poly(NIPAM-co-4-VP), which exhibits a phase transition with a LCST, is suitable as a support for the catalyst. In addition, coordination of gold with the polymer was aided by the solubility of the Au(III) salt in water. Moreover, we found the catalyst to be applicable to the A-3 coupling reaction, demonstrating excellent yields under environmentally friendly, safe, and mild reaction conditions.

We expect this catalyst to be equally suitable for other reactions catalyzed by Au(III).

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jcat.2014.11.009.

References

[1] A.S.K. Hashmi, Gold-catalyzed organic reactions, Top. Organomet. Chem. 44 (2012) 143–164.
[2] C. Obradors, A.M. Echavarren, Gold-catalyzed rearrangements and beyond, Acc. Chem. Res. 47 (2014) 902–912.
[3] A.S.K. Hashmi, Gold-catalyzed synthesis of N,O-heterocycles, Pure Appl. Chem. 82 (2010).
[4] M.C. Blanco Jaimes, F. Rominger, M.M. Pereira, R.M. Carrilho, S.A. Carabineiro, A.S. Hashmi, Highly active phosphite gold(I) catalysts for intramolecular hydroalkoxylation, enyne cyclization and furanyne cyclization, Chem. Commun. 50 (2014) 4937–4940.
[5] M.C. Blanco Jaimes, C.R. Bohling, J.M. Serrano-Becerra, A.S. Hashmi, Highly active mononuclear NAC–gold(I) catalysts, Angew. Chem., Int. Ed. 52 (2013) 7963–7966.
[6] V.K. Lo, Y. Liu, M.K. Wong, C.M. Che, Gold(III) Salen complex-catalyzed synthesis of propargylamines via a three-component coupling reaction, Org. Lett. 8 (2006) 1529–1532.
[7] B.T. Elie, C. Levine, I. Ubarretxena-Belandia, A. Varela-Ramirez, R.J. Aguilera, R. Ovalle, M. Contel, Water soluble Phosphane-Gold(I) complexes. Applications as recyclable catalysts in a three-component coupling reaction and as antimicrobial and anticancer agents, Eur. J. Inorg. Chem. 2009 (2009) 3421–3430.
[8] L. Messori, F. Abbate, G. Marcon, P. Orioli, M. Fontani, E. Mini, T. Mazzei, S. Carotti, T. O'Connell, P. Zanello, Gold(III) complexes as potential antitumor agents: solution chemistry and cytotoxic properties of some selected Gold(III) compounds, J. Med. Chem. 43 (2000) 3541–3548.
[9] M. Konishi, H. Ohkuma, K. Matsumoto, T. Tsuno, H. Kamei, T. Miyaki, T. Oki, H. Kawaguchi, G.D. Vanduyne, J.O.N. Clardy, Dynemicin A, a novel antibiotic with the anthraquinone and 1,5-diyn-3-ene subunit, J. Antibiot. 42 (1989) 1449–1452.
[10] A.A. Boulton, B.A. Davis, D.A. Durden, L.E. Dyck, A.V. Juorio, X.-M. Li, I.A. Paterson, P.H. Yu, Aliphatic propargylamines: new antiapoptotic drugs, Drug Dev. Res. 42 (1997) 150–156.
[11] R. Gurubrahamam, M. Periasamy, Copper(I) halide promoted diastereoselective synthesis of chiral propargylamines and chiral allenes using 2-dialkylaminomethylpyrrolidine, aldehydes, and 1-alkynes, J. Org. Chem. 78 (2013) 1463–1470.
[12] X. Zhou, Y. Lu, L.-L. Zhai, Y. Zhao, Q. Liu, W.-Y. Sun, Propargylamines formed from three-component coupling reactions catalyzed by silver oxide nanoparticles, RSC Adv. 3 (2013) 1732.
[13] L.L. Chng, J. Yang, Y. Wei, J.Y. Ying, Semiconductor-gold nanocomposite catalysts for the efficient three-component coupling of aldehyde, amine and alkyne in water, Adv. Synth. Catal. 351 (2009) 2887–2896.
[14] S. Samai, G.C. Nandi, M.S. Singh, An efficient and facile one-pot synthesis of propargylamines by three-component coupling of aldehydes, amines, and alkynes via C–H activation catalyzed by $NiCl_2$, Tetrahedron Lett. 51 (2010) 5555–5558.
[15] C.-J. Li, W.-W. Chen, H.-P. Bi, The first cobalt-catalyzed transformation of alkynyl C-H bond: aldehyde-alkyne-amine (A^3) coupling, Synlett 2010 (2010) 475–479.
[16] B. Sreedhar, A.S. Kumar, P.S. Reddy, Magnetically separable Fe_3O_4 nanoparticles: an efficient catalyst for the synthesis of propargylamines, Tetrahedron Lett. 51 (2010) 1891–1895.
[17] N.P. Eagalapati, A. Rajack, Y.L.N. Murthy, Nano-size ZnS: a novel, efficient and recyclable catalyst for A3-coupling reaction of propargylamines, J. Mol. Catal. A: Chem. 381 (2014) 126–131.

[18] Y. Mikami, A. Dhakshinamoorthy, M. Alvaro, H. García, Catalytic activity of unsupported gold nanoparticles, Catal. Sci. Technol. 3 (2013) 58.

[19] A.S. Hashmi, Chemistry. Sub-nanosized gold catalysts, Science 338 (2012) 1434.

[20] A.S.K. Hashmi, G.J. Hutchings, Gold catalysis, Angew. Chem., Int. Ed. 45 (2006) 7896–7936.

[21] A.S.K. Hashmi, L. Schwarz, J.-H. Choi, T.M. Frost, A new gold-catalyzed C–C bond formation, Angew. Chem., Int. Ed. 39 (2000) 2285–2288.

[22] C. Wei, C.J. Li, A highly efficient three-component coupling of aldehyde, alkyne, and amines via C–H activation catalyzed by gold in water, J. Am. Chem. Soc. 125 (2003) 9584–9585.

[23] X. Zhang, A. Corma, Supported gold(III) catalysts for highly efficient three-component coupling reactions, Angew. Chem., Int. Ed. 47 (2008) 4358–4361.

[24] G. Villaverde, A. Corma, M. Iglesias, F. Sánchez, Heterogenized gold complexes: recoverable catalysts for multicomponent reactions of aldehydes, terminal alkynes, and amines, ACS Catal. 2 (2012) 399–406.

[25] T.A. Graf, T.K. Anderson, N.B. Bowden, Extended lifetimes of Gold(III) chloride catalysts using Copper(II) chloride and 2,2,6,6-Tetramethylpiperidine 1-Oxyl (TEMPO), Adv. Synth. Catal. 353 (2011) 1033–1038.

[26] V.K.-Y. Lo, K.K.-Y. Kung, M.-K. Wong, C.-M. Che, Gold(III) (C^N) complex-catalyzed synthesis of propargylamines via a three-component coupling reaction of aldehydes, amines and alkynes, J. Organomet. Chem. 694 (2009) 583–591.

[27] M.C. Hong, M.C. Choi, Y.W. Chang, Y. Lee, J. Kim, H. Rhee, Palladium nanoparticles on thermoresponsive hydrogels and their application as recyclable Suzuki–Miyaura coupling reaction catalysts in water, Adv. Synth. Catal. 354 (2012) 1257–1263.

[28] M. Schönhoff, A. Larsson, P.B. Welzel, D. Kuckling, Thermoreversible polymers adsorbed to colloidal silica: A1H NMR and DSC study of the phase transition in confined geometry, J. Phys. Chem. B 106 (2002) 7800–7808.

[29] M.C. Gimeno, The chemistry of gold, in: Modern Supramolecular Gold Chemistry, Wiley-VCH, 2009, pp. 1–63.

[30] N. Nasser, R.J. Puddephatt, Chemistry of gold(III) with pyridine-carboxamide ligands, Polyhedron 69 (2014) 61–67.

[31] T. Sakai, H. Enomoto, K. Torigoe, H. Sakai, M. Abe, Surfactant- and reducer-free synthesis of gold nanoparticles in aqueous solutions, Colloids Surf. A 347 (2009) 18–26.

[32] O. Böse, E. Kemnitz, A. Lippitz, W.E.S. Unger, C 1s and Au 4f 7/2 referenced XPS binding energy data obtained with different aluminium oxides, -hydroxides and -fluorides, Fresenius J. Anal. Chem. 358 (1997) 175–179.

[33] M.C. Blanco Jaimes, F. Rominger, M.M. Pereira, R.M.B. Carrilho, S.A.C. Carabineiro, A.S.K. Hashmi, Highly active phosphite gold(I) catalysts for intramolecular hydroalkoxylation, enyne cyclization and furanyne cyclization, Chem. Commun. 50 (2014) 4937–4940.

[34] M.C. Blanco-Jaimes, C.R.N. Böhling, J.M. Serrano-Becerra, A.S.K. Hashmi, Highly active mononuclear NAC–Gold(I) catalysts, Angew. Chem., Int. Ed. 52 (2013) 7963–7966.