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Aldol condensation in PEG-400 catalyzed by recyclable L-proline supported on nano gold surface†

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L-Proline supported on nano gold surface in PEG-400 catalyst system has been developed for use in the direct aldol condensation of acetone with aldehydes. Successful immobilization on surface of gold nanoparticles was confirmed using multiple analytical techniques. The supported catalyst could be separated from the reaction mixture by filtration, and could be reused five times with negligible loss in activity.

Introduction

The asymmetric aldol condensation of a nucleophilic ketone donor to an electrophilic aldehyde acceptor is one of the most powerful C–C bond forming reactions and constitutes a significant challenge in synthetic chemistry.[1] The reaction yields optically active β-hydroxy carbonyl compounds and is used widely in synthetic organic chemistry to produce intermediates for anti-hypertensive drugs and calcium antagonists.[2] Chiral β-hydroxy carbonyl compounds can be readily converted to 1,3-*syn*-diols and anti-diols and amino alcohols, which are the building blocks for antibiotics, pheromones and many biologically active compounds.[3] Direct catalytic and enantioselective aldol reactions of unmodified ketones or aldehydes have been reported by the research groups of Shibasaki,[4] Trost,[5] Jorgensen,[6] MacMillan,[7] List,[8] Barbas III[9] and Cordova[10] using organometallic or purely organic catalysts. Recent work has been attempted using a recyclable ionic liquid as a solvent,[11] buffered aqueous media,[12] Zn proline complexes in aqueous media or aqueous micelles.[13] Although several catalysts have been reported for this reaction, we focus here on small chiral molecule catalysts as they are more efficient and environmentally friendly.[14–18] Proline is one such chiral molecule that is inexpensive and available in both enantiomeric forms. It is a bifunctional molecule with a carboxylic and amine group which can act both as acid or base. It also facilitates chemical transformations in concerted manner recapitulating enzyme-based catalysis.[19,20] As proline is a chiral bidentate ligand, it has the potential to bind with metal and form catalytically active metal complexes. However in order to catalyze aldol reactions, large amounts of L-proline as catalyst is required and no literature to recycle them is available. Here we show that L-proline supported on nano gold surface in PEG-400 can be used to catalyze aldol reactions with high yields. The catalysts can be recycled with ease and used multiple times with negligible loss in activity. Our group has used nanoparticles in the recent past to catalyze a number of organic reactions.[21–29]

Characterization of catalyst

Fig. 1a,b shows the IR spectrum for proline–cysteine conjugated product before and after immobilization on the

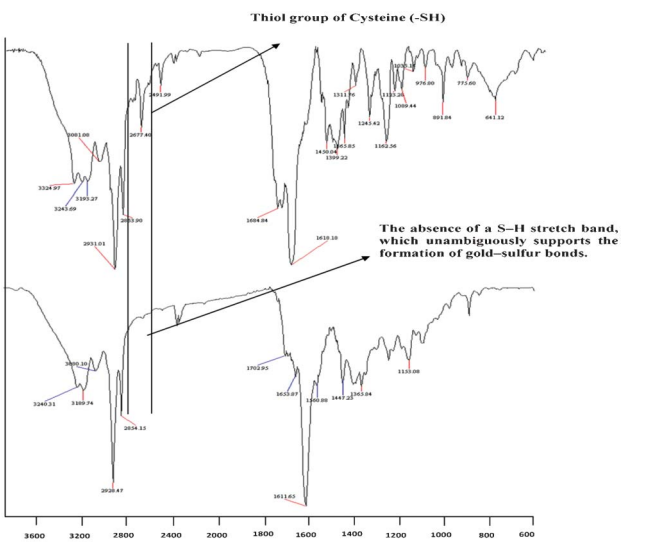

Fig. 1 IR spectra of (a) L-proline–cysteine conjugated product and (b) L-proline–cysteine conjugated product supported on Au nanoparticles (note the disappearance of the S–H stretching).

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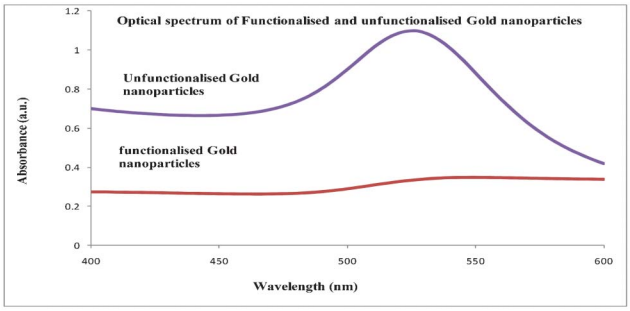


Fig. 2 UV-Visible analysis of bare Au nanoparticles and L-proline–cysteine conjugate functionalized on Au nanoparticles.

surface of Au nanoparticles respectively. Before immobilization, the L-proline–cysteine conjugate shows the characteristic peak of –SH group at 2677 cm^{-1}.

The IR spectrum for immobilization of the dipeptide to the gold surface closely resembles the previous spectrum, indicating the successful attachment of the conjugate onto the Au nanoparticles. Additionally, the absence of S–H (2677 cm^{-1}) stretch band in Fig. 1b unambiguously supports the formation of the gold–sulfur bond. Au nanoparticles were synthesised using citrate in boiling aqueous solution which acts as a reducing as well as a capping agent; absorbance at 526 nm confirmed the formation of Au nanoparticles (Fig. 2).

To confirm the functionalization of L-proline–cysteine conjugate onto the Au surface, the final solution of the functionalized Au nanoparticles was also analysed using a UV spectrophotometer. The absorbance band obtained earlier at 526 nm was completely suppressed, confirming the successful functionalisation of L-proline–cysteine conjugate. In order to confirm the immobilization of L-proline–cysteine conjugate onto the surface of Au nanoparticles, the solutions were analyzed for zeta potential and the results obtained were compared with the solution of bare Au nanoparticles. The results obtained for the functionalized and bare Au nanoparticles have been tabulated in Table 1. It was observed that the average zeta potential value for bare Au nanoparticles was −18.5 mV. This was reduced to −9.47 mV in the case of the functionalized Au nanoparticles. The successful immobilization was thus confirmed using three independent methodologies.

Table 1 Zeta potential analysis of modified and unmodified gold nanoparticles

Sample name	Reading	Temp. (°C)	Zeta potential (mV)	Av. (mV)
L-Proline–cysteine conjugate supported on Au nanoparticles	1	25	−07.31	−9.47
	2	25	−11.20	
	3	25	−09.92	
Bare Au nanoparticles	1	25	−18.50	−18.5
	2	25	−18.00	
	3	25	−19.20	

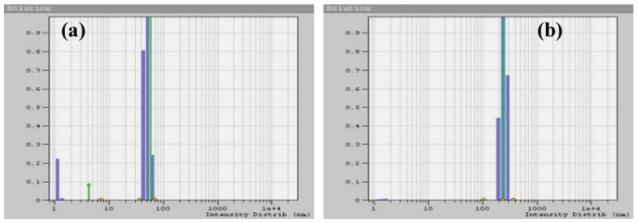


Fig. 3 Au nanoparticles (a) before modification and (b) after modification

Nanoparticles have a higher surface to volume ratio as compared to bulk material; thus they could serve as great catalysts. The size of the nanoparticles synthesized were calculated using QELS. The sizes of bare Au nanoparticles and L-proline–cysteine conjugate supported on Au nanoparticles were found to be 36 nm (80%) to 228 (95%) nm, respectively (Fig. 3a,b).Fig. 4 depicts the TEM images of modified and unmodified gold nanoparticles. The TEM micrograph clearly reveals the morphological changes that take place after modification on the surface of the Au nanoparticles. These morphological changes further confirm the functionalisation of Au nanoparticles.

Fig. 5 shows the electron diffraction analysis of modified and unmodified Au nanoparticles. Unmodified Au nanoparticles have clear ring fringes corresponding to their FCC structure. Upon modification, these rings disappeared and this indicates the amorphous nature of the modified surface of the Au nanoparticles.

The XRD pattern of unmodified Au nanoparticles shows four characteristic peaks for 2θ at 38.00°, 44.48°, 64.4° and 77.6°, marking indices of (111), (200) , (220) and (311) planes, respectively (Fig. 6a). A significant diffraction peak (111) suggests prominent growth of network structure along (111) planes compared to (200). However, the other prominent diffraction peak (220) points to the anisotropic (network) nature of the nanoparticles. X-Ray diffraction patterns of the L-proline–cysteine conjugated product Au nanoparticles does not show the prominent peaks like unmodified Au nanoparticles. This again supports the functionalization of the Au nanoparticles (Fig. 6b).

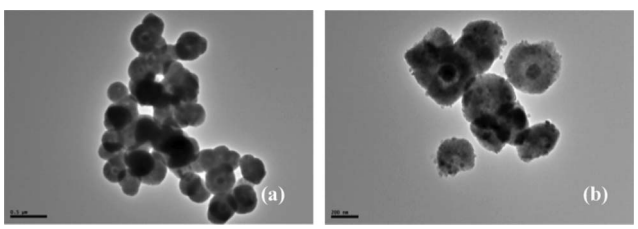


Fig. 4 TEM images of (a) citrate-capped Au nanoparticles and (b) L-proline–cysteine conjugate-modified Au nanoparticles.

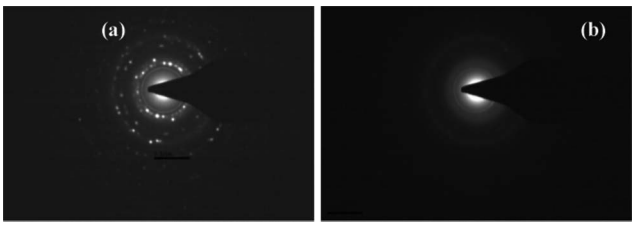


Fig. 5 Electron diffraction of (a) citrate-capped Au nanoparticles and (b) L-proline–cysteine conjugate on Au nanoparticles.

Results and discussion

A major drawback of the proline derivative-catalysed aldol reaction is its low efficiency. It may be noted that as much as10 mol% to 40 mol% (typically 20 mol%) of the catalyst is needed. In order to indirectly overcome this problem, immobilization of the catalyst onto a solid support had been studied and the results obtained have been highly encouraging. Application of metal nanoparticles in catalysis has increased tremendously in recent times because of their large surface to volume ratio and potential to bind with organic molecules. Size-controlled Au nanoparticles are relatively easy to synthesize and their excellent biocompatibility, stability at varying temperature range, tolerance of extreme harsh conditions and affinity for thiols and amines have made them excellent substrates for solid support. A proposed mechanism of the reaction that proceeds *via* enamine intermediates is shown in Scheme 1. An important feature in this mechanism is the H-bond formation between an acidic proton of the catalyst and an acceptor carbonyl of the aldehyde. In the transition state for iminium ion formation, the H-bond donor is the cysteine carboxyl unit, while the acceptor is the proline carbonyl oxygen.

The mechanism is substantiated by our data which shows that presence of electron-withdrawing groups on the aldehyde increases the yield, while the presence of bulky *ortho* groups substantially reduces the yield because of steric effects. A carboxyl group on the catalyst is essential to catalyze this reaction. Keeping these points in mind, a method to immobilize L-proline on the surface of the Au nanoparticles using cysteine as a linker was designed so as to use them to catalyse asymmetric synthesis of aldol products in high yields. It is important to be able to recycle any catalyst. The catalyst

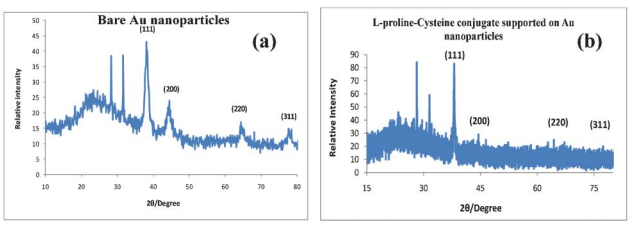
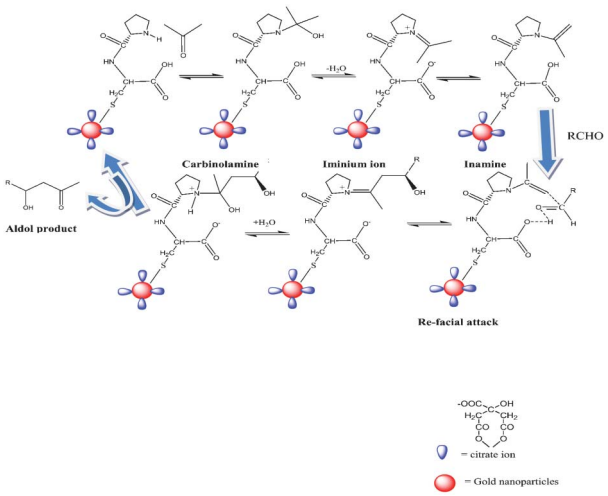


Fig. 6 (a) X-ray diffraction of citrate-capped Au nanoparticles and (b) L-proline–cysteine conjugate supported on Au nanoparticles.



Scheme 1 Proposed mechanism of the direct aldol reaction catalyzed by L-proline–cysteine conjugate on citrate-capped Au nanoparticles.

we developed is advantageous because the products can be easily separated from the reaction mixture by simple filtration and washing. It has been found that the immobilized proline catalyst could be repeatedly used at least five times without any loss of yield.

Solvent plays an important role in deciding the yield of the aldol product and is a crucial factor in this methodology. Various solvents were screened and studied to evaluate their effect on the reaction. The results obtained have been tabulated in Table 2. It was found that solvents like DMSO, DMF and THF slowed down the reaction rate and also provide a poor dispersal media for the catalyst. Additionally, the catalyst instantly aggregates in these solvents.

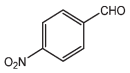
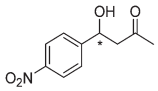
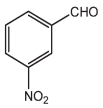
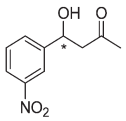
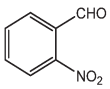
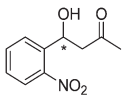
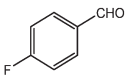
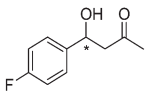
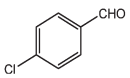
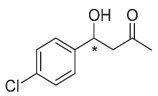
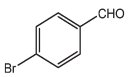
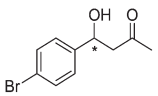
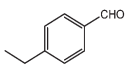
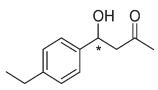
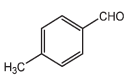
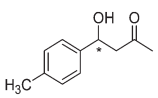
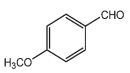
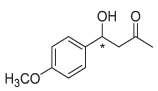
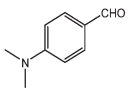
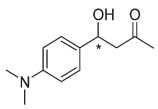
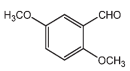
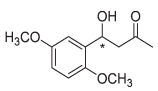
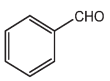
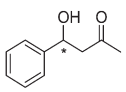
This might be the reason for the decrease in reaction rate and yield. However, in PEG-400 the results obtained were highly promising. Using L-proline–cysteine conjugate immoblized on Au nanoparticles, various aldol products were efficiently synthesised in reusable PEG-400 as solvent (Table 3) and recyclability studies are tabulated in Table 4. Catalyst in PEG showed very little decrease in product yield in all the runs conducted.

Table 2 Aldol reaction between *p*-nitrobenzaldehyde and acetone with different solvents by using L-proline–cysteine conjugate immoblized on Au nanoparticles at room temperature[a]

Entry	Solvent	Time (h)	Yield (%)[b]
1	THF	3	72
2	DMSO	3	40
3	DMF	3	45
4	$CHCl_3$	3	10
5	PEG-400	3	96
6	Neat	3	61

[a] Reaction conditions: aldehyde (4 mmol), acetone (20 mmol), catalyst (5 mg). [b] Isolated yields.

Table 3 Asymmetric aldol reaction catalyzed by L-proline–cysteine conjugate on Au nanoparticles in PEG-400[a]

Entry	Carbonyl compound	Ketone	Products	Time (min)	Yield (%)[b]
1				30	98
2				30	89
3				30	94
4				30	86
5				30	82
6				30	82
7				30	72
8				30	84
9				30	69
10				30	89
11				30	62
12				30	74

[a] Reaction conditions: Aldehyde (4 mmol), acetone (20 mmol), catalyst (5 mg), PEG-400 (5 mL); [b] Isolated yields.

Table 4 Recyclability of proline immobilized on gld nanoparticles *via* cysteine[a]

Entry	Run	Yield (%)	Time (h)[b]
1	1st	96	3
2	2nd	95	3
3	3rd	96	3
4	4th	96	3
5	5th	96	3

[a] Reaction conditions: 4-nitrobenzaldehyde (4 mmol), acetone (20 mmol), catalyst (5 mg), PEG-400 (5 mL). [b] Isolated yields.

Conclusions

L-Proline–cysteine conjugate on functionalized Au nanoparticles has been shown to serve as an efficient, recyclable, clean catalyst for catalyzing asymmetric aldol reaction in recyclable PEG-400 media. The catalyst can be reused multiple times with negligible loss in activity The presented methodology addresses environmental concerns and encompasses the principles of green chemistry.

Experimental

In a 50 mL round-bottomed flask, L-proline–cysteine conjugated Au nanoparticles (5 mg) in 5 mL PEG solution was taken and stirred for 5 min at room temperature (25 °C) in the presence of 20 mmol of anhydrous acetone. After stirring for 5 min, 4 mmol aldehyde was added and the reaction mixture was allowed to stir for appropriate times as mentioned in Table 3. The progress of the reaction was monitored by TLC (thin-layer chromatography) and after completion the mixture was centrifuged at 10 000 rpm for 10 min. This provides the catalytic nanoparticle system as a solid pellet at the bottom of the centrifuge tube. The nanoparticles were washed with acetone and subsequently washed four times with water to ensure the complete removal of any residual material. The particles were then re-dispersed in acetone for further catalytic cycles. 15 mL anhydrous ether was added to dilute the reaction mixture (obtained from the upper layer of the centrifuge tube) and stirred for 5–10 min so as to separate out the ether layer. This process was repeated three times to obtain the products in ether. The solvent was removed by rotary evaporator under reduced pressure.

Acknowledgements

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