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LIGAND-BASED IMPROVEMENT OF ENANTIOSELECTIVITY IN THE CATALYTIC ASYMMETRIC DIHYDROXYLATION OF DIALKYL SUBSTITUTED OLEFINS

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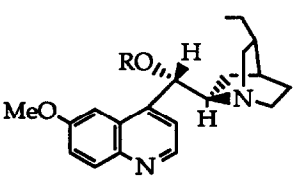
Summary: A high level of asymmetric induction was achieved in the asymmetric dihydroxylation of dialkyl substituted olefins using 9-*O*-aryldihydroquinidines as ligands.

The catalytic asymmetric dihydroxylation (ADH) of *trans*-disubstituted olefins mediated by a cinchona alkaloid-osmium tetroxide complex[3,4] is now well established, and useful applications of the chiral diol products are starting to appear.[5] In our previous reports[3] we showed that, while the enantiomeric excesses of the diols resulting from ADH of aryl substituted olefins using dihydroquinidine (DHQD) *p*-chlorobenzoate **3** were satisfactory (>90%), there was room for improvement in the enantioselectivity of the ADH of dialkyl substituted olefins. As a part of a continuing effort to develop more effective ligands for the ADH, we have prepared and screened a number of cinchona alkaloid derivatives in the stoichiometric ADH process.[6] One result of this study is the finding that aryl ethers of dihydroquinidine (e. g. **1** and **2**)[6,7] are excellent ligands for the ADH of dialkyl substituted olefins.



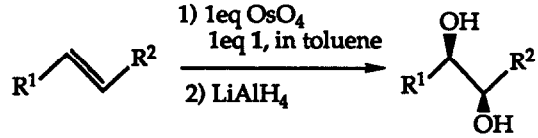
1 R: phenyl

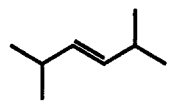
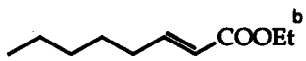
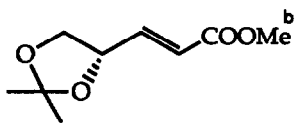
2 R: *o*-methoxyphenyl

3 R: *p*-chlorobenzoate

We first examined the stoichiometric ADH of various dialkyl substituted olefins using the phenyl ether derivative **1** (Table 1). The stoichiometric ADH of olefins was performed by adding 1 eq of olefin to a 1:1 mixture of OsO_4 and **1** in dry toluene (0.1M in **1**) followed by a reductive work-up using $LiAlH_4$ to give the (*R,R*)-diol in 60-95% yield with good to excellent enantiomeric excess. It is noteworthy that reactions with α,β-unsaturated esters also proceeded with much improved enantio- and diastereoselectivities (≥90%, entries 7 and 8, Table 1) using this new ligand **1**. By lowering the reaction temperature to -78°C, the reaction with straight chain dialkyl substituted olefins proceeded with very high enantioselectivities (≥93%, entries 2, 4 and 6, Table 1). In the several cases which were plotted the variance in ee with temperature closely followed the Arrhenius relationship.

Table 1. Stoichiometric ADH using **1**



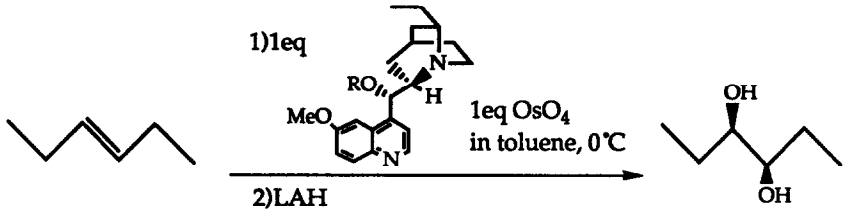
Entry	Olefins	Reaction temp (℃)	%ee[a]	%ee[a] with 3 (for comparison)
1		0	85	71
2		-78	95	
3		0	88	73
4		-78	93	
5		0	89	79
6		-78	94	
7		0	90	67
8		0	97[c]	77[c]

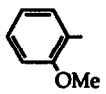
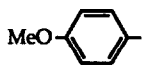
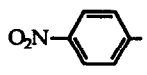
[a]Enantiomeric excess was determined by GLC or HPLC analysis of the bis-Mosher ester derivatives.[8,9] [b]The reaction was worked up with $NaHSO_3$ in H_2O-THF[12c]. [c]Diastereomeric excess.

Next, various DHQD aryl[10] ether derivatives were examined as chiral ligands for the ADH of (*E*)-3-hexene (Table 2). Reactions with all of the aryl ether derivatives tried exhibited higher enantioselectivities than that with DHQD *p*-chlorobenzoate **3**. The highest enantioselectivitiy was obtained with 9-*O*-(2'-methoxyphenyl)-dihydroquinidine (entry 2, Table 2).

Finally, we examined the new ligand in the catalytic ADH of (*E*)-3-hexene. The results are summarized in Table 3. The catalytic ADH reactions (entries 1-3, Table 3) were carried out by slow addition of (*E*)-3-hexene (1 eq) to a mixture of **1** (0.25 eq), *N*-methylmorpholine

Table 2. Stoichiometric ADH of (*E*)-3-hexene[a]



Entry	1	2	3	4	5
R					
%ee	85	88	81	76	75

[a]Ee with DHQD *p*-chlorobenzoate 3 was 71%

N-oxide (NMO, 1.5 eq) and OsO_4 (0.004 eq) in acetone-water (10/1, v/v) at 0°C, followed by work-up with $Na_2S_2O_5$[3b]. The catalytic reaction was slow, and slower addition of olefin than that in the reaction with 3 was required. However, the reaction proceeded much faster upon addition of tetraethylammonium acetate (2 eq) to the reaction mixture (entry 4, Table 3). Potassium ferricyanide[11] was also examined as the secondary oxidant (entries 5 and 6, Table 3). In these cases, slow addition of olefin was not required. To a mixture of (*E*)-3-hexene (1 eq), 1 or 2 (0.25 eq), $K_3Fe(CN)_6$ (3 eq) and K_2CO_3 (3 eq) in *tert*-butyl alcohol-water (1/1, v/v) was added OsO_4 (0.0125 eq) at rt; the resulting mixture was stirred at rt for 20 hr. Reductive work-up (Na_2SO_3) gave the diol in 85-90% yield with essentially the same ee as that obtained in the stoichiometric reaction.[11b]

Table 3. Catalytic ADH of (*E*)-3-hexene

Entry	Ligand	OsO_4	Secondary oxidant	Additive	Reaction Temp (°C)	Reaction Time (hr)	%ee
1	1	0.4mol%	NMO		0	16	70
2	1	0.4	NMO		0	30	75
3	1	0.4	NMO		0	120	85
4	1	0.4	NMO	Et_4NOAc	0	16	82
5	1	1.25	$K_3Fe(CN)_6$	K_2CO_3	rt	20	83
6	2	1.25	$K_3Fe(CN)_6$	K_2CO_3	rt	20	89

In conclusion, DHQD *p*-chlorobenzoate **3** is preferable for the ADH of aryl substituted olefins while DHQD aryl ether **1** or **2** is advised for the reaction of dialkyl- or alkyl carboalkoxy-substituted olefins. Enantioselectivities in the dihydroxylation of dialkyl substituted olefins which were previously only possible through the use of stoichiometric reagents at low temperature[12] can now be obtained in the catalytic ADH using these newly developed ligands at room temperature.

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References and Notes

1. On leave from Sankyo Co. Ltd., Tokyo, Japan.
2. On leave from the Department of Chemistry, St. Patricks College, Maynooth, Ireland.
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7. Prepared by treating lithiated dihydroquinidine sequentially with cuprous chloride and phenyl iodide in dry THF/pyridine and refluxing for 36 hr; G. M. Whitesides, J. S. Sadowski and J. Lilburn, *J. Am. Chem. Soc.* **1974**, *96*, 2829.
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9. We have found no difficulty in reproducing these ee determinations. Contrary to a previous suggestion[12c], kinetic resolution is not a problem provided both the Mosher chloride (2.5 eq) and 4-DMAP (3 eq) are used in excess in dry CH_2Cl_2 and the reaction is monitored by TLC.
10. The stoichiometric ADH of (*E*)-3-hexene using DHQD methyl ether in toluene at 0 °C and following reductive work-up with LAH gave the corresponding diol with 37%ee.
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