Supported Catalysts

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

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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

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desired properties by judicious choice of the building blocks.[1] The use of biphenyl-derived bridging ligands has, for example, led to novel microporous pillared zirconium phosphonates[2] as well as ordered mesoporous organosilica hybrid solids.[3] 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.[4] We have recently synthesized single-crystalline, chiral porous lanthanide bisphosphonates for potential chiral separations.[4a,b] Herein we report novel chiral porous zirconium phosphonates for the highly enantioselective asymmetric hydrogenation of β-keto esters.

Catalytic asymmetric hydrogenation is one of the most efficient strategies for the synthesis of optically active molecules.[5] 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.[5a,6] 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.[7] 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), $\mathbf{L_1}$-H_4, and 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl-4,4′-bis(phosphonic acid), $\mathbf{L_2}$-H_4. Such hybrid materials will combine the robust framework structure of metal phosphonates[8] and enantioselectivity of metal complexes of the pendant chiral bisphosphanes,[5] and may find applications in heterogeneous asymmetric catalysis.

Enantiopure $\mathbf{L_1}$-H_4 was synthesized in three steps starting from previously reported 2,2′-dihydroxy-1,1′-binaphthyl-6,6′-bis(diethylphosphonate)[4b] in 47% overall yield (Figure 1). The key step involves nickel-catalyzed phosphonation of 2,2′-bis(triflato)-1,1′-binaphthyl bis(diethylphosphonate). All the intermediates and $\mathbf{L_1}$-H_4 were characterized by ^{1}H, $^{13}C\{^{1}H\}$, and $^{31}P\{^{1}H\}$ NMR spectroscopy and mass spectrometry. $\mathbf{L_2}$-H_4 was synthesized according to a literature procedure.[9]

$[Ru(\mathbf{L_1}\text{-}H_4)(dmf)_2Cl_2]$ and $[Ru(\mathbf{L_2}\text{-}H_4)(dmf)_2Cl_2]$ intermediates were synthesized by treating $\mathbf{L_1}$-H_4 and $\mathbf{L_2}$-H_4 with 0.46 equivalents of $[\{Ru(benzene)Cl_2\}_2]$ in DMF at 100 °C.[10] Chiral porous zirconium phosphonates with approximate formulae $[Zr\{Ru(\mathbf{L_1})(dmf)_2Cl_2\}]\cdot 2\,MeOH$ (Zr-Ru-$\mathbf{L_1}$) and $[Zr\{Ru(\mathbf{L_2})(dmf)_2Cl_2\}]\cdot 2\,MeOH$ (Zr-Ru-$\mathbf{L_2}$) were synthesized

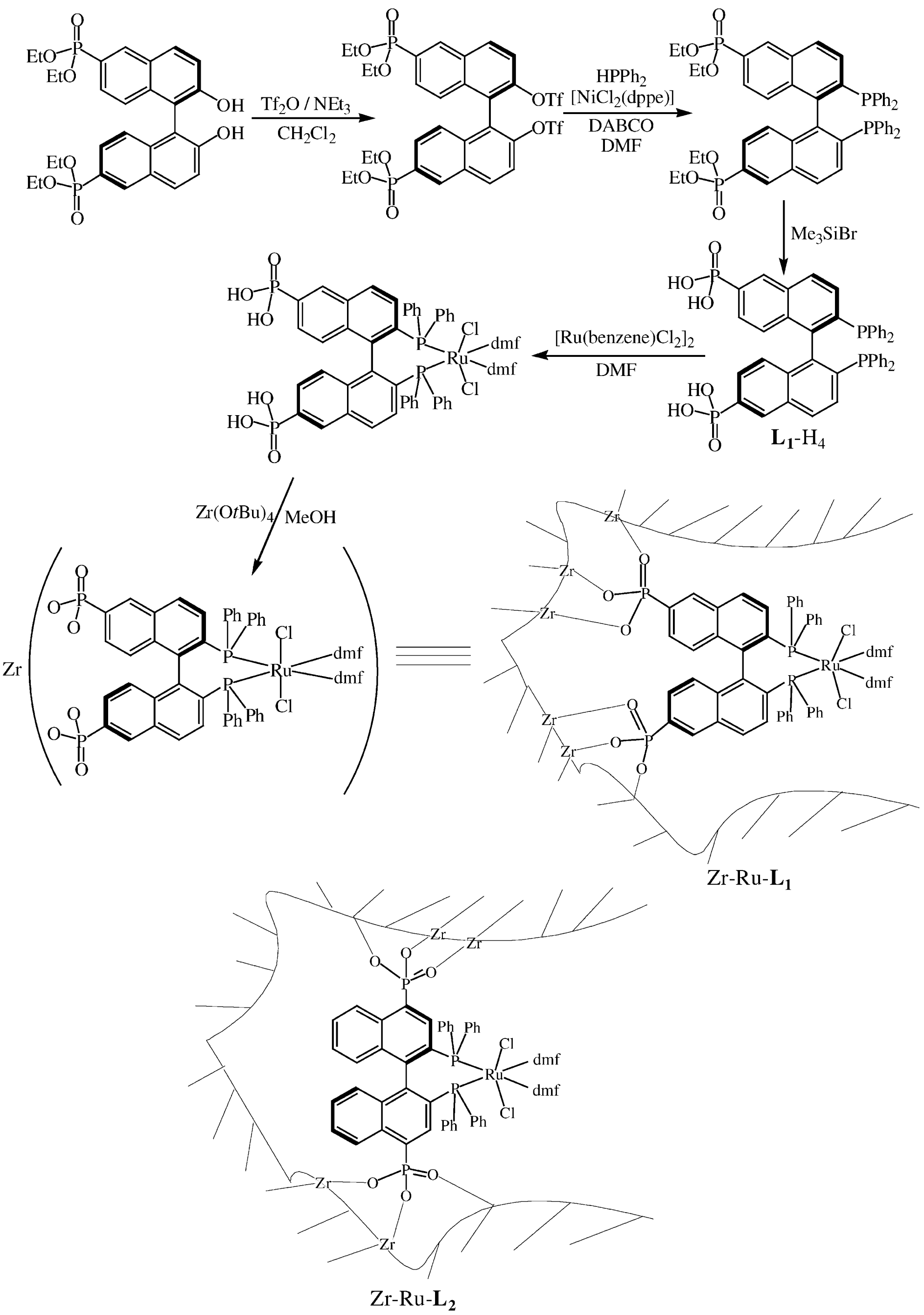


Figure 1. Preparation of $\mathbf{L_1}$-H_4, Zr-Ru-$\mathbf{L_1}$, and Zr-Ru-$\mathbf{L_2}$. dppe = 1,2-bis(diphenylphosphanyl)ethene, DABCO = 1,4-diazabicyclo[2.2.2]octane, Tf = Trifluoromethanesulfonyl.

by refluxing $Zr(OtBu)_4$ and 1 equivalent of $[Ru(\mathbf{L_1}\text{-}H_4)(dmf)_2Cl_2]$ and $[Ru(\mathbf{L_2}\text{-}H_4)(dmf)_2Cl_2]$ 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 Zr-Ru-**L₁** and Zr-Ru-**L₂** were established by TGA and microanalysis results, the IR spectra supported the formation of zirconium phosphonate bonds as the P–O stretches at 950–1150 cm^{-1} are at lower wave numbers than those of $[Ru(\mathbf{L_1}\text{-}H_4)(dmf)_2Cl_2]$ and $[Ru(\mathbf{L_2}\text{-}H_4)(dmf)_2Cl_2]$. The IR spectra also exhibit intense and broad O–H stretching vibrations at around 3400 cm^{-1}, consistent with the presence of MeOH solvates.[11] Nitrogen-adsorption measurements indicate that both Zr-Ru-$\mathbf{L_1}$ and Zr-Ru-$\mathbf{L_2}$ are highly porous with rather wide pore size distributions (Figure 2). Zr-Ru-$\mathbf{L_1}$ exhibits a total BET surface area of 475 $m^2 g^{-1}$ with a microporous surface area of 161 $m^2 g^{-1}$ and a pore volume of 1.02 $cm^3 g^{-1}$ (by BJH method). Zr-Ru-$\mathbf{L_2}$ exhibits a total BET surface area of 387 $m^2 g^{-1}$ with a microporous surface area of 154 $m^2 g^{-1}$ and a pore volume of 0.53 $cm^3 g^{-1}$ (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.

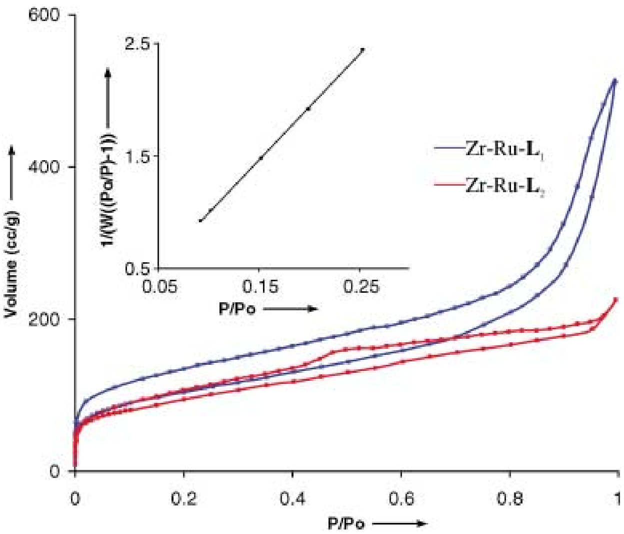


Figure 2. N_2 adsorption isotherms for Zr-Ru-$\mathbf{L_1}$ and Zr-Ru-$\mathbf{L_2}$ at 77 K. The inset shows BET plot for Zr-Ru-$\mathbf{L_1}$ in the mesoporous region.

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 Zr-Ru-$\mathbf{L_1}$ and Zr-Ru-$\mathbf{L_2}$ are highly active catalysts for asymmetric hydrogenation of β-keto esters. Zr-Ru-$\mathbf{L_1}$ catalyzes the hydrogenation of a wide range of β-alkyl-substituted β-keto esters with complete conversions and *ee* values ranging from 91.7 to 95.0% with the same enantio-enrichment as the parent homogeneous binap-Ru catalyst. This level of enantioselectivity is only slightly lower than that of their best homogeneous counterparts.[5,6,12] Zr-Ru-$\mathbf{L_1}$ gave a turnover frequency (TOF) of 364 h^{-1} with a 0.1% solid loading, in comparison with a TOF of 810 h^{-1} for the homogeneous binap-Ru catalyst under identical conditions.[13] Similar to the binap-Ru catalyst,[6a] Zr-Ru-$\mathbf{L_1}$ catalyzes the hydrogenation of β-aryl-substituted β-keto esters with modest *ee* value.[14]

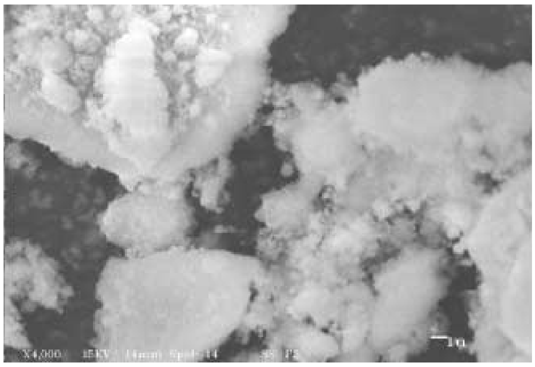
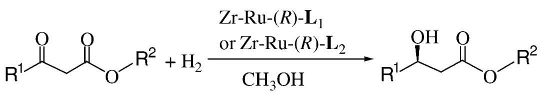
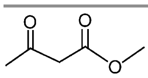
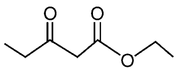
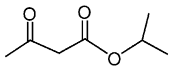
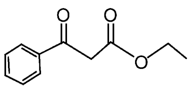
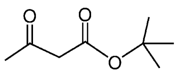
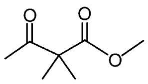


Figure 3. SEM image of the Zr-Ru-$\mathbf{L_1}$ solid precatalyst. The scale bar indicates 1 μm.

In contrast, Zr-Ru-$\mathbf{L_2}$ catalyzes the hydrogenation of β-keto esters with only modest *ee* values. Supernatants of Zr-Ru-$\mathbf{L_1}$ and Zr-Ru-$\mathbf{L_2}$ in MeOH did not catalyze the hydrogenation of β-keto esters, which unambiguously demonstrates

Table 1: Heterogeneous asymmetric hydrogenation of β-keto esters.[a]



Substrate	Catalyst loading [%]	*T*	H_2 pressure [psi][b]	Zr-Ru-$\mathbf{L_1}$ *ee* (yield [%])	Zr-Ru-$\mathbf{L_2}$ *ee* (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 γ-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 ^1H 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-$\mathbf{L_1}$ system for asymmetric hydrogenation of methyl acetoacetate without significant deterioration of enantioselectivity. The Zr-Ru-$\mathbf{L_1}$ 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 β-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-$\mathbf{L_1}$**:** $\mathbf{L_1}$-H_4 was synthesized in three steps from 2,2′-dihydroxy-1,1′-binaphthyl-6,6′-bis(diethylphosphonate) and treated with [{Ru(benzene)Cl_2}$_2$] (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-$\mathbf{L_1}$ solid precatalyst. This solid was first dissolved in anhydrous degassed methanol, and heated overnight under reflux with Zr(O*t*Bu)$_4$ (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 $C_{52}H_{52}Cl_2N_2O_{10}P_4RuZr$, [Zr{Ru($\mathbf{L_1}$)(dmf)$_2$$Cl_2$}]·2 MeOH: 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 µL, 0.5 mmol) and anhydrous methanol (1 mL) were added to solid precatalyst (6.0 mg, 5 µmole) in a test tube under argon. The test tube was quickly transferred into a stainless steel autoclave, and sealed. After purging with H_2 six times, the final H_2 pressure was adjusted to 1400 psi or 700 psi (9652.664 and 4826.332 kPa). H_2 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 ^{1}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($\mathbf{L_1}$-H_4)(dmf)$_2$$Cl_2$] and [Ru($\mathbf{L_2}$-$H_4$)(dmf)$_2$$Cl_2$] 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.
[14] The homogeneous Ru-binap catalyst gave an *ee* value of 80.3 % for hydrogenation of ethyl benzoylacetate.

