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Asymmetric Dihydroxylation of Olefins Using Cinchona Alkaloids on Highly Ordered Inorganic Supports

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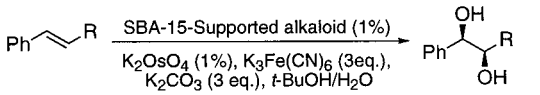
ABSTRACT



up to 99% ee

A modified cinchona alkaloid was grafted onto a mesoporous molecular sieve and onto amorphous silica gel. These heterogeneous ligands were employed in the asymmetric dihydroxylation of olefins under Sharpless conditions. The supported ligands yielded equivalent enantioselectivity compared with that of the homogeneous system and were easily recovered and reused.

Despite the variety of transformations that can be effected with transition metal complexes modified by chiral ligands, the use of these complexes in organic synthesis remains relatively limited. This is primarily because of the limited scope of many catalytic reactions and the sacrificial way the chiral ligands are treated. Since chiral ligands are often more expensive than the metals themselves, this can be a deterrent to the large scale application of asymmetric catalysis.

The asymmetric dihydroxylation (AD) of alkenes is a rare example of a reaction that has a wide and well-defined scope.[1] The generality of the AD reaction has prompted several research groups to investigate the preparation of supported versions of the cinchona alkaloid based chiral ligands[2] including the most generally effective ligand, $DHQD_2PHAL$ (**1**, Figure 1). Alkaloids such as **1** and its derivatives have been incorporated into various insoluble[3,4] or soluble organic polymers[5,6] and onto inorganic supports such as silica gel.[7] Cinchona alkaloids immobilized on *soluble* poly(ethylene glycol) polymers described by Janda[5]

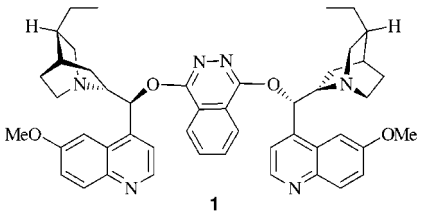


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Figure 1. $DHQD_2PHAL$.

(1) Jacobsen, E. N.; Marko, I.; Mungall, S.; Schroeder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968. Sharpless, K. B.; Amberg, W.; Beller, M.; Chen, H.; Hartung, J.; Kawanami, Yl; Lubben, D.; Manoury, E.; Ogino, Y.; Shibata, T.; Ukita, T. *J. Org. Chem.* **1991**, *56*, 4585. Kolb, H. C.; Van Nieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.

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(6) Bolm, C.; Maischak, A.; Gerlach, A. *Chem. Commun.* **1997**, 2357. Bolm, C.; Gerlach, A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 741.

(7) Lohray, B. B.; Nandanan, E.; Bhushan, V. *Tetrahedron: Asymmetry* **1996**, *7*, 2805. Song, C. E.; Yang, J. W.; Ha, H.-J. *Tetrahedron: Asymmetry* **1997**, *8*, 841.

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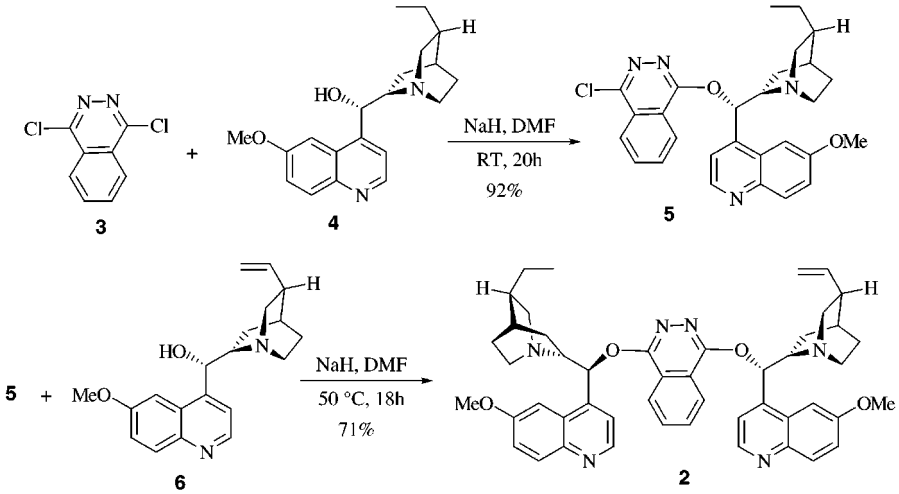
Scheme 1. Synthesis of Modified Cinchona Alkaloid **2**



and by Bolm[6] provide by far the best mimicry of the homogeneous system.

Insoluble supports would be preferable for several reasons: they are readily recovered; they have potential applications in flow processes; and they do not require extra solvent for precipitation. Insoluble organic polymers can be effective supports as shown by Salvadori,[4] but the polymer needs to be carefully tuned and caution taken to ensure that the chiral ligand is chemically bound to, and not merely occluded in, the organic support.[8] Inorganic supports such as amorphous silica gel have been generally less effective in the asymmetric dihydroxylation reaction.[7] This reaction is particularly challenging for supported ligands because the reaction must be run in highly polar solvent (1:1 *t*-BuOH/H_2O) in order to obtain the highest enantioselectivities.[1] Thus significant tuning of either the polymer[3,4] or the ligand[9] has been necessary to obtain high yields and enantioselectivities in this medium. In many of the successful cases, a long spacer is used to distance the chiral ligand from the amorphous polymer.[6]

An alternative approach to distancing the chiral ligand from the amorphous support is to use a support that puts the catalyst in an ordered microenvironment.[10] We[11] and others[12] are studying a newly developed class of silicates called mesoporous molecular sieves[13] for this purpose. Unlike regular, amorphous silica gel, mesoporous molecular sieves have well-defined nanometer-sized pores, with a very narrow pore size distribution. The exact size of the pores and even their shape can be tailored depending on how they are prepared.[14] We have employed hexagonal mesoporous molecular sieves of the SBA-15 type[15] as supports for heterogeneous cinchona alkaloids. We find that these supported ligands give extremely close agreement with the solution phase dihydroxylation reaction in terms of rate and enantioselectivity.

Two different grafting techniques were examined for the preparation of the supported alkaloids. Both routes begin with compound **2**, which was prepared as shown in Scheme 1. Dichlorophthalazine (**3**) was reacted with dihydroquinidine (**4**) under mild conditions to give the product of monosubstitution, **5**. Treatment of **5** with quinidine (**6**) at 50 °C gave compound **2**.

Our initial attempts at grafting this material onto the surface followed the commonly employed method of adding a functionalized thiol across the alkene under radical conditions. Thus the molecular sieve was pretreated with 3-mercaptopropyl trimethoxysilane and then reacted with **2** in the presence of AIBN. Although this method did provide an active catalyst for the AD reaction, the mesoporous structure

(8) Sherrington et al. have shown that certain methods reported for the synthesis of supported alkaloids do not lead to chemically bound alkaloid but instead give alkaloid occluded in the insoluble polymer: Canali, L.; Song, C. E.; Sherrington, D. C. *Tetrahedron: Asymmetry* **1998**, *9*, 1029. Nandanan, E.; Sudalai, A.; Ravindranathan, T. *Tetrahedron Lett.* **1997**, *38*, 2577. Song, C. E.; Yang, J. W.; Ha. H. J.; Lee, S.-G. *Tetrahedron: Asymmetry* **1996**, *7*, 645.

(9) Compare refs 7a and b where an alkaloid supported at one point gives marginal enantioselectivities, whereas immobilizing the ligand at two positions gives significantly better results.

(10) A highly ordered microenvironment can be achieved using polymers composed *entirely* of the chiral ligand. For this innovative approach, see: Pu, L.; Yu, H. B. *Chem. Rev.* **2001**, *101*, 757 and references therein.

(11) Crudden, C. M.; Allen, D.; Mikoluk, M.; Sun, J. *Chem. Commun.* in press.

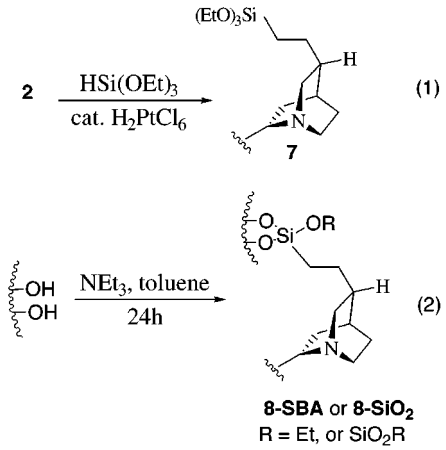
(12) Brunel, D. *Micro. Meso. Mater.* **1999**, *27*, 329 and references therein. Johnson, B. F. G.; Raynor, S. A.; Shephard, D. S.; Maschmeyer, T.; Thomas, J. M.; Sankar, G.; Bromley, S.; Oldroyd, R.; Gladden, L.; Mantle, M. D. *Chem. Commun.* **1999**, 1167. Catalytic applications: Ying, J. Y.; Mehnert, C. P.; Wong, M. S. *Angew. Chem., Int. Ed.* **1999**, *38*, 56.

(13) Kresge, C. T.; Leonowicz, M. E.; Roth, W. J.; Vartulli, J. C.; Beck, J. S. *Nature* **1992**, *359*, 710. Zhao, D.; Feng, J.; Huo, Q.; Melosh, N.; Fredrickson, G. H.; Chmelka, B. F.; Stucky, G. D. *Science* **1998**, *279*, 548. Zhao, D.; Huo, Q.; Feng, J.; Chmelka, B. F.; Stucky, G. D. *J. Am. Chem. Soc.* **1998**, *120*, 6024.

(14) Melosh, N. A.; Davidson, P.; Chmelka, B. F. *J. Am. Chem. Soc.* **2000**, *122*, 823. Feng, P.; Bu, X.; Stucky, G. D.; Pine, D. J. *J. Am. Chem. Soc.* **2000**, *122*, 994. Melosh, N. A.; Lipic, P.; Bates, F. S.; Wudl, F.; Stucky, G. D.; Fredrickson, G. H.; Chmelka, B. F. *Macromolecules* **1999**, *32*, 4332. Lu, Y.; Ganguli, R.; Drewien, C. A.; Anderson, M. T.; Brinker, C. J.; Gong, W.; Guo, Y.; Soyez, H.; Dunn, B.; Huang, M. H.; Zink, J. I. *Nature* **1997**, *389*, 364, Bruinsma, P. J.; Kim, A. Y.; Liu, J.; Baskaran, S. *Chem. Mater.* **1997**, *9*, 2507. Lin, H. P.; Cheng, Y.-R.; Mou, C.-Y. *Chem. Mater.* **1998**, *10*, 3772.

(15) Hereafter referred to as SBA, prepared using the method described in ref 13 (Stucky et al.).

of the silicate was not retained. Hydrosilylation[16] proved to be a better option. Treatment of **2** with $HSi(OEt)_3$ in the presence of H_2PtCl_6 (eq 1) provided **7**, which was grafted onto hexagonally ordered SBA[17] at room temperature by condensation of the siloxane with surface hydroxyl groups to give **8**-SBA (eq 2).



As shown in Figure 2, after grafting the alkaloid via a silicon tether, the silicate is still highly ordered, with an average pore size[18] of 72 Å, decreased slightly from 78 Å in the unfunctionalized SBA. The surface area was determined to be 761 m^2/g, also decreased from the original 975 m^2/g. These decreases are consistent with the low loading of the catalyst, which is 0.13 mmol/g as determined by elemental analysis.

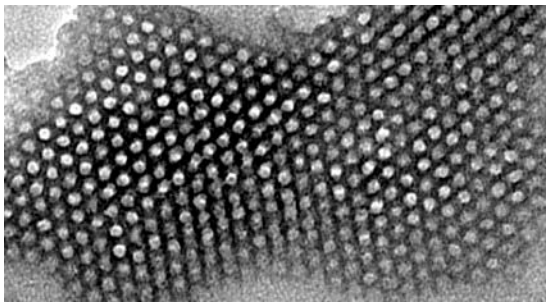
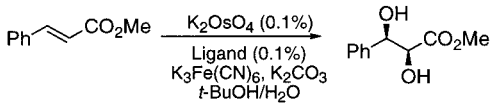


Figure 2. TEM of supported cinchona alkaloid **8**-SBA.

To evaluate the effect of the ordered structure, compound **7** was grafted onto regular amorphous silica gel with an average pore size of 100 Å. The main differences between this support and SBA are that the pores are not uniform in size or shape, there is no long range order, and the surface area is approximately half that of SBA (436 m^2/g). Reaction of **7** with silica gel yielded **8**-SiO_2 with a loading of 0.09 mmol/g. The catalytic activity and the enantioselectivity of this material were compared with the homogeneous system and the ordered ligand **8**-SBA.[19] The results for the dihydroxylation of methyl cinnamate are compiled in Table 1.

Table 1. Activity of Heterogeneous and Homogeneous Ligands in the Asymmetric Dihydroxylation of Methyl Cinnamate[a]



ligand	loading	conversion
$DHQD_2PHAL$	0.1%	44%
8-SBA	0.1%	54%
8-SiO_2	0.1%	46%

[a] Reaction conditions: 3 mmol of $K_3Fe(CN)_6$ and 3 mmol of K_2CO_3 were dissolved in 5 mL of H_2O, and the inorganic-supported ligand was added (0.01 mmol). $K_2OsO_4 \cdot 2H_2O$ (0.01 mmol) and 5 mL of *t*-BuOH were added. After cooling to 0 °C in an ice bath, the substrate (1 mmol) was added with stirring in one portion. The mixture was stirred for 14 h at 0 °C and then allowed to warm to room temperature for ca. 4 h. An extractive workup was performed, and the crude material was analyzed by ^1H NMR.

To compare the reactivities of the various catalysts, the dihydroxylation of methyl cinnamate was performed at 0.1% loading of both ligand and Os (usual conditions call for 2% ligand and 1% Os)[1]. As can be seen from Table 1, the amorphous silica gel supported dihydroxylation ligand **8**-SiO_2 gives approximately the same yield as the homogeneous system, while **8**-SBA was marginally superior.

The enantioselectivity of the AD was also assessed using various ligands and substrates, at a 1% loading. The results are presented in Table 2. As can be seen, the cinchona alkaloid supported on mesoporous, ordered SBA-type silica gives virtually perfect agreement with the homogeneous catalyst in terms of enantioselectivity. This is quite remarkable considering how closely the chiral ligand is tethered to the support and the fact that optimization of the ligand was not attempted. All of these results were obtained using a 1:1 ratio of ligand to Os, which is more efficient than the homogeneous procedure that employs an excess of ligand. The cinchona alkaloid supported on amorphous silica gel gives lower enantioselectivies for all the substrates we have tried, although the differences between it and the ordered SBA support are not large.

Finally, we assessed the reusability of the supported ligand. The insoluble ligand can be recovered and reused several times. The enantioselectivity remains within 3% of the initial run, and yields are ±5% (isolated). Although the ligand is recovered unchanged from the reaction and can be used multiple times, the Os is not retained on the surface and must be added prior to reuse of the ligand.[20]

Although we cannot rule out the possibility that a small amount of the alkaloid is removed from the support and is

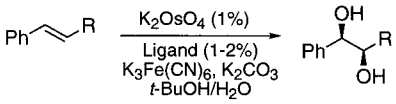
(16) Pirkle, W. H.; Pochapsky, T. C.; Mahler, G. S.; Corey, D. E.; Reno, D. S.; Alessi, D. M. *J. Org. Chem.* **1986**, *51*, 4991 and ref 11.

(17) See Supporting Information for the precise method used to synthesize the molecular sieve.

(18) The pore size is determined from analysis of the TEM and analysis of nitrogen adsorption isotherms.

(19) Note that for the heterogeneous ligands, the amount of catalyst used (1:1 with the ligand) is normalized based on the % loading of the alkaloid on the support.

Table 2. Enantioselectivity of the AD Reaction Using Supported and Homogeneous Ligands[a]



ligand	R	isolated yield	enantio-selectivity (ee)[b]
$DHQD_2PHAL$	Ph	99%	>99%[c]
8-SBA	Ph	97%	>99%
$DHQD_2PHAL$	CO_2Et	*d*	97%[c]
8-SBA	CO_2Me	67%	98%
8-SiO_2	CO_2Me	72%	94%
$DHQD_2PHAL$-PEG-OMe[e]	Me	83%	99%
8-SBA	Me	98%	98%
8-SiO_2	Me	85%	96%
$DHQD_2PHAL$	H	95%	96%[f]
8-SBA	H	73%	92%
8-SiO_2	H	85%	87%

[a] Experimental conditions are as listed in Table 1, with the exception that flash chromatography was performed after the extraction and that 1% catalyst and 1% ligand loading were employed in the heterogeneous cases (2% ligand in homogeneous). [b] Enantioselectivity determined by preparation of bis Mosher's esters (see Supporting Information) and confirmed by optical rotation of the unreacted diols. [c] Sharpless, K. B.; Amberg, W.; Beller, M.; Chen, H.; Hartung, J.; Kawanami, Y.; Lubben, D.; Manoury, E.; Ogino, Y.; Shibata, T.; Ukita, T. *J. Org. Chem.* **1991**, *56*, 4585. [d] Yield not provided in original reference. [e] Han, H.; Janda, K. D. *Tetrahedron Lett.* **1997**, *38*, 1527. [f] Corey, E. J.; Noe, M. C. *J. Am. Chem. Soc.* **1993**, *115*, 12579.

responsible for the catalysis, this is unlikely for two reasons. When the supported ligand is compared with the homogeneous $DHQD_2PHAL$ ligand at very low loadings (0.1%, Table 1), an increased yield is obtained.[21] This would be unlikely if the active catalyst was composed of a small percentage of leached alkaloid. The reusability of the supported ligand is also good evidence that it is the heterogeneous ligand that is responsible for the catalysis.

In conclusion, we have demonstrated that mesoporous molecular sieves are valuable supports for the preparation of recoverable cinchona alkaloids. Supporting the alkaloids on structured silicates of the SBA-15 type gave enantioselectivities identical or nearly identical to those observed in the homogeneous case. No optimization of the tether or support was carried out. Supporting the same ligand on amorphous silica gel gave slightly lower enantioselectivities.

Acknowledgment. We thank Dr. Robert Young, Merck & Company, the Natural Sciences and Engineering Research Council of Canada, the Canada Foundation for Innovation, and the Atlantic Canadian Opportunities Agency for generous funding of this research.

Supporting Information Available: ^1H NMR spectra used to determine the enantiomeric excess of the product diols and experimental details for the preparation of the mesoporous materials. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) The best method for recovery of Os involves the preparation of microencapsulated Os: Kobayashi, S.; Endo, M.; Nagayama, S. *J. Am. Chem. Soc.* **1999**, *121*, 11229. Note that although this method is extremely valuable for the recovery of osmium, it involves the use of a homogeneous chiral ligand.

(21) Note that the isolated yields (unoptimized) are sometimes lower for the supported alkaloid than those reported for the homogeneous ligand (see Table 2). This is a less accurate comparison because some of the diol may be lost upon chromatography.