

**Supported Catalysts**

**Chiral, Porous, Hybrid Solids for Highly Enantioselective Heterogeneous Asymmetric Hydrogenation of  $\beta$ -Keto Esters\*\***

*Aiguo Hu, Helen L. Ngo, and Wenbin Lin\**

The chemistry of hybrid solids constructed from organic linkers and metal nodes has received much recent attention, owing to the propensity of incorporating and fine-tuning

[\*] Prof. W. Lin, Dr. A. Hu, H. L. Ngo  
Department of Chemistry, CB 3290  
University of North Carolina  
Chapel Hill, NC 27599 (USA)  
Fax: (+1) 919-962-2388  
E-mail: wlin@unc.edu

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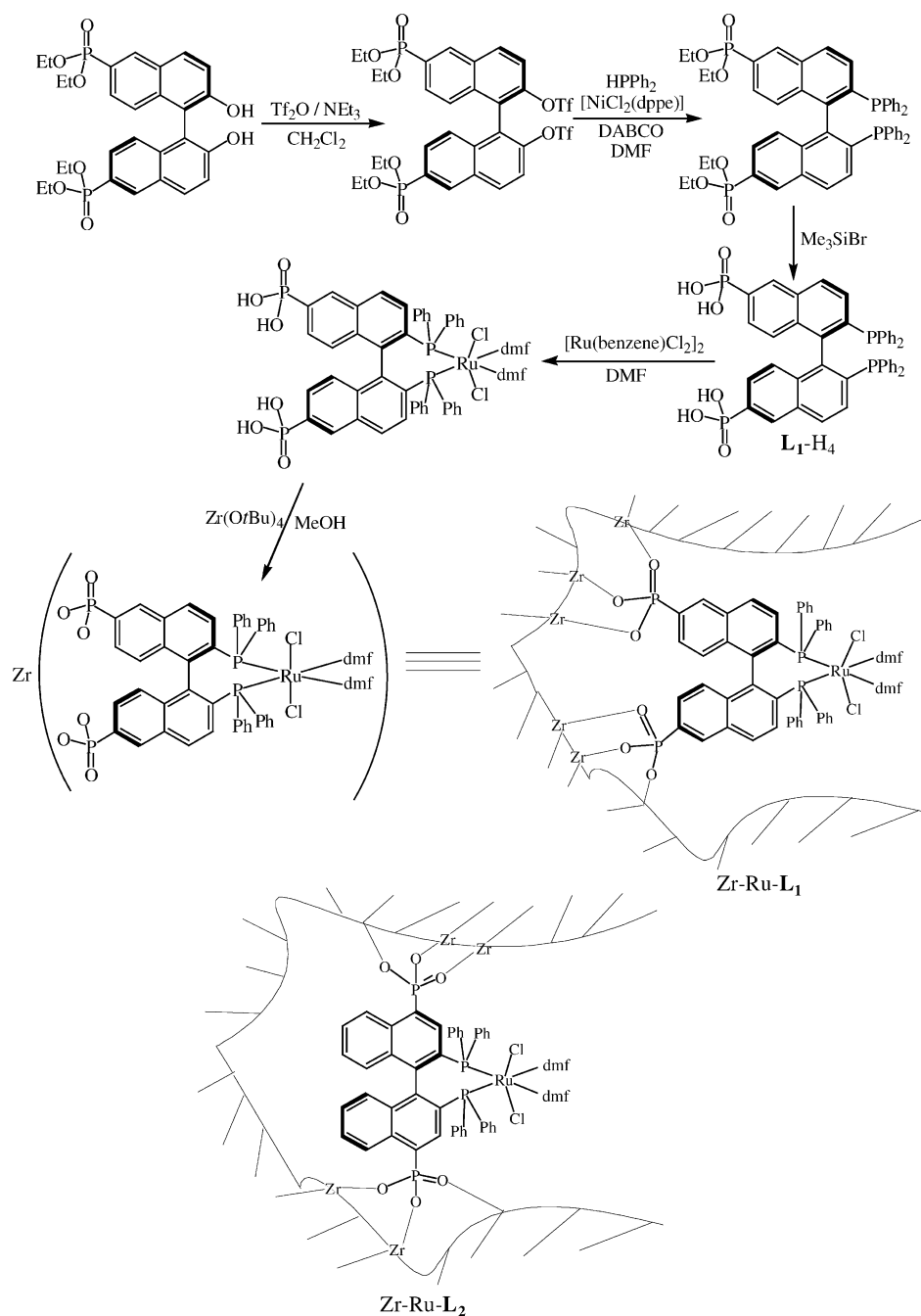
desired properties by judicious choice of the building blocks.<sup>[1]</sup> The use of biphenyl-derived bridging ligands has, for example, led to novel microporous pillared zirconium phosphonates<sup>[2]</sup> as well as ordered mesoporous organosilica hybrid solids.<sup>[3]</sup> We believe that the incorporation of axially chiral rigid organic linkers into such hybrid materials can lead to porous solids exploitable for heterogeneous asymmetric catalysis and chiral separations.<sup>[4]</sup> We have recently synthesized single-crystalline, chiral porous lanthanide bisphosphonates for potential chiral separations.<sup>[4a,b]</sup> Herein we report novel chiral porous zirconium phosphonates for the highly enantioselective asymmetric hydrogenation of  $\beta$ -keto esters.

Catalytic asymmetric hydrogenation is one of the most efficient strategies for the synthesis of optically active molecules.<sup>[5]</sup> The ruthenium and rhodium complexes of 2,2'-bis(diphenylphosphanyl)-1,1'-binaphthyl (binap) are particularly useful for the reduction of a wide range of substrates including keto esters, alkenes, and ketones with high enantioselectivity.<sup>[5a,6]</sup> Both high costs of Ru–binap and Rh–binap precatalysts and the necessity to remove trace amounts of metals from the organic products have, however, hindered their applications in many industrial processes. Heterogenization of these homogeneous asymmetric catalysts presents an interesting solution to both recycling and reusing expensive catalysts and preventing the leaching of metals. To date, several approaches have been used to heterogenize homogeneous asymmetric catalysts including attachment to porous inorganic-oxide and insoluble organic-polymer supports, incorporation into soluble organic macromolecules and membranes, and immobilization through biphasic systems.<sup>[7]</sup> We envision that metal phosphonates containing pendant chiral chelating bisphosphanes can be designed using rigid bisphosphonic acid ligands, 2,2'-bis(diphenylphosphanyl)-1,1'-binaphthyl-6,6'-bis(phosphonic acid), **L<sub>1</sub>-H<sub>4</sub>**, and 2,2'-bis(diphenylphosphanyl)-1,1'-binaphthyl-4,4'-bis(phosphonic acid), **L<sub>2</sub>-H<sub>4</sub>**. Such hybrid materials will combine the robust framework structure of metal phosphonates<sup>[8]</sup> and enantioselectivity of metal complexes of the pendant chiral bisphosphanes,<sup>[5]</sup> and may find applications in heterogeneous asymmetric catalysis.

Enantiopure **L<sub>1</sub>-H<sub>4</sub>** was synthesized in three steps starting from previously reported 2,2'-dihydroxy-1,1'-binaphthyl-6,6'-bis(diethylphosphonate)<sup>[4b]</sup> in 47% overall yield (Figure 1). The key step

involves nickel-catalyzed phosphonation of 2,2'-bis(triflate)-1,1'-binaphthyl bis(diethylphosphonate). All the intermediates and **L<sub>1</sub>-H<sub>4</sub>** were characterized by <sup>1</sup>H, <sup>13</sup>C{<sup>1</sup>H}, and <sup>31</sup>P{<sup>1</sup>H} NMR spectroscopy and mass spectrometry. **L<sub>2</sub>-H<sub>4</sub>** was synthesized according to a literature procedure.<sup>[9]</sup>

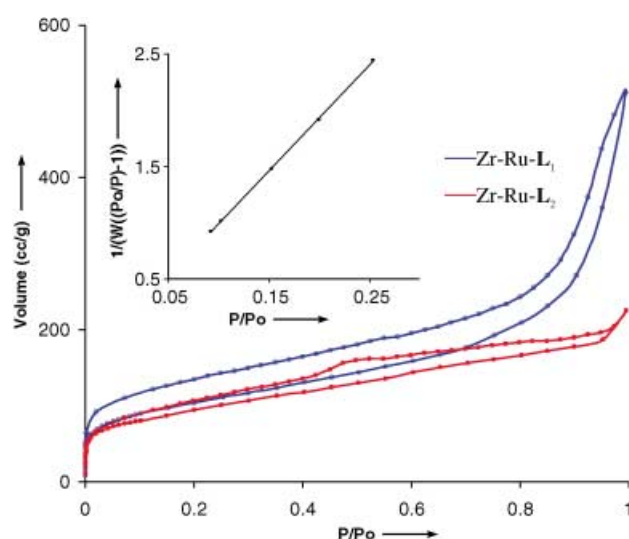
[Ru(**L<sub>1</sub>-H<sub>4</sub>**)(dmf)<sub>2</sub>Cl<sub>2</sub>] and [Ru(**L<sub>2</sub>-H<sub>4</sub>**)(dmf)<sub>2</sub>Cl<sub>2</sub>] intermediates were synthesized by treating **L<sub>1</sub>-H<sub>4</sub>** and **L<sub>2</sub>-H<sub>4</sub>** with 0.46 equivalents of [[Ru(benzene)Cl<sub>2</sub>]<sub>2</sub>] in DMF at 100 °C.<sup>[10]</sup> Chiral porous zirconium phosphonates with approximate formulae [Zr{Ru(**L<sub>1</sub>**)(dmf)<sub>2</sub>Cl<sub>2</sub>}]·2MeOH (Zr–Ru–**L<sub>1</sub>**) and [Zr{Ru(**L<sub>2</sub>**)(dmf)<sub>2</sub>Cl<sub>2</sub>}]·2MeOH (Zr–Ru–**L<sub>2</sub>**) were synthesized



**Figure 1.** Preparation of **L<sub>1</sub>-H<sub>4</sub>**, Zr–Ru–**L<sub>1</sub>**, and Zr–Ru–**L<sub>2</sub>**. dppe = 1,2-bis(diphenylphosphanyl)ethene, DABCO = 1,4-diazabicyclo[2.2.2]octane, Tf = Trifluoromethanesulfonyl.

by refluxing  $\text{Zr}(\text{O}i\text{Bu})_4$  and 1 equivalent of  $[\text{Ru}(\text{L}_1\text{-H}_4)(\text{dmf})_2\text{Cl}_2]$  and  $[\text{Ru}(\text{L}_2\text{-H}_4)(\text{dmf})_2\text{Cl}_2]$  in methanol. These chiral porous zirconium phosphonates have been characterized with a variety of techniques including thermogravimetric analysis (TGA), nitrogen adsorption isotherms, X-ray diffraction (XRD), SEM, IR spectroscopy, and microanalysis.

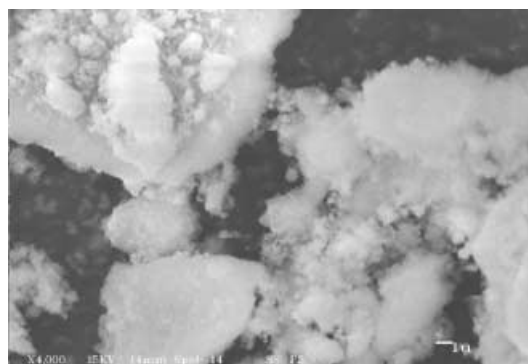
While the compositions of  $\text{Zr-Ru-L}_1$  and  $\text{Zr-Ru-L}_2$  were established by TGA and microanalysis results, the IR spectra supported the formation of zirconium phosphonate bonds as the P–O stretches at  $950\text{--}1150\text{ cm}^{-1}$  are at lower wave numbers than those of  $[\text{Ru}(\text{L}_1\text{-H}_4)(\text{dmf})_2\text{Cl}_2]$  and  $[\text{Ru}(\text{L}_2\text{-H}_4)(\text{dmf})_2\text{Cl}_2]$ . The IR spectra also exhibit intense and broad O–H stretching vibrations at around  $3400\text{ cm}^{-1}$ , consistent with the presence of MeOH solvates.<sup>[11]</sup> Nitrogen-adsorption measurements indicate that both  $\text{Zr-Ru-L}_1$  and  $\text{Zr-Ru-L}_2$  are highly porous with rather wide pore size distributions (Figure 2).  $\text{Zr-Ru-L}_1$  exhibits a total BET surface area of



**Figure 2.**  $\text{N}_2$  adsorption isotherms for  $\text{Zr-Ru-L}_1$  and  $\text{Zr-Ru-L}_2$  at 77 K. The inset shows BET plot for  $\text{Zr-Ru-L}_1$  in the mesoporous region.

$475\text{ m}^2\text{ g}^{-1}$  with a microporous surface area of  $161\text{ m}^2\text{ g}^{-1}$  and a pore volume of  $1.02\text{ cm}^3\text{ g}^{-1}$  (by BJH method).  $\text{Zr-Ru-L}_2$  exhibits a total BET surface area of  $387\text{ m}^2\text{ g}^{-1}$  with a microporous surface area of  $154\text{ m}^2\text{ g}^{-1}$  and a pore volume of  $0.53\text{ cm}^3\text{ g}^{-1}$  (by BJH method). SEM images show that both solids are composed of sub-micrometer particles (Figure 3), while powder X-ray diffraction (PXRD) indicate that both solids are amorphous.

Although the amorphous nature of the present chiral porous zirconium phosphonates has prevented us from elucidating their exact structures, we have successfully utilized the binap-Ru moieties on the surfaces for heterogeneous asymmetric catalysis. As Table 1 shows, both  $\text{Zr-Ru-L}_1$  and  $\text{Zr-Ru-L}_2$  are highly active catalysts for asymmetric hydrogenation of  $\beta$ -keto esters.  $\text{Zr-Ru-L}_1$  catalyzes the hydrogenation of a wide range of  $\beta$ -alkyl-substituted  $\beta$ -keto esters with complete conversions and *ee* values ranging from 91.7 to 95.0% with the same enantio-enrichment as the parent

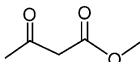
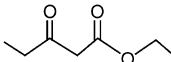
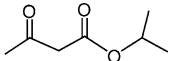
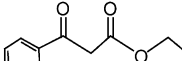
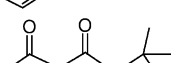
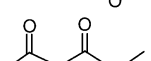


**Figure 3.** SEM image of the  $\text{Zr-Ru-L}_1$  solid precatalyst. The scale bar indicates  $1\text{ }\mu\text{m}$ .

homogeneous binap-Ru catalyst. This level of enantioselectivity is only slightly lower than that of their best homogeneous counterparts.<sup>[5,6,12]</sup>  $\text{Zr-Ru-L}_1$  gave a turnover frequency (TOF) of  $364\text{ h}^{-1}$  with a 0.1% solid loading, in comparison with a TOF of  $810\text{ h}^{-1}$  for the homogeneous binap-Ru catalyst under identical conditions.<sup>[13]</sup> Similar to the binap-Ru catalyst,<sup>[6a]</sup>  $\text{Zr-Ru-L}_1$  catalyzes the hydrogenation of  $\beta$ -aryl-substituted  $\beta$ -keto esters with modest *ee* value.<sup>[14]</sup>

In contrast,  $\text{Zr-Ru-L}_2$  catalyzes the hydrogenation of  $\beta$ -keto esters with only modest *ee* values. Supernatants of  $\text{Zr-Ru-L}_1$  and  $\text{Zr-Ru-L}_2$  in MeOH did not catalyze the hydrogenation of  $\beta$ -keto esters, which unambiguously demonstrates

**Table 1:** Heterogeneous asymmetric hydrogenation of  $\beta$ -keto esters.<sup>[a]</sup>

| $\text{R}^1-\text{C}(=\text{O})-\text{CH}_2-\text{C}(=\text{O})-\text{OR}^2 + \text{H}_2 \xrightarrow[\text{CH}_3\text{OH}]{\text{Zr-Ru-(R)-L}_1 \text{ or Zr-Ru-(R)-L}_2} \text{R}^1-\text{CH}(\text{OH})-\text{CH}_2-\text{C}(=\text{O})-\text{OR}^2$ |                      |          |  |  |  |
|---|----------------------|----------|--|--|--|
| Substrate   | Catalyst loading [%] | <i>T</i> | $\text{H}_2$ pressure [psi] <sup>[b]</sup> | $\text{Zr-Ru-L}_1$ <i>ee</i> (yield [%]) | $\text{Zr-Ru-L}_2$ <i>ee</i> (yield [%]) |
|    | 1                    | 60 °C    | 700  | 94.0 (100)                               |  |
|   | 1                    | RT       | 1400                                       | 95.0 (100)                               | 73.1 (90)                                |
|   | 0.1                  | 60 °C    | 700  | 93.3 (100)                               |  |
|    | 1                    | RT       | 1400                                       | 92.0 (100)                               | 65.0 (90)                                |
|    | 1                    | RT       | 1400                                       | 91.7 (100)                               | 68.1 (85)                                |
|    | 1                    | RT       | 1400                                       | 69.6 (100)                               | 15.7 (50)                                |
|    | 1                    | RT       | 1400                                       | 93.1 (100)                               | 64.0 (100)                               |
|    | 1                    | RT       | 1400                                       | 93.3 (100)                               | 78.8 (70)                                |

[a] All the reactions were carried out in 20 h, and the *ee* values (%) were determined by GC on a Supelco  $\gamma$ -Dex 225 column. The absolute configurations of the products are identical to those obtained by the Ru-(R)-binap catalyst. The conversions were determined by the integrations of  $^1\text{H}$  NMR spectra. [b] 1 psi = 6.89476 kPa.

heterogeneous nature of the present asymmetric catalytic systems. We have further confirmed the heterogeneous nature of the present systems using direct current plasma (DCP) spectroscopy. DCP results indicated that less than 0.01 % of the ruthenium has leached into the organic solution for each round of hydrogenation.

We have also successfully reused the Zr-Ru-L<sub>1</sub> system for asymmetric hydrogenation of methyl acetoacetate without significant deterioration of enantioselectivity. The Zr-Ru-L<sub>1</sub> system was used for five cycles of hydrogenation with complete conversions and *ee* values of 93.5, 94.2, 94.0, 92.4, and 88.5 %, respectively.

In summary, we have synthesized novel chiral porous zirconium phosphonates. These ruthenium-containing chiral porous solids have been used for heterogeneous asymmetric hydrogenation of  $\beta$ -keto esters with *ee* values of up to 95 % and can be readily recycled and reused. Ready tunability of such a molecular building-block approach will allow the optimization of the catalytic performance of these hybrid materials and lead to practically useful heterogeneous asymmetric catalysts.

## Experimental Section

Zr-Ru-L<sub>1</sub>: L<sub>1</sub>-H<sub>4</sub> was synthesized in three steps from 2,2'-dihydroxy-1,1'-binaphthyl-6,6'-bis(diethylphosphonate) and treated with [Ru(benzene)Cl<sub>2</sub>]<sub>2</sub> (0.46 equivalents) in DMF at 100 °C under argon for 40 min and then cooled to 40 °C. All the volatile components were removed under vacuum, and the dark-red solid was directly used for the synthesis of Zr-Ru-L<sub>1</sub> solid precatalyst. This solid was first dissolved in anhydrous degassed methanol, and heated overnight under reflux with Zr(OtBu)<sub>4</sub> (1 equivalent). After centrifugation and rinsing with anhydrous methanol three times, the residue was dried under vacuum to give a dark-brown solid in 96 % yield. This dark-brown solid is not soluble in common organic solvents including methanol. Elemental analysis (%) calcd for C<sub>52</sub>H<sub>52</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>10</sub>P<sub>4</sub>RuZr, [Zr{Ru(L<sub>1</sub>)(dmf)<sub>2</sub>Cl<sub>2</sub>}]<sub>2</sub>·2MeOH: C 49.9, H 4.19, N 2.24, Cl 5.66, P 9.90, Ru 8.07, Zr 7.29; found: C 50.6, H 3.87, N 2.54, Cl 4.98, P 9.32, Ru 7.87, Zr 7.70.

**General procedure for catalysis:** Methyl acetoacetate (55  $\mu$ L, 0.5 mmol) and anhydrous methanol (1 mL) were added to solid precatalyst (6.0 mg, 5  $\mu$ mole) in a test tube under argon. The test tube was quickly transferred into a stainless steel autoclave, and sealed. After purging with H<sub>2</sub> six times, the final H<sub>2</sub> pressure was adjusted to 1400 psi or 700 psi (9652.664 and 4826.332 kPa). H<sub>2</sub> pressure was released 20 h later, and methanol was removed in vacuo. The hydrogenated product was extracted with diethyl ether and passed through a mini silica-gel column. The conversions were assessed based on the integration of peaks in the <sup>1</sup>H NMR spectra of the products and starting materials, while the *ee* values were determined using chiral GC.

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- [10] A slight excess of ligand is used to ensure that no ligand-free Ru centers are present in the solid catalyst.
- [11] There may also be residual protons on the bisphosphonic acids that contribute to the O–H stretching vibrations.
- [12] Both [Ru(L<sub>1</sub>-H<sub>4</sub>)(dmf)<sub>2</sub>Cl<sub>2</sub>] and [Ru(L<sub>2</sub>-H<sub>4</sub>)(dmf)<sub>2</sub>Cl<sub>2</sub>] gave 98.3 % *ee* for homogeneous hydrogenation of methyl acetoacetate in MeOH.
- [13] This level of TOF value is comparable to those reported in the literature for the Ru-bisphosphane catalysts. See: H.-U. Blaser, C. Malan, B. Pugin, F. Spindler, H. Steiner, M. Studer, *Adv. Synth. Catal.* **2003**, 345, 103.
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