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Communication

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New Insights into Aldol Reactions of Methyl Isocyanoacetate Catalyzed by Heterogenized Homogeneous Catalysts

Rong Ye^{†, ‡, #, ⊥}, Jie Zhao^{†, ‡, ⊥}, Bing Yuan^{†, ⊥}, Wen-Chi Liu^{†, §, #}, Joyce Rodrigues De Araujo^{§, #}, Franco F. Faucher[†], Matthew Chang[†], Christophe V. Deraedt^{†, ‡}, F. Dean Toste^{*, †, ‡}, Gabor A. Somorjai^{*, †, ‡, §, #}

[†]Department of Chemistry, ^{*n*}Kavli Energy NanoScience Institute, University of California, Berkeley, California 94720, United States

^{*}Chemical Science Division, [§]Materials Science Division, Lawrence Berkeley National Laboratory, 1 Cyclotron Road, Berkeley, California 94720, United States

ABSTRACT. The Hayashi-Ito aldol reaction of methyl isocyanoacetate (MI) and benzaldehydes, a classic homogeneous Au(I)-catalyzed reaction, was studied with heterogenized homogeneous catalysts. Among dendrimer encapsulated nanoparticles (NPs) of Au, Pd, Rh, or Pt loaded in mesoporous supports and the homogeneous analogs, the Au NPs led to the highest yield and highest diastereoselectivity of products in toluene at room temperature. The Au catalyst was

stable, and was recycled for at least six runs without substantial deactivation. Moreover, larger pore sizes of the support and the use of a hydrophobic solvent led to a high selectivity for the *trans* diastereomer of the product. The activation energy is sensitive to neither the size of Au NPs nor the support. A linear Hammett plot was obtained with a positive slope, suggesting an increased electron density on the carbonyl carbon atom in the rate-limiting step. IR studies revealed a strong interaction between MI and the gold catalyst, supporting the proposed mechanism, in which rate-limiting step involves electrophilic attack of the aldehyde on the enolate formed from the deprotonated MI.

KEYWORDS. Heterogenized homogeneous catalyst, aldol reaction, selectivity, support effect, mechanism, gold catalyst

Heterogeneous catalysis offers the benefit of easy separation of the catalyst from reaction mixtures.¹ For reactions reaching nearly 100% conversion, the filtration of the catalyst is the only necessary work-up, besides solvent removal (if any). In addition, heterogeneous catalysts can be applied to flow reactions,² and easily recycled.³ These economically and ecologically beneficial aspects of heterogeneous catalysts are in agreement with the concepts of green chemistry. However, optimizing the product selectivity in traditional heterogeneous catalysts remains an important challenge.⁴ Improvements in supported metal catalysts have predominantly focused on engineering the metal sites.⁵⁻¹² The solid support is also an important consideration in the design of a heterogeneous catalyst.¹³ Strong metal-support interactions (SMSI), where the support greatly affects the *activity* of active sites,¹⁴ are a good example of this phenomenon. However, the effects of the support properties on the product *selectivity* have not been thoroughly studied.¹⁵⁻¹⁷

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The last two decades have seen numerous advances in gold catalysis.¹⁶⁻²³ Since the first publication by Ito et al., the aldol reaction of methyl isocyanoacetate (MI) and aldehydes forming 2-oxazolines has stood as a milestone in catalytic asymmetric synthesis.²⁴ Later, this reaction was widely studied with gold-based²⁵⁻²⁶ and other²⁷ homogeneous catalysts in order to explore its synthetic scope, reaction mechanism and the effect of the ligand structure on selectivity. For example, Togni and Pastor²⁸ provided valuable insights into the reaction mechanism, the ratedetermining step and the enantiodeterming transition states of Au(I)-complex-catalyzed aldol reaction through NMR, kinetic isotope, and linear free energy studies. Recently, van Koten et al.²⁹ immobilized Pd(II) complexes with pincer ligands³⁰ on mesoporous silica SBA-15 as a heterogenized homogeneous catalyst for the aldol reaction of MI and benzaldehyde in the presence of a base. Even though good activity and recycling results were achieved, the trans product selectivity was limited to 84%. Herein, we describe bridging the advantages of heterogeneous and homogeneous catalysts using dendrimer-supported heterogenized homogeneous catalyst developed in our group.³¹⁻³⁶ Additionally, the reaction mechanism of the aldol reaction was investigated, providing insights into the factors that affect the product selectivity in the heterogeneous reaction.



Figure 1. (A) A scheme of the aldol reaction. (B) The kinetics of the aldol reaction: 1 mol% catalyst, 22 °C in toluene. (C) Recycle tests with the same batch of $Au_{40}/G4OH/MP$ -SBA-15 for six runs: 1 mol% catalyst in chloroform, 22 °C, 2 h per run. (D) Structures of Au(I)-complexes used in this study. The codes originate from their corresponding CAS numbers.

Catalyst screening. NPs of Au, Pd, Rh, or Pt encapsulated in fourth generation polyamidoamine with hydroxyl terminal groups (G4OH) were prepared, purified, and loaded into mesoporous silica MP-SBA-15 (MP denotes medium-sized pores, *vide infra*), following published protocols.³⁷⁻⁴¹ The typical loading amount was 0.05 mmol of metal per gram of a supported metal catalyst. In a typical reaction test, 0.05 mmol of 4-nitrobenzaldehyde (**1a**), 0.075 mmol of

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MI, and 10 mg of a catalyst (containing ca. 0.5 µmol of metal, determined by ICP-OES) were mixed with a solvent in a reaction tube with magnetic stirring. For 18-h reaction time at room temperature using toluene as the solvent (Figure 1A), the $Au_{40}/G4OH/MP$ -SBA-15 catalyzed reaction provided the desired oxazoline in >99% yield and 97/3 of *trans/cis* ratio, based on ${}^{1}\text{H}$ NMR (see Supporting Information for details). In contrast, the use of the Pd, Rh, and Pt counterparts as catalysts under identical conditions gave low yields and poor product selectivity (Table 1). These observations highlight the critical role of the gold catalysts and rule out G4OH or MP-SBA-15 as the sole catalysts for the reaction. It is also worth noting that **1a** was a challenging substrate for the optimized homogeneous Au(I) catalyst, providing the corresponding oxazoline in only 80% yield with a *trans/cis* ratio of 83/17.²⁵ Three commercially available Au(I) complexes (Figure 1D) were used as catalysts under the same reaction condition; however, these catalysts showed lower activity and selectivity than the optimized Au(I) catalyst. The yield and selectivity of the aldol reaction under similar conditions catalyzed by transition metal ion complex catalysts of Pd, Pt, and Rh are highly dependent on the ligand structures (Table 1).⁴²⁻⁵⁵ However, the Au₄₀/G4OH/MP-SBA-15 catalyst offers the highest activity and selectivity, along with easy recyclability. Intrigued, we proceeded to further investigate the reaction by heterogenized gold catalysts.

Table 1. Comparison of yields and *trans/cis* selectivity for aldol reactions with selected transition metal catalysts.

entry	catalyst	yield (%)	trans/cis	ref.
1 ^a	Au ₄₀ /G4OH/MP-SBA-15	99.9	97/3	this work
2^{a}	Pd ₄₀ /G4OH/MP-SBA-15	42.7	81/19	this work
3 ^a	Pt ₄₀ /G4OH/MP-SBA-15	5.1	73/27	this work

4 ^a	Rh ₄₀ /G4OH/MP-SBA-15	1.8	87/13	this work
5 ^a	Au(I)-81-9	61.6	68/32	this work
6 ^a	Au(I)-82-0	79.1	68/32	this work
7^{a}	Au(I)-83-1	57.4	70/30	this work
8	Au(I) complex	80	83/17	25
9 ^b	Pd complexes	75-95	56/44-94/6	27
10 ^b	Pt complexes	70-96	56/44-94/6	27
11 ^b	Rh complexes	95-98	89/11-92/8	27

^aThe reactions were carried out with 0.05 mmol of **1a**, 0.075 mmol of MI, 1 mol% catalyst in toluene at 22 °C for 18 h. Yield and product selectivity were determined by ¹H NMR (same below). ^bBases (*i*-Pr₂NEt or Et₃N) were used. See ref. 12 for detailed reaction conditions.

Kinetics Study. The reaction kinetics were probed, and first order kinetics was found on both reactants (Figure 1B). When the reaction mixture was filtered after an hour, the starting materials in the filtrate showed no change over time, suggesting that the reaction was catalyzed by heterogeneous gold, and that no catalyst leaching into the supernatant had occurred (Figure 1B). In fact, a blank run revealed that in the absence of a catalyst or a base, the aldol reaction did not proceed at room temperature. Furthermore, Au³⁺/G4OH/MP-SBA-15, which contained Au(III) ions from HAuCl₄, was synthesized according to a published procedure.³⁵ Under the same reaction condition, this Au(III) catalyst gave the product in only 3% yield, demonstrating that Au(III) has very low activity compared to the heterogeneous Au catalysts.

Recycling test. A recycling test using the same batch of a catalyst was carried out. The product solution was separated via centrifugation after each run, and a fresh reactant solution was mixed with the catalyst immediately. The catalyst did not show a decrease in activity after six reaction runs (Figure 1C), providing evidence for the stability and recyclability of the catalyst.

Size effect study. To study the effect of size of the NPs on the catalytic reaction, Au₂₀/G4OH, Au₄₀/G4OH, and Au₆₀/G4OH were synthesized. Though the NPs described in this study are denoted as such, they are not perfectly uniform in size: the subscript refers to the HAuCl₄/G4OH molar ratios used in the synthesis, not to the exact number of atoms in each NP. The size distribution of these NPs was obtained from the TEM images (Figure 2). Concurrently, SP-SBA-15 and LP-SBA-15 were prepared to probe the effect of the pore profile of the support.³⁷⁻⁴¹ SP and LP denote small pore and large pore, respectively. The nitrogen physisorption isotherms (Figure 3) were obtained, and the Barrett-Joyner-Halenda (BJH) model was used to calculate the pore size distribution. The results were summarized in Table 2.



Figure 2. TEM images and corresponding particle size distribution statistics of Au₄₀/G4OH (A), (B); Au₂₀/G4OH (C), (D); Au₆₀/G4OH (E), (F). Scale bars are 10 nm.



Figure 3. N₂ adsorption-desorption isotherms of solid supports at 77 K with adsorption and desorption points represented by closed and open symbols, respectively.

Table 2. Physisorption characterizations of the solid supports.^a

material	$S_{\rm BET}/{\rm m}^2 \cdot {\rm g}^{-1}$	D _{pore} /nm	$V_{\rm pore}/{\rm cm}^3 \cdot {\rm g}^{-1}$
SP-SBA-15	342	4.5	0.22
MP-SBA-15	799	5.8	0.93
LP-SBA-15	966	8.0	1.16

^aParameters: S_{BET} : the BET surface area. D_{pore} : average pore diameter calculated from the adsorption branch of the N₂ isotherm by the BJH model. V_{pore} : total pore volume, determined at $p/p_0 = 0.984$.

Au NPs with different sizes were loaded into SBA-15 supports with various pore sizes,

respectively. As a result, nine supported catalysts were prepared and used to catalyze the aldol reaction, under the same conditions as shown in Figure 1A, and the *trans/cis* selectivity results have been summarized in Table 3. In general, *trans* selectivity was higher in catalysts with larger pores, probably due to the lower free energy of the *trans* product. However, in the confined

space of the catalysts with smaller pores, the ratio of the *cis* product was relatively high, likely because of its smaller kinetic diameter. The solvent was another important factor for the *trans/cis* ratio of the product. A series of solvents were tested (Table 4). In general, hydrophobic solvents favored the *trans* product strongly, while hydrophilic solvents led to a relatively high ratio of the *cis* product.

Table 3. Ratios of *trans/cis* products from catalysts with various sizes of NPs and pore diameters.^a

Au ₂₀ /G4OH	Au ₄₀ /G4OH	Au ₆₀ /G4OH
80/20	78/22	79/21
93/7	97/3	96/4
100/0	96/4	95/5
	Au ₂₀ /G4OH 80/20 93/7 100/0	Au20/G4OH Au40/G4OH 80/20 78/22 93/7 97/3 100/0 96/4

^aAll reactions were carried out with 0.05 mmol of **1a**, 0.075 mmol of MI, 1 mol% catalyst in toluene at 22 °C for 24 h. The yield was over 90% in each case.

Table 4. Solvent effects on the aldol reaction.^a

entry	solvent	yield (%)	trans/cis
1	Toluene-d8	99.9	97/3
2	Benzene-d6	99.9	91/9
3	CDCl ₃	99.9	88/12
4	CDCl ₂ CDCl ₂	96.8	83/17
5	DMSO-d6	99.9	79/21
6	Acetone-d6	99.1	65/35
7	CD ₃ CN	99.9	59/41

^aAll reactions were carried out with 0.05 mmol of **1a**, 0.075 mmol of MI, 1 mol% catalyst in the corresponding solvent at 22 °C for 18 h.

Substituent effect study. A Hammett study was used to probe the rate limiting step of the Au₄₀/G4OH/MP-SBA-15 catalyzed aldol reaction.^{28, 56} The reaction rates of benzaldehydes with different substitution groups were compared (see Table S1). The rate data were fitted with σ , σ^+ , and σ^- , respectively. The σ series fit generally well, except for **8** and **9**, much better than that of σ^+ or σ^- (larger R^2 values, plots not shown here), with the slope $\rho = 0.64$, as shown in Figure 4B. The deviation of **8** and **9** might be caused by the oxygen's interaction with electrophiles, further lowering the reactivity of these two compounds. The slope was smaller than that obtained for the reaction catalyzed by the homogeneous the Au(I)-complex ($\rho = 1.4$), indicating that the reaction was less sensitive to the electronic effect on the surface of the Au NP than on the Au(I)-complex. However, the positive slope suggested the increased electron density on the carbonyl carbon atom in the rate-limiting step, which was similar in these two types of catalysts, i.e. they involved electrophilic attack of the aldehyde on the MI (*vide infra*).²⁸



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Figure 4. (A) Structures and abbreviations of aldehydes used in this study. (B) A Hammett plot of the reaction of substituted benzaldehydes with MI. The linear fit (blue line) did not include **8** and **9**.



Figure 5. Arrhenius plots of selected cases, focusing on (A) different catalysts, and (B) solvents and reactants. The reaction conditions and the corresponding calculated activation energies are given in Table 5.

Activation Energy study. The Arrhenius plots were obtained for selected cases, as shown in Figure 5, and the calculated activation energies were listed in Table 4. For catalysts with different sizes of Au NPs or pore profile of the support, the activation energies were very similar (entries 1-5, Table 5). Changing the solvent from toluene to acetonitrile using the same catalyst gave distinct *trans/cis* product ratio (entries 1 and 7, Table 4), however, overall reaction rates and activation energies were very close (Figure 5B). On the contrary, benzaldehydes with various substituents showed substantial variations in reactivity for the same catalyst. Namely, electron-donating groups increased the activation energy (Table 5).

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 Table 5. Calculated activation energies of selected cases.^a

entry	catalyst	reactant	$E_{\rm a}$ (kJ/mol)
1	Au ₂₀ /G4OH/MP-SBA-15	1a	23.2
2	Au ₄₀ /G4OH/SP-SBA-15	1a	22.4
3	Au ₄₀ /G4OH/MP-SBA-15	1a	23.3
4	Au ₄₀ /G4OH/LP-SBA-15	1a	28.6
5	Au ₆₀ /G4OH/MP-SBA-15	1a	23.9
6	Au ₄₀ /G4OH/MP-SBA-15	$1a^{b}$	24.2
7	Au ₄₀ /G4OH/MP-SBA-15	6	47.5
8	Au ₄₀ /G4OH/MP-SBA-15	7	50.1
9	Au ₄₀ /G4OH/MP-SBA-15	8	57.4

^aAll reactions were carried out with 0.05 mmol of aldehydes, 0.075 mmol of MI, 1 mol% catalyst in toluene (except entry 6) at 0-35 °C for 2 h. ^bSolvent: CD₃CN.

IR study. A series of FT-IR experiments was carried out to elucidate the reaction mechanism. For the pure MI, the stretching vibration frequency of the CN group was 2163 cm⁻¹; for the C=O group it was 1763 cm⁻¹. A fresh solution of Au₆₀/G4OH was concentrated by rotary evaporation to dryness, redispersed in methanol, and used in the IR study, to avoid the strong IR absorption by SBA-15. However, after addition of MI to the Au₆₀/G4OH in methanol, the gold NPs precipitated. The precipitate was transferred onto the IR window for study. The observed CN stretching resonance was split into two bands, the major one at 2223 cm⁻¹, and the minor one at 2159 cm⁻¹. In addition, the C=O stretching peak shifted to 1753 cm⁻¹. These shifts could be explained by the formation of the enolate formed via proton abstraction from the MI, where the blue shift of the CN stretching was caused by the delocalized π -electron conjugation. 2 µL of MI was added to the Au₆₀/G4OH in methanol before a portion of the mixture was used for data

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collection, and such a procedure was repeated several times. The CN stretching peak at 2163 cm⁻ ¹ grew gradually until it had a larger intensity than the 2223 cm⁻¹ peak, because the surface of the Au NPs was gradually saturated with bound MI molecules. To the best of our knowledge, there are few precedents²⁷ in the literature for this phenomenon, observed by IR spectroscopy of the cyano group stretching vibration. On the contrary, mixing 1a and Au₆₀/G4OH in methanol did not cause apparent peak shifts of 1a, as shown in Figure 6C. These observations supported our proposal that the reaction mechanism on the Au surface was likely the same on the Au(I) complex. The tertiary amine groups on the G4OH might serve as the base to accept the proton from MI. The proposed intermediate structure is shown in Figure 6D.



Figure 6. (A) Full FT-IR spectra and (B) zoom-in view of (a) pure MI, and (b)-(e) increasing amount of MI in a Au₆₀/G4OH-methanol suspension. (C) Full FT-IR spectra of (a) G4OH/MeOH, (b) 1a/MeOH, and (c) 1a/G4OH/MeOH. (D) The proposed intermediate structure: the deprotonated MI forms an enolate on the gold surface, and the tertiary amines in the dendrimer function as the Brønsted base to accept the proton from MI.

The current work provides a firm basis for the development of efficient heterogenized homogeneous catalysts with high stereoselectivity in aldol reactions. We established that larger pore sizes of the support and the use of a hydrophobic solvent leads to a high selectivity for the *trans* product in the conversion of aldehydes and MI to 2-oxazolines. The reaction mechanism on the Au surface was found to be analogous to the homogeneous Au(I) catalyzed transformation. The rate-limiting step involves electrophilic attack of the aldehyde on the enolate formed from the deprotonated MI, which was supported by the Hammett study and IR study. Furthermore, the use of a heterogenized homogenous gold catalyst at room temperature in a hydrophobic solvent did not cause any observable leaching or catalyst deactivation. Thus, the high selectivity of our catalyst in the studied aldol reaction adds to the benefits of simple post-reaction work-up and catalyst recyclability, which will lead to a green version of this chemistry.

ASSOCIATED CONTENT

Supporting Information.

Supporting Information Available: Experimental Details and supplementary data (PDF). This material is available free of charge via the Internet at <u>http://pubs.acs.org</u>.

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AUTHOR INFORMATION

Corresponding Author

*fdtoste@berkeley.edu

*somorjai@berkeley.edu

Present Addresses

#Divisão de Metrologia de Materiais, Instituto Nacional de Metrologia, Qualidade e Tecnologia,

Av. Nossa Senhora das Graças, 50, 25250-020, Duque de Caxias, RJ, Brazil.

Author Contributions

 \perp R. Y., J. Z., and B. Y. contributed equally.

Notes

The authors declare no competing financial interests.

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