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Heterogeneous Catalytic Asymmetric Dihydroxylation of Olefins: a New Polymeric Support and a Process Improvement

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Abstract: A new polymeric support containing a derivative of quinine 4-chlorobenzoate and alcoholic pendent groups was found to give good enantioselectivity in many cases comparable to those obtained with the free alkaloid in homogeneous reaction conditions, providing also the known advantages of the heterogeneous process. Both aromatic and aliphatic olefins were screened, using either N-methylmorpholine-N-oxide (NMO) or potassium ferricyanide ($K_3Fe(CN)_6$) as secondary oxidants.

Polymer supported catalysts, reagents or substrates have found numerous applications in synthetic organic chemistry[1]. The ease of recovery and recycling the polymeric reactants makes their use particularly attractive in the field of asymmetric catalysis.

The exciting potential of polymer bound chiral auxiliaries coupled with the advent of the highly effective catalytic asymmetric dihydroxylation procedure[2] led us to explore the possibility of employing polymer bound cinchona alkaloid derivatives in this reaction[3].

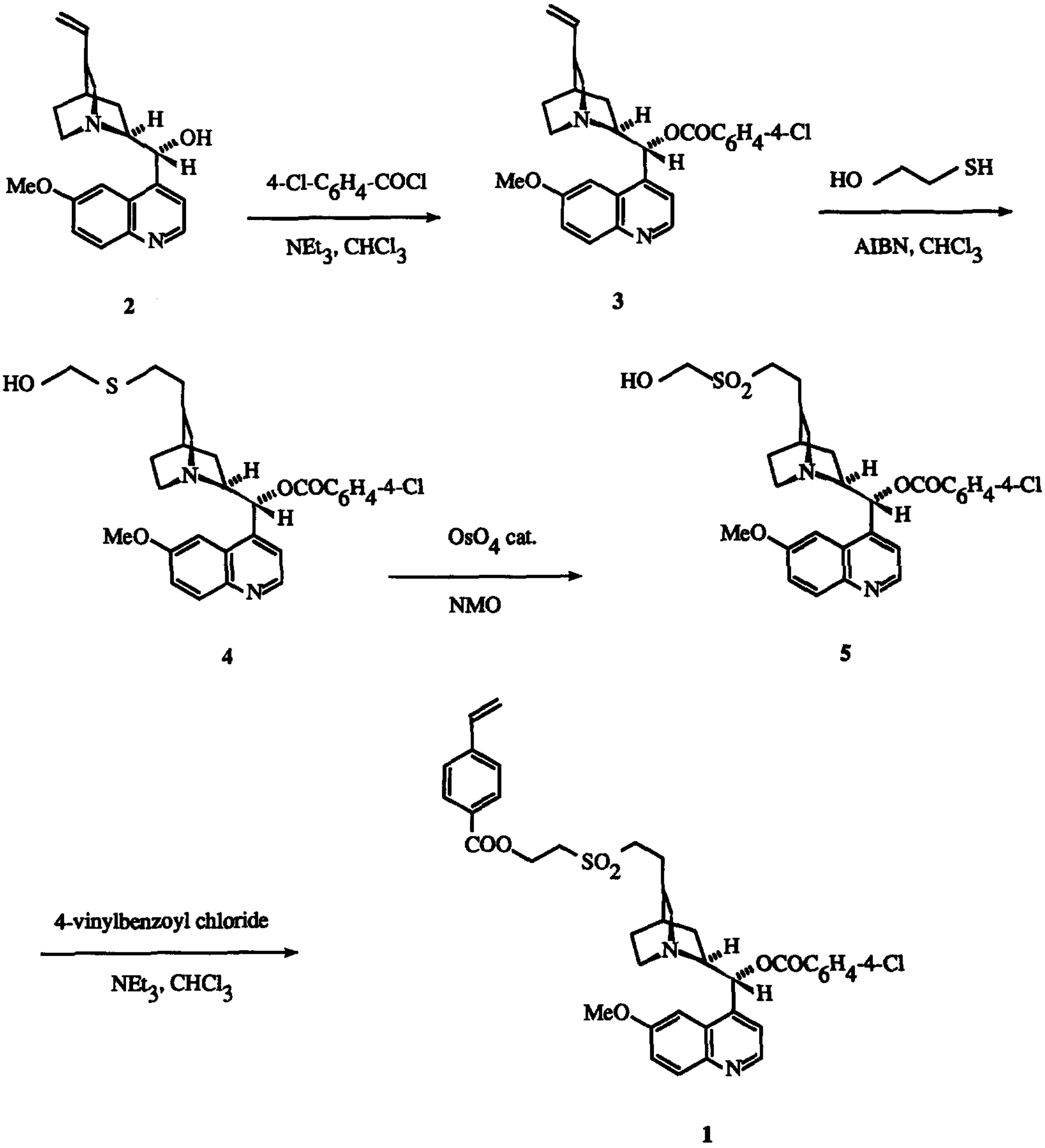
Significant advantages have been pointed out when performing the asymmetric dihydroxylation with polymer support, particularly because the chiral auxiliary reagent complexed with the expensive osmium tetroxide can generally be recovered by simple filtration.

Thus far, only few papers[4] appeared dealing with the heterogeneous catalytic asymmetric dihydroxylation, although the homogeneous process has been improved steadily during the past five years thanks to the development of more effective chiral cinchona alkaloid derived ligands reported by the Sharpless group[5].

We have recently reported[3c], the use of a chiral monomer, containing the 4-chlorobenzoate ester of quinine, in the synthesis of a crosslinked polystyrene catalyst which furnished diols from alkenes in high chemical yields and good enantioselectivity.

In this paper we describe the synthesis of monomer **1** (Scheme 1) and its insertion in a new polymeric support, showing that the heterogeneous catalytic asymmetric dihydroxylation of alkenes can be effective for obtaining optically active diols, with almost the same enantioselectivity as that achieved with the homogeneous counterparts.

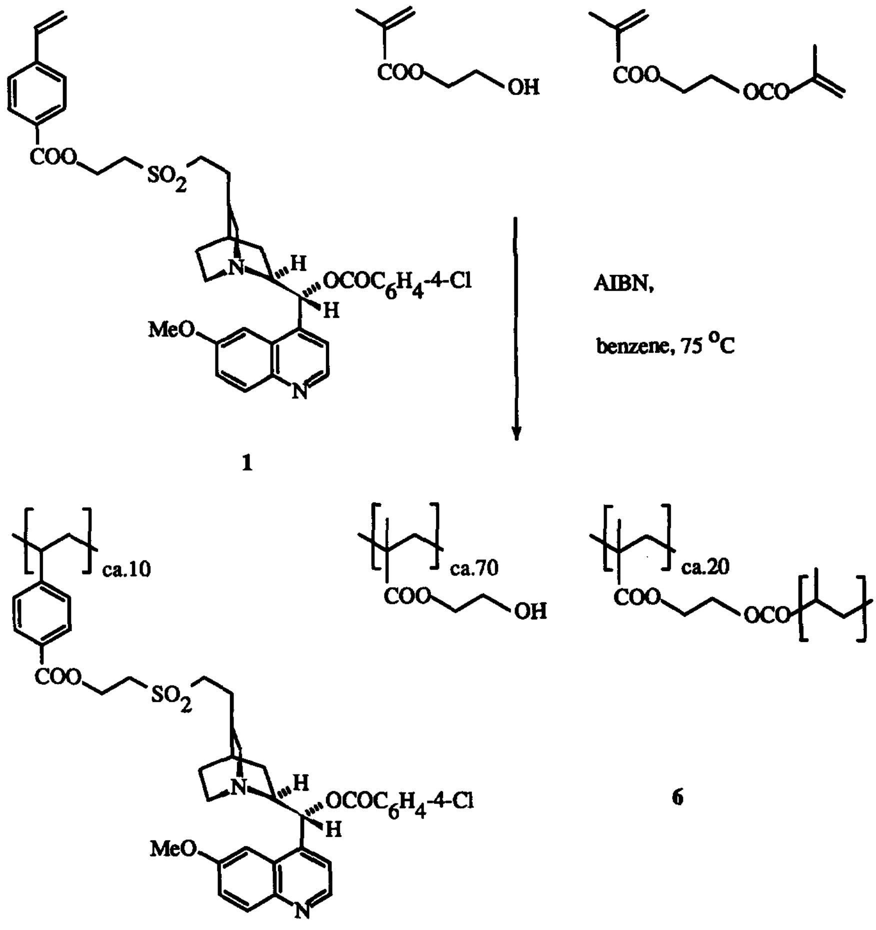
The chiral monomer 1 was obtained by the synthetic sequence shown in the Scheme 1.



Scheme 1

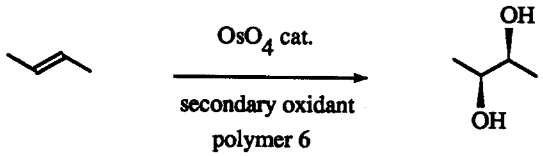
Quinine 2 was converted to the 4-chlorobenzoate 3 by reaction at room temperature with 4-chlorobenzoyl chloride and triethylamine in chloroform. This quinine derivative is one of the most used and effective ligand employed in the homogeneous dihydroxylation of alkenes. A spacer group was also introduced to let the quinuclidinic moiety of the ligand, responsible of the complexation with osmium tetroxide, unaffected by the steric hindrance of the polymeric chain. So the derivative **3** was treated with an excess of 2-mercaptoethanol[6] in chloroform using α,α'-azobis(isobutyronitrile) (AIBN) as radical initiator at 80°C for 48 hours. In order to avoid the oxidation of the sulfide during the dihydroxylation process, compound **4** was oxidized to sulfone **5** under mild reaction conditions by using N-methylmorpholine-N-oxide and a catalytic amount of osmium tetroxide, following a procedure previously described[7]. The sulphone **5** was then converted in the corrisponding 4-vinylbenzoate **1** by reaction with 4-vinylbenzoyl chloride and triethylamine in chloroform at 0°C for 24 hours.

The chiral monomer **1** was copolymerized with hydroxyethyl methacrylate by free radical initiator, using ethylene glycol dimethacrylate as crosslinking agent (Scheme 2). The obtained polymer **6**, was filtered and extracted with acetone to avoid the presence of non reacted chiral monomer.



Scheme 2

This new crosslinked polymer, containing alcoholic pendent groups, was tested in the catalytic asymmetric dihydroxylation of *trans*-stilbene and other olefins (Scheme 3) : the results obtained are summarized in Table I.



Scheme 3

Polymer **6** was insoluble in all solvents and swelled very well in polar protic solvents, in contrast to the polymer above cited[3c], which collapsed in alcohols. The reaction was performed using as secondary oxidants either N-methylmorpholine-N-oxide (NMO) in acetone:H_2O (10:1) (method A) or potassium ferricyanide ($K_3Fe(CN)_6$) in $^tBuOH:H_2O$ (method B), following the typical experimental procedures previously described[3,5].

High chemical yields were observed with nearly all olefins; the osmylation of *trans*-stilbene and styrene (entries 1A and 6A) afforded the corresponding diols accompanied by overoxidation products. By using $K_3Fe(CN)_6$, lower yields were obtained: entries 2B and 3B reveal that the reaction with *trans*-methyl cinnamate and cinnamylacetate is particularly slow even at 25°C.

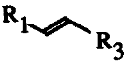
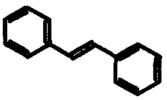
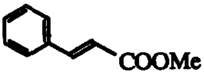
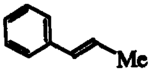
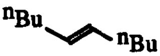
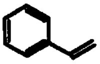
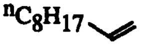
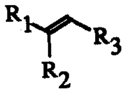
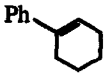
Both aliphatic and aromatic olefins, terminal and internal, were screened and the reaction proceded with good extents of enantioselectivity (up to 95%), in many cases comparable to those obtained with the free alkaloid in similar reaction conditions. Higher enantiomeric excesses were obtained with all classes of olefins using $K_3Fe(CN)_6$ as secondary oxidant, as it is to be expected from the earlier finding[10] that using this oxidant in place of NMO excludes, in the catalytic process, the non-enantioselective "second cycle", which is believed to afflict the NMO system.

Therefore by using polymer **6**, the scope of the heterogeneous catalytic asymmetric dihydroxylation can be expanded for the first time to use both secondary oxidants, not only with *trans*-stilbene but also with other aromatic or aliphatic olefins, reaching quite good extents of enantioselectivity.

The improvement obtained with this new polymeric support suggests that a suitable insoluble catalyst can be designed for the asymmetric dihydroxylation process, which retains the advantages of a homogeneous catalyst in terms of activity and mild reaction conditions, in addition to the ease of handling and recyclability of a heterogeneous catalyst.

Further studies are in progress to introduce different chiral ligands on polymeric supports in a continuing effort to improve the enantioselectivity of the process and to widen the applicability of the heterogeneous system to other classes of alkenes.

Table I. Heterogeneous Catalytic Asymmetric Dihydroxylation of Olefins with Polymer 6.

class of olefin	entry	olefin	method[a]	% yield	% ee[b]	confign.[c]
	1		A	60	90 (78)	(*S*,*S*)
			B	70	95(97)	
	2		A	81	60(60)	(2*R*,3*S*)
			B	40[d]	80(91)	
	3		A	81	43(76)	(*S*,*S*)
			B	40[d]	75(91)	
	4		A	69	60(65)	(*S*,*S*)
			B	71	81(91)	
	5		A	80	13(20)	(*S*,*S*)
			B	70	75(70)	
	6		A	65	40(54)	(*S*)
			B	75	65(73)	
	7		A	89	14(-)	(*S*)
			B	65	50(41)	
	8		A	53	5(8)	(*S*,*S*)
			B	85	81(91)	

[a] The asymmetric dihydroxylation reactions were run using as secondary oxidant NMO in acetone:H_2O 10:1 (method A) or $K_3Fe(CN)_6$ in $^tBuOH:H_2O$ 1:1 (method B); for a typical experimental procedure see ref.3(c) and 4(a). [b] In parentheses, the e.e. values reported[5a,8] for the reaction in the homogeneous phase using as chiral catalytic ligands the 4-chlorobenzoate of quinine (entries 1AB, 5B, 6A, 7B) or the corresponding quinidine derivative (entries 2AB, 3AB, 5A, and 6B)[9]. [c] The absolute configurations of the diols were determined by comparison of their optical rotations with the literature values[5a,3c]. [d] The reaction was run at 0°C for 24 h, then at 25°C for further 24 h.

EXPERIMENTAL SECTION

All chemicals were purchased from commercial sources and used without further purification except for hydroxyethylmethacrylate and ethylene glycol dimethacrylate which were distilled prior the use.Melting points are uncorrected. Proton magnetic resonance were measured at 200MHz with a Varian Gemini 200 spectrometer. Signal positions are reported in ppm downfield from tetramethylsilane (δ scale) as internal standard, and $CDCl_3$ as solvent; the number of protons and multiplicity are indicated in parentheses. Optical rotations were measured with a Perkin-Elmer Model 241 Polarimeter. The enantiomeric excesses (e.e.) of the diols were determined by comparison of their optical rotations with literature values[3c,11a] or by ^{1}H-NMR analysis of the derived bis MTPA esters[11b].

9-O-(4-chlorobenzoyl)-quinine **3**. 8 mL (62.9 mmol) of 4-chlorobenzoyl chloride were added at 0°C to a solution of 20 g (61.6 mmol) of quinine and 10 mL (71 mmol) of triethylamine in 150 ml of $CHCl_3$. The resulting mixture was stirred at room temperature for 24 hours, then was washed with a 10% aqueous solution of $NaHCO_3$ and then with water. The dried organic layer was evaporated and the residue was purified by crystallization from CCl_4/pentane obtaining 22 g (77% yield) of a white solid. m.p. 165-166°C. ^{1}H-NMR δ: 8.75 (d, 1H); 8.0 (d, 3H); 7.5-7.3 (m, 5H); 6.75 (d, 1H); 6.1-5.9 (m, 1H); 5.2-5.0 (m, 2H); 3.95 (s, 3H); 3.5-1.6 (m, 11H). Anal. Calcd for $C_{27}H_{27}N_2O_3Cl$: C, 70.05;H, 5,88; N, 6.05. Found: C, 69.01; H, 5.91; N, 6.01.

9-O-(4-chlorobenzoyl)-11-(2-hydroxyethylthio)-10,11-dihydroquinine **4**. 12 g (25.9 mmol) of compound **3** were added under nitrogen atmosphere to a solution of 14.4 mL (0.2 mol) of 2-mercaptoethanol and 0.85 g (0.52 mmol) of AIBN in 60 mL of $CHCl_3$. The mixture was refluxed with stirring (oil bath 85°C) for 48 hours. The light yellow solution was cooled to room temperature and extracted with hydrochloric acid (100 mL, 2N). The separated aqueous layers were extracted with diethylether and then treated with NaOH pellets until the solution became basic. This was then extracted with $CHCl_3$ and the organic layers were combined and concentrated at reduced pressure to give an off-white solide which was purified by column chromatography (SiO_2; $CHCl_3$:MeOH 7.5:1 as eluent), obtaining 11 g (78% yield) of **4**, as a white solid. m.p.68-70°C. ^{1}H-NMR δ : 8.7 (d, 1H); 8.2-7.9 (d, 3H); 7.7-7.3 (m, 5H); 6.75 (d, 1H); 3.95 (s, 3H); 3.7 (t, 2H); 2.65-1.25(m, 18H). Anal. Calcd. for $C_{29}H_{33}N_2O_4SCl$: C,64.37; H, 6.15; N, 5.18. Found: C, 64.10; H, 6.17; N, 5.12.

9-O-(4-chlorobenzoyl)-11-(2-hydroxyethylsulfonil)-10,11-dihydroquinine **5**. 0.28 g (1,1 mmol) of OsO_4 were added to a solution of 10.3 g (19 mmol) of **4** and 7.9 g (58 mmol) of NMO in 115 mL of THF:^{t}BuOH 4:1. The brown solution was stirred for 24 hours at room temperature and then treated with sodium hydrogen sulfite and extracted with ethyl acetate. The organic solution was dried over anhydrous sodium sulfate and evaporated under reduced pressure to give a solid which was purified by column chromatography (SiO_2; $CHCl_3$: MeOH 9:1 as eluent) obtaining 5.7 g (52% yield) of a white solid. m.p.45-47°C ^{1}H-NMR δ: 8.7 (d, 1H); 8.05 (d, 3H); 7.6-7.3 (m,5H); 6.8 (d, 1H); 4.1 (t, 2H); 3.95 (s, 3H); 3.7-1.3 (m, 18H). Anal. Calcd. for $C_{29}H_{33}N_2O_6SCl$: C, 60.82; H, 5.81; N, 4.89. Found : C, 60.08; H, 5.75; N, 4.8.

9-O-(4-chlorobenzoyl)-11-[2-(4-vinylbenzoyl)-ethylsulfonil]-10,11-dihydroquinine **1**. 1.65 g (9.9 mmol) of 4-vinylbenzoyl chloride[12] in 15 mL of $CHCl_3$ were slowly added at 0°C under nitrogen atmosphere to a solution of 5.7 g (9.9 mmol) of compound **5** and 1.66 mL (11.9 mmol) of triethylamine in 30 mL of $CHCl_3$. The solution was stirred for 24 hours and then washed with a 10% aqueous solution of $NaHCO_3$ and water. The organic layer was dried and evaporated under reduced pressure to give a solid which was purified by column chromatography (SiO_2; $CHCl_3$:MeOH 9:1 as eluent), obtaining 3,5 g (50% yield) of **1** as a white solid. m.p.63-64°C. ^{1}H-NMR δ : 8.7 (d, 1H); 8.15-7.85 (m, 5H); 7.6-7.3 (m, 8H); 6.65- 6.4 (m, 2H); 5.85-5.4 (dd, 2H); 4.75 (t, 2H); 4 (s, 3H); 3.5-1.25 (m, 18H). Anal. Calcd for $C_{38}H_{40}N_2O_7SCl$: C, 64.94; H, 5.6; N, 3.99. Found : C, 64.84; H, 5.54; N, 4.01.

Crosslinked polymer **6**. Radical polymerization of **1** (1.4 g, 2 mmol) with ethylene glycol dimethacrylate (0.76 mL, 4 mmol) and hydroxyethyl methacrylate (11,76 mL, 14 mmol) using AIBN (50 mg) as initiator was carried out in benzene at 75°C for 12 hours. The precipitated polymer was filtered and continously extracted with methanol and acetone. After drying under reduced pressure, 3 g (75% yield) of polymer **6**, as a white powder, were obtained. Nitrogen analysis indicated a loading of chiral alkaloid derivative corrisponding to 10% by mol.

General procedure for the heterogeneous catalytic dihydroxylation of alkenes. The reaction was conducted on a 2 mmol scale in a 25 mL one necked-round bottom flask at 0°C, except otherwise indicated, following the procedures previously described in ref.3c and 4a. After 24 hours, the catalyst was filtered and the diols were isolated and characterized by ^{1}H-NMR spectra.

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