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Cinchona alkaloid ester derivatives as ligands in the asymmetric dihydroxylation and aminohydroxylation of alkenes

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Cinchona alkaloid ester derivatives were adopted to asymmetric dihydroxylation and asymmetric aminohydroxylation reactions in excellent yields and enantiomeric excesses.

The catalytic asymmetric dihydroxylation (AD) and asymmetric aminohydroxylation (AA) of olefins using cinchona alkaloid derivatives as ligands have become a useful and reliable transformation in organic synthesis.[1–5] High regio- and stereoselectivity for a broad range of substrates are the most outstanding characteristics of these reactions. To date, many ligands have been tested and a few superior structural types have been identified,[6–9] and our group had developed ligands for the AD and AA reactions.[10–13]

Here, we synthesized a range of analogues using phthaloyl or pyridyl spacer groups between two chiral moieties[14] (the following alkaloid moieties were used: quinine **a** and its pseudo-enantiomer quinidine **c** and their dihydro analogues hydroquinine **b** and hydroquinidine **d**, which afforded a set of ligands capable of performing the transformation across a broad range of alkene substrates by asymmetric AD and AA reactions) (Figure 1).†

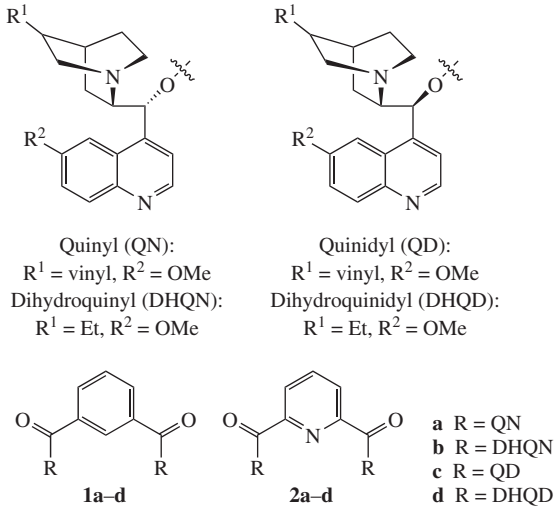
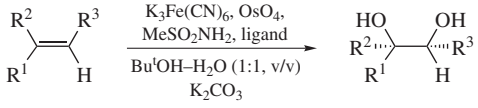
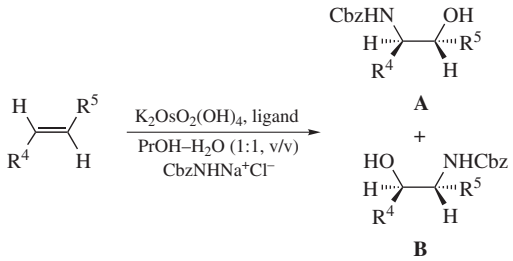


Figure 1 The structure of ester derivatives.

The asymmetric AD reaction (Scheme 1) gave good results for eight substrates furnishing the chiral diol products in good yields 94–99% (Table 1) with satisfying enantioselectivities.



Scheme 1 The AD reactions.



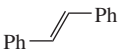
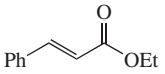
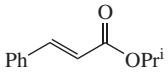
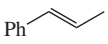
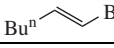
Scheme 2 The AA reactions.

† *The synthesis of cinchona alkaloid ester derivatives.* Into a solution of 2 mmol of cinchona alkaloid in 10 ml of anhydrous CH_2Cl_2, 2 ml of anhydrous Et_3N was added at 0 °C and the mixture was stirred. A solution of dicarbonyl dichloride (0.2 g, 1 mmol) in CH_2Cl_2 was slowly added for 10 min using a dropping funnel. After 1 h, the reaction mixture was warmed to room temperature and stirred for 2 h. Upon completion of the reaction as indicated by TLC, the mixture was poured into 10 ml of water; the organic layer was separated and washed with a saturated NH_4Cl solution and then with water. The organic solution was dried by anhydrous $MgSO_4$ and evaporated *in vacuo*, followed by purification by flash chromatography on silica gel (EtOAc–EtOH–Et_3N, 7:3:0.5).

Typical procedure for the AD reactions.[15] A ligand (0.05 mmol), $K_3Fe(CN)_6$ (0.99 g, 3 mmol), K_2CO_3 (0.42 g, 3 mmol) and OsO_4 (0.005 mmol) were dissolved in 10 ml of Bu^tOH–water (1:1, v/v) at room temperature. For 1,2-disubstituted olefins, $MeSO_3NH_2$ (0.095 g, 1 mmol) was added. The solution was cooled to 0 °C and the olefin (1 mmo1) was added. The mixture was stirred at 0 °C usually for 12 h. In the workup, Na_2SO_3 (0.8 g) was slowly added, and the suspension was warmed to room temperature with vigorous stirring. Ethyl acetate (20 ml) was added, and the aqueous layer was further extracted with ethyl acetate (2×5 ml). If $MeSO_3NH_2$ was used, the combined organic layers were washed with 20 ml of 2 M aqueous NaOH. Then, the combined organic layers were dried over $MgSO_4$ and concentrated. The crude product was purified by flash chromatography on silica gel to afford the diol.

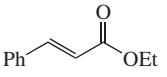
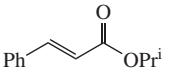
Typical procedure for the AA reactions.[16] An aqueous solution of sodium hydroxide (0.122 g in 7.5 ml of water) was added to a solution of benzyl carbamate (0.469 g, 3.1 mmo1) in 4 ml of propan-1-ol at room temperature. Then, *tert*-butyl hypochlorite (0.35 ml, 3.05 mmol) and a solution of ligand (0.05 mmol) in 3.5 ml of propan-1-ol were successively added to the mixture. The solution was sonicated to ensure homogeneity. A substrate olefin (1 mmol) and then potassium osmate dihydrate (0.414 mg, 0.04 mmol) were added to the reaction mixture. The mixture was stirred at ambient temperature for 5 h and the reaction was controlled by TLC. Then, propan-1-ol was distilled off from the reaction solution under reduced pressure and the rest was extracted with diethyl ether (2×15 ml). The combined organic extract was washed with brine, dried with $MgSO_4$ and concentrated under reduced pressure to give the crude product, which was purified by flash chromatography on silica gel to afford the amino alcohols.

Table 1 The results of asymmetric dihydroxylation.[a]

Entry	Olefin	Yield (%)	*ee* (%)							
			1a	**1b**	**1c**	**1d**	**2a**	**2b**	**2c**	**2d**
1		94–96	98	97	98	99	99	97	98	99
2		94–97	97	98	97	99	98	99	98	99
3		95–97	97	99	98	99	98	97	99	98
4		94–98	91	93	92	91	93	94	92	90
5		96–99	92	91	93	94	94	92	92	93
6		94–99	93	94	94	94	95	94	94	95
7	2-Allyloxynaphthalene	96–98	99	98	98	99	97	98	99	98
8		95–98	89	88	90	91	91	89	90	91

[a]Determined by chiral HPLC.

Table 2 The results of asymmetric aminohydroxylation.[a]

Entry	Olefin	Yield (%)	ee (%)							
			1a	**1b**	**1c**	**1d**	**2a**	**2b**	**2c**	**2d**
1		95–97	81	79	78	80	79	78	85	84
2	*p*-Chlorostyrene	94–96	84	89	85	79	84	85	87	79
3	2-Vinylnaphthalene	95–97	92	91	89	90	93	93	91	90
4		94–97	> 99	99	> 99	97	98	99	98	99
5		95–96	98	98	99	> 99	98	97	> 99	98

[a]Determined by chiral HPLC.

The asymmetric AA reaction (Scheme 2) successfully proceeded for five substrates furnishing the chiral amino alcohol products in good yields 94–97% (Table 2) with satisfying enantioselectivity and regioselectivity (**A**:**B**, > 20:1). The influences of different cinchona alkaloids, bridging groups and substrates were investigated.

Note that, in most cases, the enantioselectivities of the phthaloyl ester catalysts **1a–d** were similar to those of pyridyl ester derivatives **2a–d**. According to Tables 1 and 2, the catalyst derived from different cinchona alkaloid exhibited parallel asymmetric induction patterns. It is demonstrated that the vinyl or ethyl substitution in the structure of cinchona alkaloids had no influence on the asymmetric induce. The ester derivatives have the same excellent asymmetric induction as the previously reported, such as $(DHQD)_2PHAL$[17] and $(DHQD)_2PDZ$,[18] and the result suggested average C_2 symmetry with respect to an axis through the plane of the aromatic ring and, therefore, a preferred anti-arrangement of the two alkaloid units. The two alkaloid units and aromatic bridging group systems set up a binding pocket, and an aromatic olefin inside such a pocket would experience not only parallel stacking but also attractive edge-to-face interactions, which may lead to even further stabilization of the transition state.[19] This hypothesis may also account for the extraordinary enantioselectivities since chirality transfer based on such effects should be very efficient. This mechanism demonstrated that the type of aromatic ring was inessential, and the carbon or nitrogen atom in the bridging group had no influence on the enantioselectivity.

The catalytic asymmetric reaction of alkenes with osmium tetroxide or potassium osmate dihydrate in the presence of bis-cinchona alkaloid derivatives has provided a remarkable tool by which optically pure diols or amino alcohols can be easily obtained in high yields and with excellent enantioselectivities.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2010.03.013.

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