Published in final edited form as:

React Funct Polym. 2009 September 1; 69(9): 650–654. doi:10.1016/j.reactfunctpolym.2009.04.006.

Nanostructured Biomimetic Catalysts for Asymmetric Hydrogenation of Enamides using Molecular Imprinting Technology

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Abstract

A new class of heterogeneous catalysts for asymmetric hydrogenation of enamides was synthesized using molecular imprinting technology. These new catalysts are molecularly imprinted polymers (MIPs) made from rhodium (I) and copper (II) complexes with the bis(oxazoline) chiral ligands. One of the Rh-MIPs showed 87% ee toward L-enantiomeric product while the Cu-MIP showed 82% ee toward D-enantiomeric product. Both MIPs are easy to separate and reusable.

Keywords

biomimetic catalyst; heterogeneous catalysts; molecular imprinting; asymmetric hydrogenation; bis(oxazoline); enamides

Introduction

Enantiomers of bioactive compounds usually have distinctly different physiological effects because their biological receptors recognize them differently. For example, the amino acids *R*-phenylalanine and *S*-phenylalanine taste sweet and bitter, respectively. In 1992, FDA issued a policy statement for the development of new stereoisomeric drugs. Since then, there has been a persistent move toward development of single-enantiomer drugs. As of 2001, racemic mixtures are virtually no longer registered with the FDA [1]. Asymmetric synthesis, which produces predominately one enantiomer, has become one of the most important areas in synthetic chemistry. It plays an important role in the pharmaceutical industry [2], the petrochemical industry [3], as well as fine chemical and agrochemical industries [4]. The current approaches for asymmetric synthesis use enzymes, homogeneous chiral metal-containing complexes [5], or a combination of the two [6]. Enzymes are biocatalysts which possess high selectivity and efficiency. They often suffer from poor stability and availability for many reactions. Homogeneous asymmetric catalysts consist of a central metal atom (Ru, Rh, Ti, Zr, Pd, etc) and a chiral ligand. While these catalysts have been successfully used in asymmetric synthesis, they also have following drawbacks. (a) It is difficult to extrapolate the results obtained for a particular substrate to even a close analog. As customized synthesis becomes more widely used, a technology suitable for tailor-made asymmetric synthesis is

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needed. (b) These chiral ligands and metals are usually very expensive and not easily available. (c) There are also drawbacks associated with homogenous catalysts, such as poor stability, separation difficulties, and loss of catalysts. To this end, efforts have been made to prepare heterogeneous asymmetric catalysts including modified classical heterogeneous catalysts, chiral polymers, and immobilized metal complexes. However, only limited success has been achieved [7–9].

Molecular imprinting (sometimes called templated polymerization) is a technique for making synthetic polymers that have specific recognition properties [10–12]. During molecular imprinting, the template molecule and functional monomers first arrange in a certain fashion according to their interactions that include both functional and shape complementarity. The preorganized complex is then copolymerized with a crosslinker. After polymerization, the template molecule is extracted, leaving a specific site for rebinding the template molecule. Using this technique, nanostructured materials with specific recognition sites are generated [13]. It has been demonstrated that this technique can be used effectively in chiral separation [14], synthesis of artificial antibodies [15], and even making biomimetic catalysts [11,16].

Introduction of a catalytic metal into the imprinted cavity thus may create an environment similar to the aforementioned chiral metal-containing complex in which the transformation is performed by metal catalysis, whereas the stereochemistry is controlled by the chiral environment surrounding the metal. Recently, there have been several reports on synthesis of heterogeneous catalysts with immobilized transition metals using molecular imprinting [17–22]. Among these reports, a few of the imprinted polymer catalysts are for asymmetric synthesis. For example, Lemaire et al studied the enantioselective reduction of prochiral ketones [23] using Rh-containing MIPs. In this system, both the monomer (diamine ligand) and the template (sodium 1-(R or S)-phenylethanolate) are chiral. The molecularly imprinted polymer (MIP) catalyzed the reduction with an ee of 70%. Asymmetric ketone reduction using MIPs was also studied by Polborn and Severin using a chiral rhodium (III) catalyst [24]. They used a polymerizable chiral Rh-ligand complex as the monomer, and a transition state analog (which is achiral) as the template to synthesize the MIP catalyst. The Rh-MIP catalyzed the asymmetric reduction of acetophenone with a remarkable 95% ee. Gagne et al studied the enantioselective ene reaction using Pt-containing MIPs [18,25]. In this system, a defined coordination to the metal-template was used to set up geometry and stereochemistry in the site that would dictate subsequent ligand (or reactant) binding and enantioselectivity. One of the MIP catalysts could catalyze the ene reaction with an ee of 72%.

As one can see, MIPs with transition metals can be very effective catalysts for asymmetric syntheses. The principle behind the approach is similar to that of metalloenzymes and homogenous asymmetric catalysts [20]. The activity and stereoselectivity is determined by the nature of the metal ion and the first coordination sphere (where the chiral ligands are involved). Furthermore, a well-defined second coordination sphere is also important (where the chiral cavity is involved).

Asymmetric hydrogenation of olefins is a type of reaction that is very important in understanding fundamental chemistry as well as practical applications [26,27]. Recently, the reaction was studied using polymer-supported rhodium complexes [28,29]. However, to our knowledge, no study has been reported on asymmetric hydrogenation of olefins using metal-containing molecularly imprinted polymers. The paper presents a new class of heterogeneous catalysts for asymmetric hydrogenation, combining transition metal catalysis and molecular imprinting technology. The ligands are nitrogen-based chiral bis(oxazolines); while the metals include rhodium and copper. Asymmetric hydrogenation of enamides (Figure 1) is used as a model reaction due to its significance in the pharmaceutical industry. Hydrogenation products

of this class of compounds include widely used drugs such as L-DOPA (a drug used for treatment of Parkinson's disease) and many other biologically active compounds.

Material and Methods

Material

Styrene and α -acetamidocinnamic acid were purchased from Fluka; $[\text{Rh}(\text{cod})_2]\text{BF}_4$ was from Strem Chemicals; N-Acetyl-D-phenylalanine methyl ester (Ac-D-Phe-OMe) and N-Acetyl-L-phenylalanine methyl ester (Ac-L-Phe-OMe) were from BACHEM. The following chemicals were purchased from Sigma-Aldrich: 2,2'-azoisobutyronitrile (AIBN), methyllithium, methacrylic acid (MAA), ethylene glycol dimethacrylate (EDMA), (trimethylsilyl) diazomethane (TMSCHN_2), 2,2'-methylenebis[(4S)-4-phenyl-2-oxazoline], allyl bromide, [(S)-BINAPINE(cod)Rh] BF_4 , $\text{Rh}(\text{cod})_2\text{BF}_4$, and copper(II) trifluoromethanesulfonate. Other chemical used were of analytical or HPLC grade. CHIRALCEL OD-H HPLC column (4.6 $\times$ 250 mm) was purchased from Chiral Technologies Inc.

Methods

1. Synthesis of methyl-(Z)- α -N-acetamidocinnamate (MAC) [30]—One gram of α -acetamidocinnamic acid (4.9 mmol) was dissolved in 10 mL toluene/methanol (3:2 v/v) in a 50-mL round-bottom flask. To which, 3.9 mL trimethylsilyldiazomethane (TMSCHN_2) (7.8 mmol) was added dropwise until the solution turns yellow. The solution was then stirred for additional 30 min. Evaporation of solvents yielded 0.98 g of yellow crystal (98% yield). TLC showed single spot using acetonitrile/methanol (70/30 v/v) as the mobile phase. ^1H NMR (CDCl_3 , 300 MHz): δ (ppm) 2.01 (s, 3H), 3.78 (s, 3H), 7.2–7.5 (m, 6H), 7.7 (s, 1H). ^{13}C NMR (CDCl_3 , 300 MHz): δ (ppm) 169.4, 165.6, 137.6, 133.4, 132.4, 129.6, 129.2, 128.8, 128.3, 128.0, 125.1, 124.5, 52.3, 22.8, 21.1. IR(KBr): 3011, 2949, 1720, 1667, 1536, 1470, 1380, 1249, 1131, 772, 698 cm^{-1} .

2. Synthesis of the bis(oxazoline) chiral ligand: 2,2'-(1-Allylbut-3-enylidene)bis[(4S)-4-phenyl-4,5-dihydro-2-oxazole] (Figure 2) [31]—2,2'-methylenebis[(4S)-4-phenyl-2-oxazoline] (0.250 g, 0.816 mmol) was placed in a 100-mL three-neck round bottom flask. The flask was put in a dry ice bath (-55°C) prepared using dry ice and ethylene glycol/ethanol (60:40 v/v) [32]. Then 50 mL anhydrous THF was added into the flask until the solution turns clear while purging with nitrogen. Methyllithium (1.38 mL, 2.2 mmol) was added, and the mixture was stirred for 1 h. Allyl bromide (0.19 mL, 2.2 mmol) was then added dropwise using a syringe. The reaction was stirred at -10°C for 3 h. The reaction mixture was extracted with 3 $\times$ 30 mL of saturated NH_4Cl . The organic layer was dried with MgSO_4 , and filtered. Evaporation of solvent yielded 0.225 g solid chiral ligand (88% yield). The ligand was further purified by column chromatography using end-capped silica gel as by described by Fraile et al.[33]

^1H NMR (CDCl_3 , 300 MHz): δ (ppm) 7.2–7.3 (m, 10H) 5.8 (m, 2H), 5.3 (dd, 2H), 5.2 (m, 4H), 4.7 (dd, 2H), 4.2 (t, 2H), 2.9 (d, 4H). ^{13}C NMR (CDCl_3 , 300 MHz): δ (ppm) 167.9, 142.2, 132.8, 128.7, 127.6, 126.8, 118.9, 75.2, 69.7, 46.1, 37.7. IR(KBr): 3084, 3027, 2868, 1654, 1491, 1029, 731 cm^{-1} .

3. Synthesis of metal complexes with the bis(oxazoline) chiral ligand

a. Synthesis of rhodium complex [34]: Dichloromethane (15 mL) was purged with nitrogen to final volume of 10 mL, while a 100-mL three-neck round bottom flask was purged with nitrogen in a glove box. In the glove box, the rhodium complex $\text{Rh}(\text{cod})_2\text{BF}_4$ (0.3 g, 0.8 mmol) and dichloromethane were transferred to the beaker that contained the bis(oxazoline) chiral ligand (0.256 g, 0.658 mmol). The mixture was then transferred to the round bottom flask. The

flask was sealed with rubber septum and stirred for 1h at room temperature. The product was further purified by column chromatography using end-capped silica gel as by described by Fraile et al. [33]

^1H NMR (CDCl_3 , 300 MHz): δ (ppm) 7.2–7.3 (m, 10H) 5.8 (m, 2H), 5.3 (dd, 2H), 5.2 (m, 4H), 4.7 (dd, 2H), 4.2 (t, 2H), 2.9 (d, 4H). ^{13}C NMR (CDCl_3 , 300 MHz): δ (ppm) 167.9, 142.2, 132.8, 128.7, 127.6, 126.8, 118.9, 75.2, 69.7, 46.1, 37.7. IR(KBr): 3084, 3027, 2868, 1658, 1491, 1029 (weak), 735 cm^{-1} .

b. Synthesis of copper complex [35]: The same procedure as the above was used except that Cu(II) trifluoro methane sulfonate (Copper (II) triflate) was added in place of Rh(cod) $_2$ BF $_4$. The complexation was verified by TLC and UV/Vis scan spectrum.

4. Synthesis of imprinted polymers

a. Synthesis of MAC-MIP: In the glove box, after purging with nitrogen, MAC (the imprint or template, 0.144g, 0.658 mmol), MAA (0.0566g, 0.658 mmol), Styrene (0.0685g, 0.658 mmol) and EDMA (1.57g, 7.90 mmol) were added (1:1:1:12 molar ratio) with the Rh-ligand or Cu-ligand complex (0.256g, from step 3) and 10 mL degassed dichloromethane into a 25-mL test tube. The test tube was put in the fridge at 4 °C for 2h for prearrangement. AIBN (45 mg) was then added into test tube, followed by purging with nitrogen for 5 min. The polymerization was done in an incubator/shaker at 69°C overnight. Once the polymerization is completed, the test tube was crushed and the polymer was ground into small particles (ca 10 micron) in the glove box (ca. 86.7% yield). The particles were rinsed with methanol to remove the template. IR (KBr): 3500 (broad), 2980, 1699, 1634, 1380, 1237 cm^{-1}

b. Synthesis of L-MIP or D-MIP: The same procedure as the above was used except that Ac-L-Phe-OMe or Ac-D-Phe-OMe was used in place of MAC as the template.

IR (KBr): 3500 (broad), 2980, 1699, 1634, 1380, 1237 cm^{-1}

c. Synthesis of the control polymer: The same procedure as the above was used except that no template was added for polymerization.

IR (KBr): 3500 (broad), 2980, 1740, 1642, 1384 (strong), 1229 cm^{-1} (weak)

5. Hydrogenation of MAC—In a typical run, a 50 mL stainless steel pressure vessel (model 4792, Parr Instrument) was charged with catalyst (e.g., 5 mg of [(S)-BINAPINE(cod)Rh] BF $_4$), MAC (0.110 g, 0.50 mmol), and 20 mL of methanol in a glove box. The pressure vessel was then closed, set on a magnetic stirrer, and connected to H $_2$ and Ar gas lines. The reaction vessel was purged with argon then H $_2$ three times each. The hydrogen pressure was then increased to 150 psi and the hydrogenation was stopped after 24 h at room temperature. The products were analyzed by chiral HPLC using hexane:2-propanol (80:20) as mobile phase with the UV detection at 254nm. With a flow rate of 1 mL/min, MAC, D- and L- products had retention times of 20.5 min, 11.7 min, and 14.1 min, respectively. Yields and the enantiomeric excess (ee) were subsequently calculated based on calibration curves. For recycling experiments, after the hydrogenation the MIP catalysts were washed with methanol until the filtrates became clear (30 mL to 50 mL methanol); the MIP catalysts were then used for the next round of hydrogenation.

Results and Discussion

Asymmetric hydrogenation has been studied extensively and employed in the pharmaceutical industry using homogenous chiral metal complexes [26]. The mechanism of the asymmetric

hydrogenation was elucidated by Halpern in the 80's [36] and is consistent with the recent studies [27]. The catalyst, Rh (I) complex, first interacts with a bidentate enamide substrate to form a chelate complex to which hydrogen is added. The resulting Rh (III) dihydride transfers the two hydrogen atoms to the olefin bond to form the five-membered organorhodium hydride. The addition of H₂ should occur to the Rh-coordinated face of the olefin in the Rh-olefin adduct. Subsequent reductive elimination gives the chiral product and the free catalyst.

Chiral phosphine ligands have been proven very successful in homogenous asymmetric hydrogenation. However, they suffer from high cost and low stability. Thus, alternative ligands are being sought. Nitrogen-containing ligands are attractive alternatives as they are less expensive and more stable [37]. In nature, nitrogen-containing ligands are most common in metalloenzymes. Chiral bis(oxazoline) ligands have received a great deal of attention through their use in various catalytic process [38]. They are easy to synthesize, and many of them are commercially available in enantiomeric forms. They can form stable complexes with many metals including rhodium, ruthenium, palladium, copper, nickel, cobalt, titanium, etc. [39].

For the enamide, MAC, the hydrogenation products are Ac-D-Phe-OMe and Ac-L-Phe-OMe which can be separated completely on a CHIRALCEL OD-H HPLC column. To find out an optimum condition for the hydrogenation study, we started with commercially available rhodium complexes [(S)-BINAPINE(cod)Rh]BF₄ and Rh(cod)₂BF₄. Various time and H₂ pressures were applied for hydrogenation to determine the optimum hydrogenation conditions. It was found that 150 psi and 24 h are good conditions for the study. Thus, these conditions were used for most of our hydrogenation reactions.

Two strategies were employed to prepare the molecularly imprinted metal catalysts. Strategy 1 was imprinting against the substrate MAC. Strategy 2 was imprinting against a particular enantiomeric product, i.e., Ac-L-Phe-OMe or Ac-D-Phe-OMe. Table 1 summarizes results with rhodium catalysts. Figure 3 shows a scheme of Strategy 1.

One of the most effective catalysts available for asymmetric hydrogenation is [(S)-BINAPINE(cod)Rh]BF₄. One can see it produced good yield and enantiomeric excess with the preference for D- enantiomer (entry 1). The chiral preference is attributed to the chiral ligand BINAPINE. However, this catalyst is homogenous, and quite expensive. Rh(cod)₂BF₄, on the other hand, has no chiral ligand. It can catalyze the hydrogenation, but it has no enantiomeric excess within experimental uncertainty of 3% ee (entry 2). When rhodium is complexed with our synthesized bis(oxazoline) chiral ligand, it showed moderate enantiomeric preference toward L- enantiomer (24% ee), presumably due to the effect of the chiral ligand. (entry 3). When this ligand was polymerized, the enantiomeric excess decreased slightly to 20% ee (entry 4). This is not uncommon as it has been noted that in most cases immobilization process (such as polymerization) is accompanied by a decrease of enantioselectivity [40]. MIPs synthesized using MAC as the template showed significant improvement in enantioselectivity compared with the control polymer (entry 5). Although its enantiomeric excess is still modest (42% ee), it presents a 110% increase in enantioselectivity compared with the control polymer. This is likely due to the imprinting effect. MIPs synthesized using L-product as the template showed highest improvement in enantioselectivity compared with the control polymer with an 87% ee toward L-enantiomer (entry 6). This is likely due to the fact that the template itself is chiral, thus the imprinted cavity becomes chiral resulting in the preferential production of the L- enantiomeric product; while in the case of MAC-MIP, the template MAC is achiral, thus the cavity's effect on enantioselectivity of the product is not as demanding as a chiral cavity introduced by the L-product. Moreover, the ligand's chiral preference and the imprinted cavity's chiral preference are cooperative (both prefer L- enantiomer), therefore it resulted in a substantially enhanced enantioselectivity. This enantioselectivity is remarkable for a solid catalyst, and presents a 335% increase in enantioselectivity compared with the control polymer.

This is among the best MIPs in terms of enantiomeric excess. When the template was switched from L-enantiomer to D-enantiomer, the MIP still showed enantiomeric excess toward L-product (entry 7). In this case, the ligand's chiral preference and the imprinted cavity's chiral preference oppose one another (one prefers L- enantiomer, the other prefers D- enantiomer), resulting in counterproductive enantioselectivity. This also indicates that the first coordination sphere is more important than the second coordination sphere in dictating enantioselectivity. While the imprinted cavity can enhance enantioselectivity dictated by the chiral ligand as shown in entry 6, it is unlikely that the imprinted cavity can reverse that enantioselectivity.

Precious metals such as rhodium and ruthenium have shown effectiveness in asymmetric hydrogenation. However, less expensive metals such as Cu^{2+} , Co^{2+} and Ni^{2+} have not been very effective in asymmetric synthesis [41]. One of the goals of this study is to see if these metals can be effective as enantioselective catalysts when combined with molecular imprinting. Copper (II) was first selected and studied for hydrogenation of MAC, and results are summarized in Table 2. The commercially available copper(II) trifluoromethanesulfonate showed no enantioselectivity within experimental uncertainty (entry 1). The control polymer that was made from the copper (II) complex with the bis(oxazoline) chiral ligand showed moderate enantioselectivity with 46% ee toward D-enantiomeric product. To our knowledge, there has been no report of use of Cu-bis(oxazoline) based polymers for hydrogenation reaction. It has been reported that polymeric catalyst made with bis(oxazoline)-copper(II) complexes were very effective in enantioselective cyclopropanation reaction, with over 70% ee; and in some cases, the polymer catalysts showed higher ee than the homogenous counterparts [40]. MIPs made with bis(oxazoline)-copper(II) complexes using MAC as the template showed significant improvement in enantioselectivity compared with the control polymer with an impressive 82% ee toward D-enantiomeric product(entry 3). This presents a 78% increase in enantioselectivity compared with the control polymer that already has fairly good enantioselectivity. It is interesting to note that the copper MIP and rhodium MIP showed opposite enantiomeric preference, with the former for D-product and the latter for L-product. Again, this is not surprising as it had been found that different metal complexes with the same chiral ligands may display opposite enantioselectivity. For example, the Rh and Ru complexes with the same chiral diphosphine often exhibit an opposite sense of enantioselectivity in asymmetric hydrogenation [27].

One of the main advantages that heterogeneous catalysts have over homogenous catalysts is reuse of the catalyst. Homogenous catalysts are difficult to reuse due to their poor stability and separation difficulties while heterogeneous catalysts often exhibit better stability and are easy to separate. Both Rh-MIP and Cu-MIP were tested for reuse. When the first hydrogenation reaction completed, the reaction vessel was opened and the MIP catalyst was separated easily by vacuum filtration. Then methanol (65 mL) was used to wash the MIP catalyst. The catalyst was then put back into the reaction vessel for the next cycle of hydrogenation reaction. A Rh-MIP made from the chiral ligand, 2,2'-[2-(4-vinylphenyl)-1-(4-vinylbenzyl)ethyldiene]bis [(4S)-4-phenyl-4,5-dihydro-2-oxazole], was tested five times for the reusability study, no loss of enantioselectivity was observed. In contrast, the Cu-MIP retained half of its enantioselectivity for the reuse.

Conclusion

In summary, we have successfully synthesized a new class of heterogeneous catalysts for asymmetric hydrogenation of enamides combining transition metal catalysis and molecular imprinting technology. These new catalysts are MIPs made from rhodium (I) and copper (II) complexes with the bis(oxazoline) chiral ligands. One of the Rh-MIPs showed 87% ee toward L-enantiomeric product while the Cu-MIP showed 82% ee toward D-enantiomeric product. Both MIPs are easy to separate and reusable.

Acknowledgments

The authors thank Prof. Philip Beauchamp for NMR support. This work was supported by National Institutes of Health (NIH Grant 3S06GM053933).

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Figure 1.

The model reaction: asymmetric hydrogenation of an enamide

Figure 2.
The chiral bis(oxazoline) ligand used for molecular imprinting

Figure 3. Preparation of metal-containing asymmetric heterogeneous catalysts by molecular imprinting against the substrate (R_1 , R_2 = Me, Et; Cl = one ligand example)

Table 1

Hydrogenation results with rhodium (I) catalysts

Rh catalyst	Time (h)	Yield (%)	ee (%)	Enantiomer preference
[(S)-BINAPINE(cod)Rh]BF ₄	18	99.9	71	D
Rh(cod) ₂ BF ₄	24	99.9	3	—
Rh-bis(oxazoline)	24	67.5	24	L
Control polymer	24	37.5	20	L
MAC-MIP	72	99.9	42	L
L-MIP	24	49.7	87	L
D-MIP	24	66.5	22	L

Table 2

Hydrogenation results with copper (II) catalysts

Cu catalyst	Time (h)	Yield (%)	ee (%)	Enantiomer preference
Cu(II)trifluoromethane sulfonate	24	80.4	3	—
Cu-Control polymer	24	46.6	46	D
Cu-MAC MIP	24	54.2	82	D