Catalytic Asymmetric Synthesis of Highly Functionalised Compounds with Six Contiguous Stereocentres

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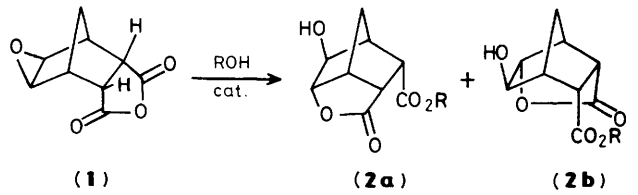
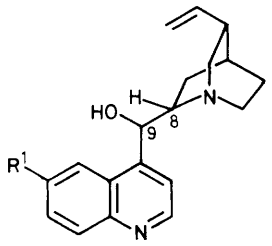
Alcoholysis of the achiral epoxyanhydride (**1**) in the presence of a catalytic quantity of a cinchona alkaloid gives, in a single step, the chiral products (**2**) in up to 99% enantiomeric excess.

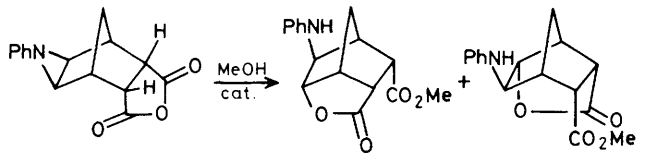
The chemical differentiation of two identical but enantiotopic groups in an achiral substrate remains one of the major challenges of asymmetric synthesis. As an example the enantioselective reaction of achiral *meso*-compounds has so far only been possible using enzymes[1] with their accompanying disadvantages of high cost and substrate specificity. Other approaches have involved the use of stoicheiometric quantities of enantiomerically pure compounds either as leaving groups[2] or reagents.[3] Most recently, and while our work was in progress, Oda and co-workers reported the enantioselective methanolysis of monocyclic acid anhydrides catalysed by cinchonine.[4] We now report the application of a similar



(1) (2a) (2b)



	Configuration R¹	C-8	C-9	
(3)	H	*R*	*S*	Cinchonine
(4)	H	*S*	*R*	Cinchonidine
(5)	OMe	*S*	*R*	Quinine
(6)	OMe	*R*	*S*	Quinidine



(7) (8)

method to substrates of more complex symmetry which provides direct access to products with six contiguous stereocentres with an enantiomeric purity, after a single recrystallisation, of up to 99%.

The substrate chosen for initial study was the epoxide (**1**) of the cyclopentadiene–maleic anhydride Diels–Alder adduct. This is readily available[5] with rigidly defined stereochemistry (*exo*-epoxide, *endo*-anhydride) and has the additional advantage that opening of the anhydride is accompanied by intramolecular attack on the epoxide function [for example hydrolysis of (**1**) gives (**2**, R = H)[6]] thus relaying any enantioselectivity and resulting in complete chemical differentiation between the four functionalised sites in the molecule. As catalysts the four readily available cinchona alkaloids cinchonine (**3**), cinchonidine (**4**), quinine (**5**) and quinidine (**6**) which are effective catalysts for many asymmetric reactions[7] were examined.

When (**1**) was stirred with 3 equiv. of methanol and 0.1 equiv. of triethylamine in toluene at room temperature, the reaction was complete within 2 h to give, upon evaporation, an essentially quantitative yield of racemic (**2**).† Replacement of Et_3N by alkaloids (**3**)—(**6**) gave non-racemic (**2**) (Table 1). As expected cinchonine and quinidine gave products of opposite rotation (+ve) to those obtained with cinchonidine and quinine which are enantiomeric at the 8- and 9-positions, but the selectivities differed markedly within each diastereoisomeric pair, possibly indicating some involvement of the normally inert vinyl part of the catalysts.

Table 1. Alcoholysis of (**1**) in toluene to give (**2**).

R	Catalyst	Equiv. of catalyst	Yield of (2) (%)	E.e. (%)[a]
Me	(**3**)	0.1	85	6.0
Me	(**4**)	0.1	77	4.4
Me	(**5**)	0.1	80	38.0
Me	(**6**)	0.1	73	2.6
Bu^tCH_2	(**5**)	0.1	62	37.0
Ph_2CH	(**5**)	0.1	35	33.3
Me	(**5**)	0.2	66	56.0
Me	(**5**)	0.4	55	69.0
Me	(**5**)	0.5	57	76.0

[a] Determined from the 300 MHz ^1H n.m.r. spectrum of (**2**) (CO_2R signal) in the presence of Eu(hfc)$_3$ (hfc = 3-heptafluoropropylhydroxymethylenecamphorato).

In an attempt to avoid difficulties encountered in separating the catalyst from (**2**) after the reaction [(**2**) is acid sensitive] the polymer supported alkaloids prepared by copolymerisation of (**3**)—(**6**) with acrylonitrile[8] were examined. These give efficient reactions but always with poorer selectivity than the corresponding non-polymeric catalysts.

Retaining the obvious advantage of quinine over the other catalysts, the other reaction parameters were examined. Either lowering the temperature to 0 or −30 °C, or replacing methanol by neopentanol or benzhydrol resulted in a dramatic reduction in the rate of reaction but no increase in selectivity. Previous work points to the involvement of alkaloid–substrate complexes in catalytic reactions of this type[7] and the independence of selectivity on the bulk of the attacking alcohol suggests that the enantioselectivity is determined by the enzyme-like complexation of substrate here too. The replacement of toluene by more polar solvents such as ethyl acetate gave much lower selectivity and in ether no reaction took place at all, indicating failure of the alkaloid–substrate complexation.

A highly significant result was the observation that the monohydrochloride of quinine was an efficient catalyst but gave *racemic* product. This suggests that for quinine there is competition between enantioselective catalysis by the quinuclidine nitrogen and non-selective catalysis by the quinoline nitrogen.‡ Attempts to produce new, highly efficient catalysts in which the latter is blocked are now in progress. In the meantime a simpler if less elegant solution to the problem was found by increasing the proportion of catalyst (Table 1). A single recrystallisation of the product with 0.5 equiv. of quinine furnished material of >99% enantiomeric excess (e.e.), $[\alpha]_D^{25}$ −36.55° (*c* 1.0, $CHCl_3$).

The reaction is not confined to epoxyanhydrides: the aziridine (**7**)[9] reacted under the same conditions, with 0.1 equiv. of quinine, to give (**8**) in 86% yield with an e.e. of 40%. This method provides ready access to highly functionalised enantiomerically pure compounds and the scope and mechanism of the reaction as well as uses for the products are now under investigation.

† Under these conditions the rate of reaction in the absence of a basic catalyst is negligible.

‡ This also provides a possible explanation for the poorer selectivity produced by the polymer supported alkaloids since the attachment of the quinuclidine vinyl group to the polymer chain makes the quinoline nitrogen relatively more accessible to the substrate.

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