CHIRAL Rh/SiO₂ CATALYSTS FOR ENANTIOSELECTIVE HYDROGENATION REACTIONS. THE ROLE OF (S,S)-DIPAMP AS CHIRAL MODIFIER AND STABILIZER ON METALLIC NANOPIERCLES SYNTHESIS

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ABSTRACT

Rhodium nanoparticles were successfully stabilized by the (S,S)-1,2-ethanediylbis[(2-ethoxyphenyl)phenylphosphine] (S,S)-DIPAMP deposited on SiO₂ prepared by a facile reduction and impregnation method. The chiral catalysts obtained were efficient for the enantioselective hydrogenation reactions of prochiral compounds. The catalysts synthesized from [Rh(μ-OMe)(COD)]₂, in the presence of different amounts of a ligand used as chiral stabilizer, showed good metal dispersion. As shown by TEM, the metal particle size ranged between 1 and 2 nm using stabilizer and 9.1 nm was achieved without chiral ligand. Other techniques were used to characterize the chiral catalysts such as X-ray diffraction (XRD), electron diffraction, thermogravimetric analysis (TGA) and N₂ adsorption-desorption isotherms.

(S,S)-DIPAMP was used as the stabilizer of metal particles to prevent growing and agglomeration, and it also acts as chiral modifier inducing enantioselectivity in the asymmetric hydrogenation of 3,4-hexanodione (HD), ethyl pyruvate (EP), ketopantolactone (KP), and acetophenone (AP). Under specific conditions such as 25 °C, 40 bar of H₂ and substrate/Rh=100, 1%Rh-(S,S)-DIPAMP/SiO₂ chiral catalysts showed excellent catalytic performance with conversion and enantiomeric excess (ee) levels up to 99% and 54% respectively.

Keywords: (S,S)-DIPAMP, stabilized nanoparticles, enantioselective hydrogenation, rhodium, chiral ligand.

INTRODUCTION

Nowadays, catalysis is one of the most essential research areas of metal nanoparticles¹-³. Controlled sized metal nanoparticles (NPs) have received considerable attention due to their high surface area compared to bulk catalytic materials⁴-⁵. Metal agglomeration is an undesired process, mainly in catalytic reactions, because it leads to loss some properties associated with the “nano state”. Chiral stabilizer agents control metal growing generating high amount of metal particles on the asymmetry surface⁶-⁷. One of the strategies to take advantage of the abilities of the stabilizer agents and use them for catalytic applications is the deposition of chiral nanostructured metal colloids on catalyst supports such as SiO₂ and other mesoporous materials. Chiral modification of metal surfaces has expanding successfully the powerful potential of heterogeneous metal catalysts⁸-¹⁰. One of the most successful reactions in this area is the asymmetric hydrogenation of α, β-keto esters and ketones¹¹. Synthesis of enantiopure alcohols is of vital importance in pharmaceutical and flavoring industries¹²-¹⁴. Alcohols are commonly synthesized by metal NPs such as Rh, Ru, Ir and Pt. A few research groups have focused their studies in this area, the asymmetric hydrogenation of α, β-keto esters and ketones¹⁵. Considering previous statements, both composition of NPs and prevention of particle aggregation of immobilized systems are critical features required by heterogeneous catalysts to be used in enantiomeric reactions.

This paper report the effective performance of a synthesized catalysts having rhodium nanoparticles supported on SiO₂¹⁶,¹⁷,¹⁸. The catalysts were synthesized by ligand and reduced oxygen displacement from organometallic precursor in the presence of (S,S)-DIPAMP (see Fig. 1) and SiO₂ on H₂. Adding different amounts of a chiral ligand controls the metal average diameters, increasing specific metal surface area, metal dispersion and also obtaining asymmetric heterogeneous catalysts useful in enantioselective hydrogenation of HD, EP, KP and AP, as shown in figure 1. All products of these reactions have applications in chiral drugs syntheses¹⁹-⁰⁰.

EXPERIMENTAL

Unless noted otherwise, all experiments were carried out using standard Schlenk and vacuum-lines. Substrates and solvents used in this study were analytical grade and treated by standard methods²¹,²²,²³. Materials

RhCl₃·3H₂O, ethyl pyruvate (98%, 1.045 g mL⁻¹), cis,cis-1,5-cyclooctadiene (COD) ≥95%, (S,S)-DIPAMP ≥95% and KOH (≥85%) were used as received from Aldrich without further purification.

Acetophenone (99.0%, 1.03 g mL⁻¹), was purchased from Fluka and distilled prior reactions.

Ketopantolactone (97%), 3,4-hexanodione (95%, 0.939 g mL⁻¹), pentane, tetrahydrofuran and dichloromethane (all of them from Aldrich), chloroform, cyclohexane, methanol, diethylether and ethanol (96%), all from Merck, were distilled prior reactions. THF was treated with metallic sodium. Precursors and catalysts were prepared under purified N₂ atmosphere.

N₂ and H₂ (99.995% of purity) were purchased from Linde. SiO₂ BASF was heated at 150 °C for 2 h before use to remove surface residues. Chemical structure of the key compounds used in this work, such as the chiral ligand, organometallic precursor and substrates are shown in Figure 1.

Synthesis of organometallic precursor

The organometallic precursor [Rh(μ-Cl)(COD)]₂ was prepared from Rh(μ-Cl)(COD)]₂.

Rh(μ-Cl)(COD)]₂ (175 mg, 0.36 mmol) dissolved in 2RhCl₃ + 2COD + 2CH₂CH₂OH → [Rh(μ-Cl)(COD)]₂ + 4HCl + 2CH₂CHO (eq. 1)

Finally, [Rh(μ-Cl)(COD)]₂ (175 mg, 0.36 mmol) dissolved in
dichloromethane (15 mL) was added to a solution of KOH (40 mg, 0.71 mmol) in methanol (5 mL). Immediately a dark yellow solid, [Rh(μ-OMe)(COD)], precipitates. After 30 minutes of stirring at room temperature, the solvent was removed under vacuum. Yellow precipitate was mixed with 10 mL of methanol and 15 mL of water. Then, the solution was filtered, washed (H₂O, 3x5 mL) and finally under dried vacuum without further purification. The yield of this step was 75%. The reaction controlling this step is represented below:

\[ [\text{Rh(μ-Cl)}(\text{COD})]_2 + 2\text{KOH} + 2\text{MeOH} \rightarrow [\text{Rh(μ-OMe)}(\text{COD})]_2 + 2\text{KCl} + 2\text{H}_2\text{O} \ (\text{eq. 2}) \]

**Synthesis of metal NPs supported**

The precursor, [Rh(μ-OMe)(COD)], was dissolved in 80 mL of THF, in the presence of certain amount of (S,S)-DIPAMP ligand (L). The Rh/L ratio varied from 0.2 to 1.0. The metal was reduced at 25 °C and 3 bar H₂, under stirring for 20 h.

Appropriate amount of rhodium nanoparticles was added onto dried SiO₂, obtaining 1wt% of Rh NPs on SiO₂. THF was added at the mixture, it was stirred overnight at 298 K, and then it was dried under vacuum for 3 h. Finally, chirally modified catalyst was washed overnight with pentane (3 x 25 mL) under vacuum at 40 °C.

Rhodium nanoparticles and 1wt% supported rhodium nanoparticles samples were labeled as Rh-xL and Rh-xL/Si, respectively, where L represents (S,S)-DIPAMP and x represents molar ratio of rhodium to ligand (Rh/L) ratio.

**Catalysts characterization**

Metal particle size (diameter) was determined by transmission electron microscopy (TEM) and electron diffraction using JEOL JEM-1200 model EXII. Metal dispersion on SiO₂ was calculated from the relationship between surface and total atoms. Additionally, mean particle size (cubic model) was also estimated by TEM.

Nitrogen adsorption-desorption isotherms at 77 K were obtained in a Micromeritics ASAP 2010 (CHEMI). Brunauer, Emmett and Teller (B.E.T) and Barrett, Joyner and Halenda (B.J.H) models allowed to obtain specific surface area, pore diameter and pore volume of all catalysts tested in this study.

Thermogravimetric Analyser on 100 mL/min Helium from 30 ºC to 800 ºC at 1 º/min. XRD allows to identify the phases present in the catalysts. TG analyses were conducted by TGA/SDTA 851 Mettler Toledo Thermogravimetric Analyser on 100 mL/min Helium from 30 °C to 800 °C at 10 °C/min. TG technique allows to relate the mass loss versus temperature and possible interactions between metal and ligand.

**Enantioselective hydrogenations reactions**

Hydrogenation reactions were performed in a stainless steel semibatch reactor coated with Teflon. Typically, 50 mL of solvent was used in all reactions at 40 bar of pressure, room temperature, stirring speed of 800 rpm, and molar ratio [substrate/metal] of 100. The solvent used for HD, EP and AP substrates was cyclohexane and toluene for KP.

The experimental conditions used in this study were carefully selected to avoid mass transfer limitations.

Analyses of reagents and products concentrations were determined using a SHIMADZU GC-MS, model QP5050, equipped with a chiral column Beta DEX 225 (Supelco) of 30 m long and 0.25 mm of diameter. Carrier gas used was helium (99.995% of purity). Optical yields expressed as ee values, were calculated with the following equation:

\[ \text{ee (％)} = \frac{([R]-[S]) \times 100}{([R]+[S])} \ (\text{eq.3}) \]

**RESULTS AND DISCUSSION**

**Catalysts characterization**

Stabilized Rh nanoparticles showed smaller metal diameters than non-stabilized Rh NPs for both free and supported NPs. Accordingly, stabilized rhodium NPs exhibited high dispersion (58%) having average metal diameter lower than 2 nm (see table 1). Conversely, non-stabilized Rh NPs displays an average metal diameter as high as 9.1 nm showing metal dispersion of 10%. Additionally, results showed in table 1 revealed that stabilized free and stabilized supported Rh nanoparticles possess similar metal particle size. Figure 2 shows particle size distribution and TEM micrographs and of Rh samples. As expected, these observations connected stabilizing properties of the (S,S)-DIPAMP ligand with the control of the agglomeration of supported nanoparticles, making this procedure a useful, easy and reproducible method of preparing materials for catalytic purposes.

**Table 1. Average particle size (d) and metal dispersion (D) of free, stabilized and supported NPs.**

<table>
<thead>
<tr>
<th>Sample</th>
<th>dTEM (nm)</th>
<th>D (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rh</td>
<td>4.8</td>
<td>-</td>
</tr>
<tr>
<td>Rh/Si</td>
<td>9.1</td>
<td>10</td>
</tr>
<tr>
<td>Rh-0.2L</td>
<td>1.5</td>
<td>-</td>
</tr>
<tr>
<td>Rh-0.2L/Si</td>
<td>1.6</td>
<td>58</td>
</tr>
<tr>
<td>Rh-0.4L</td>
<td>1.5</td>
<td>58</td>
</tr>
<tr>
<td>Rh-0.4L/Si</td>
<td>1.5</td>
<td>58</td>
</tr>
<tr>
<td>Rh-0.7L</td>
<td>1.5</td>
<td>-</td>
</tr>
<tr>
<td>Rh-0.7L/Si</td>
<td>1.6</td>
<td>58</td>
</tr>
<tr>
<td>Rh-1.0L</td>
<td>1.5</td>
<td>-</td>
</tr>
<tr>
<td>Rh-1.0L/Si</td>
<td>1.7</td>
<td>54</td>
</tr>
</tbody>
</table>

**Figure 2.** Size distribution histograms and TEM micrographs and of stabilized and non-stabilized Rh catalysts.
Specific surface area and pore volume determined from N\textsubscript{2} adsorption-desorption isotherms are displayed in Table 2. Supported samples, in agreement to the classification Brunauer, Deming, Deming and Teller (B.D.D.T), showed type IV isotherms with a hysteresis loop. The isotherms are characteristic of mesoporous solids mainly with pores cylindrical geometry. Specific surface area values ranged from 136 to 76 (m\textsuperscript{2} g\textsuperscript{-1}) for non-stabilized Rh and stabilized catalysts, respectively indicating that ligand partially blocks the propus structure of the support. The average pore diameter decreased from 31 to 18 nm as stabilized nanoparticles were deposited onto the pores of the support.

The molecular diameters of prochiral substrates are considerably smaller than the pore diameter of the material. Therefore, it allows an appropriate diffusion of the reactants and products from to the active sites.

Table 2 also compiles results obtained from TG analyses. All supported catalysts show thermograms indicating that desorption of physisorbed water is completed at 150°C and is followed by a broad region of weight loss, due to dehydroxylation process. In thermograms the maximum loss of mass is above to 400 °C until 550 °C. It can be seen an important increase of % weight loss according with the amount of (S,S)-DIPAMP added in the NPs synthesis, indicative of the chiral ligand is on catalysts surface. Decomposition around 500 °C is indicating that there is likely a chemical interaction between (S,S)-DIPAMP and Rh/Si\textsubscript{O}\textsubscript{2}, as shown previous reports.

Table 2. Surface area, pore volume and mass loss of stabilized and non-stabilized Rh catalysts.

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>S\textsubscript{B.E.T.}, m\textsuperscript{2} g\textsuperscript{-1}</th>
<th>V\textsubscript{pore}, cm\textsuperscript{3} g\textsuperscript{-1}</th>
<th>% wt loss\textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rh/Si</td>
<td>136</td>
<td>31</td>
<td>7.0</td>
</tr>
<tr>
<td>Rh-0.2L/Si</td>
<td>84</td>
<td>19</td>
<td>7.8</td>
</tr>
<tr>
<td>Rh-0.4L/Si</td>
<td>80</td>
<td>18</td>
<td>8.4</td>
</tr>
<tr>
<td>Rh-0.7L/Si</td>
<td>76</td>
<td>18</td>
<td>8.7</td>
</tr>
<tr>
<td>Rh-1.0L/Si</td>
<td>81</td>
<td>19</td>
<td>8.9</td>
</tr>
</tbody>
</table>

\textsuperscript{a} % wt loss from 350 °C up to 600 °C.

No visible diffraction lines attributable to rhodium crystalline phase of Rh-(x)L/Si catalysts appeared in XRD patterns, due to Rh has small particle diameter and the metal loading in these catalysts were was 1% wt of rhodium. On the contrary, non-stabilized Rh catalyst diffraction peaks, which had higher average particle diameter, showed up 29° = 41.0° and 47.3° representing (111) and (200) planes of rhodium phase. The most intense peak at 41.0° was corroborated by electron diffraction analysis showing Rh (111). As mentioned elsewhere, XRD and electron diffraction analysis allow to verify crystalline components on solid catalysts. Finally, electronic state of Rh on the surface of each catalyst, after exposure to H\textsubscript{2} at 30 °C for 1 h, was analyzed by XPS showing that rhodium-phase was mainly reduced. Previous work confirmed that rhodium 3d\textsubscript{5/2} appears mainly reduced at 307.3 eV binding energy.

**Enantioselective hydrogenation reactions**

The main objective of this study was to investigate catalytic activity and selectivity in enantioselective hydrogenation reactions of supported rhodium NPs stabilized by (S,S)-DIPAMP. Additionally, the nature of the substrate and (S,S)-DIPAMP loading on supported rhodium NPs were also studied.

Typically, asymmetric hydrogenation of EP (Fig. 3a) is used as test reaction in order to evaluate both activity and enantioselectivity of new catalysts. Consequently, Rh-xL/SiO\textsubscript{2} catalysts were tested on the enantioselective hydrogenation of EP, showed in Figure 3b, exhibiting good performance in the transformation of EP.

According to previous works, as expected, the addition of a phosphorous ligand such as (S,S)-DIPAMP allows to obtain the preferential formation of the (R) with respect to (S) isomer. In Figure 3c is shown the preferential formation of (R)-ethyl lactate using Rh-0.4L/Si catalyst.

The formation of 4-(R)-hydroxy-3-hexanone from HD achieved values up to 54%. Maximum conversion was 94% at 300 min (Table 3, Fig. 4). Although, similar behavior was expected for the reaction of AP, an aromatic ketone, low conversion was observed due probably to an increased interaction of the aromatic ring with the surface of the catalysts. However, further studies are needed to draw a conclusion. This work shows promising results of enantioselectivity in very scarcely studied substrates to date.

![Figure 3. Enantioselective hydrogenation of EP (a) Reaction scheme, (b) conversion on time with Rh-xL/Si catalysts and (c) evolution of the hydrogenation of EP on time using Rh-0.4L/Si. Reaction conditions: 0.02 mol L\textsuperscript{-1}, at 40 bar of H\textsubscript{2}, 298 K and cyclohexane as solvent using 100 mg of catalysts.](image)

![Figure 4. Enantioselective hydrogenation of HD, under following reaction conditions: 0.02 mol L\textsuperscript{-1}, 100 mg of Rh-xL/Si catalysts in cyclohexane at 40 bar of H\textsubscript{2} and 298 K. (a) Reaction scheme, (b) conversion on time.](image)

The activity of Rh-xL/Si catalysts in the enantioselective hydrogenation of KP is showed in Figure 5. All catalysts achieved complete conversion of KP excepting Rh-0.4L/Si. Among all reactants tested, KP was quickly converted at low reaction time attributed to high reactivity of these ketones. Furthermore, keto group reactivity increases with the presence of the ester carbonyl group in a position.

In contrast to high conversion of KP, low ee values were accomplished as shown in Table 3. This low enantioselectivity is probably because KP preferred unmodified metal sites. The induction time observed on Rh-0.4L/Si catalyst may be due to formation of dimers of KP. These side reactions may be limiting enantiodifferentiation.

Contamination of catalyst surfaces can not be argued as a reason of the induction time observed in this system, because it is well known that clean surfaces are favored when organometallic precursors were used in the preparation of heterogeneous catalysts.
Table 3. Conversion, enantioselectivity values and pseudo first-order rate constants of hydrogenation reactions of HD, EP, AP and KP. Conditions: 0.02 mol L\(^{-1}\) of substrate and 100 mg of Rh-xL/Si catalysts in cyclohexane at 298 K and 40 bar of H\(_2\).

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Catalyst</th>
<th>% Conv.(^a)</th>
<th>(k) (min(^{-1}) g(_{\text{cat}})^{-1} mol 10(^{-3}))(^b)</th>
<th>% ee(_{\text{max}})(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EP</td>
<td>Rh 0.2-L/Si</td>
<td>49</td>
<td>0.17</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>Rh 0.4-L/Si</td>
<td>91</td>
<td>0.63</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>Rh 0.7-L/Si</td>
<td>84</td>
<td>0.32</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>Rh 1.0-L/Si</td>
<td>84</td>
<td>0.48</td>
<td>7</td>
</tr>
<tr>
<td>HD</td>
<td>Rh 0.2-L/Si</td>
<td>94</td>
<td>1.12</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td>Rh 0.4-L/Si</td>
<td>85</td>
<td>0.62</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>Rh 0.7-L/Si</td>
<td>74</td>
<td>0.59</td>
<td>47</td>
</tr>
<tr>
<td></td>
<td>Rh 1.0-L/Si</td>
<td>85</td>
<td>0.52</td>
<td>54</td>
</tr>
<tr>
<td>KP</td>
<td>Rh 0.2-L/Si</td>
<td>98</td>
<td>0.92</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Rh 0.4-L/Si</td>
<td>77</td>
<td>0.12</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>Rh 0.7-L/Si</td>
<td>100</td>
<td>1.01</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Rh 1.0-L/Si</td>
<td>100</td>
<td>0.92</td>
<td>8</td>
</tr>
<tr>
<td>AP</td>
<td>Rh 0.2-L/Si</td>
<td>83</td>
<td>0.73</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Rh 0.4-L/Si</td>
<td>36</td>
<td>0.11</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td>Rh 0.7-L/Si</td>
<td>78</td>
<td>0.09</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Rh 1.0-L/Si</td>
<td>70</td>
<td>0.01</td>
<td>14</td>
</tr>
</tbody>
</table>

\(^a\) % Conversion at 300 min of reaction. \(^b\) Pseudo first-order rate constants was calculated up to 60 min. \(^c\) % ee max referred to maximum value of (R)-enantiomer.
Additionally, previous results also suggested no leaching of Rh during reaction. It was also found that ketones hydrogenation led to higher ee than α-keto esters hydrogenations reactions. This paper shows that the activity and selectivity of asymmetric catalysts tested for this study showed both high activity and enantioselective resolution in the evaluated reactions. Rh-0.2L/Si catalyst was the most active catalyst for HD and AP enantioselective reactions, whereas for the hydrogenation of KP was the Rh-0.7L/Si catalyst. Ethyl pyruvate showed lower activity and selectivity levels with these catalysts. In the hydrogenation of HD and AP, 54% and 46% of enantiomeric excess were obtained, respectively. It was also found that ketones hydrogenation led to higher ee than α-keto esters hydrogenations reactions. This paper shows that the activity and selectivity of catalysts are directly related to the size and nature of the metal nanoparticles. 

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CONCLUSIONS

Chiral NPs can be synthesized under mild conditions using (S,S)-DIPAMP as metal particle stabilizer. Stabilized supported Rh nanoparticles show metal average smaller than 2.5 nm, with 58% of dispersion showing that aglomeration of NPs can be controlled by this preparation method. Consequently, it was shown that asymmetric catalysts tested for this study showed both high activity and enantioselectivity in the evaluated reactions. Rh-0.2L/Si catalyst was the most active catalyst for HD and AP enantioselective reactions, whereas for the hydrogenation of KP was the Rh-0.7L/Si catalyst. Ethyl pyruvate showed lower activity and selectivity levels with these catalysts. In the hydrogenation of HD and AP, 54% and 46% of enantiomeric excess were obtained, respectively. It was also found that ketones hydrogenation led to higher ee than α-keto esters hydrogenations reactions. This paper shows that the activity and selectivity of catalysts are directly related to the size and nature of the metal nanoparticles. 

Non stabilized catalysts generated wide distribution of metal sizes on solids and makes impossible the repeatability in hydrogenation reactions, obtaining racemic mixtures of products.

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