Novel Alkaloid Modifiers for Enantioselective Heterogeneous Catalysis

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The alkaloids codeine, 7,8-dihydrocodeine, brucine and strychnine, when adsorbed on Pt/silica (EUROPT-1) induce enantioselectivity and enhance the rate of hydrogenation of the carbonyl function in methyl pyruvate and in butane-2,3-dione.

Enantioselective hydrogenation may be achieved at the surface of certain supported metal catalysts when a pre-adsorbed chiral substance (a modifier) controls the adsorption of the reactant in a configurationally selective manner.[1,2] Thus, for example, cinchonidine **1** adsorbed by the quinoline group at the surface of a supported Pt catalyst controls the adsorption of methyl pyruvate as A′ rather than A (Fig. 1) so that (*R*)-methyl lactate is produced in excess. These sites are considered to be adjacent to the quinuclidine-*N* atom.[2,3] Other sites adjacent to adsorbed cinchonidine are not so affected and give racemic methyl lactate as would be the case in the absence of adsorbed cinchonidine. The high values of enantiomeric excess (e.c.) (up to 94%)[4] obtained over cinchonidine-modified Pt are achieved because the enantioselective element of the hydrogenation is accompanied by a substantial rate enhancement which is also attributed to an effect of the presence of the quinuclidine-*N*.[5] This rate enhancement more than compensates for the deactivation expected due to the occupation of surface sites by adsorbed alkaloid.

The development of new heterogeneous enantioselective catalysts is hindered by difficulties encountered in finding new modifiers other than derivatives of cinchona alkaloids. Here we report that codeine and strychnos alkaloids generate enantioselectivity at Pt surfaces.

The reference catalyst EUROPT-1, a 6.3% Pt/silica,[6–9] has been modified by the laevorotatory alkaloids codeine **2**, 7,8-dihydrocodeine **3**, brucine **4** and strychnine **5**. Modification was carried out using our standard procedure in which the appropriate amount of alkaloid was dissolved in solvent, as indicated in Table 1, and added to 0.1 g catalyst which had been freshly re-reduced at 393 or 723 K. Catalyst and solution were stirred in air for 1 h, centrifuged, the solution decanted off, unless indicated otherwise, and the modified catalyst placed in the high pressure stirred autoclave with fresh solvent and 113 mmol organic reactant. Reaction commenced on pressurisation with H_2 to 10 bar. Analysis was achieved by chiral gas chromatography of products in solution, (Cydex B, SGE Ltd., 50 m), supported by polarimetry of product from which solvent had been distilled.

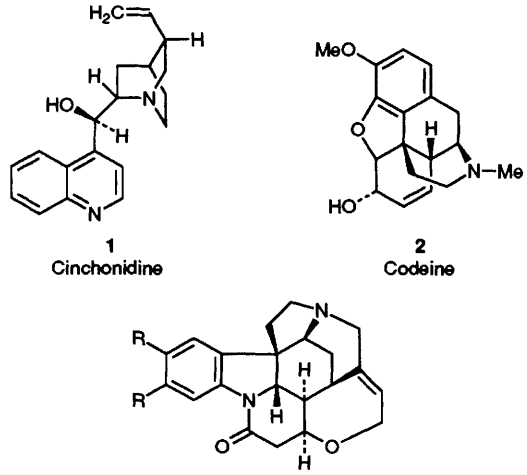

Table 1 shows the performances of these catalysts; reactions involving (−)-cinchonidine-modified catalysts are included for comparison.[10] Unmodified EUROPT-1 catalyses methyl pyruvate hydrogenation to give racemic product at a low rate (50 mmol g_{cat}^{-1} h^{-1}), whereas modification by cinchonidine **1** gives (*R*)-methyl lactate in high e.e. at greatly enhanced rate; the rate enhancement factor of *ca.* 20 shown in entry 2 is typical. Equivalent modification of the catalyst by codeine **2** successfully imparts a mild degree of enantioselectivity, (3%), to (*S*)-methyl lactate in the same reaction which is accompanied by a rate enhancement of *ca.* 5 (entry 5). The catalyst activity and selectivity were insensitive to variation of the reduction temperature from 393 to 723 K (entries 6 and 7). Faster reaction rates were observed as the concentration of alkaloid in the modification solution was decreased (compare entries 4, 5, 6). Modification using 66 or 53 μmol codeine directly in the autoclave (entries 8, 9), resulted in significantly diminished reaction rates with no loss in the e.e. Similar results were obtained using CH_2Cl_2 as solvent (entries 10, 11), as is the situation when cinchonidine is used as modifier (entry 3). No differences in the reaction rate or enantiomeric excess obtained were observed when 7,8-dihydrocodeine **3** was used as modifier (compare entries 4 and 12), indicating that the alkene functionality is not involved in either the adsorption of codeine to the catalyst surface or the formation of the enantiodirecting site.

Modification by brucine **4** under equivalent conditions achieves a substantially higher e.e. (12%) to (*S*)-methyl lactate at a similar reaction rate (entries 13, 14). However strychnine **5** is less effective on both counts (entry 15), indicating the importance of the methoxy functional groups in brucine, presumably to anchor this alkaloid more effectively to the catalyst surface.

Hydrogenation of butane-2,3-dione to 3-hydroxybutan-2-one has been achieved over codeine- and brucine-modified Pt (Table 1, entries 16 to 22). The codeine-modified reaction provided significant rate enhancement of 13 which exceeds that for cinchonidine of *ca.* nine, accompanied by a slight e.e. to the (*S*)-isomer.[11] As above, no significant differences were observed when CH_2Cl_2 was used as solvent. Brucine was a poor modifier for this reaction, although it provided an enhanced rate.

Codeine, brucine and strychnine were selected for study because, like cinchonidine, they each possess an aromatic moeity capable of interacting with the metal surface and so provide for alkaloid adsorption and an aliphatic-*N* atom which might provide an enantiodirecting adsorption site or facilitate a rate enhancement. Observations of an e.e. confirm that sites exist (presumably) adjacent to the adsorbed alkaloid, at which configurational selection of methyl pyruvate adsorption oc-

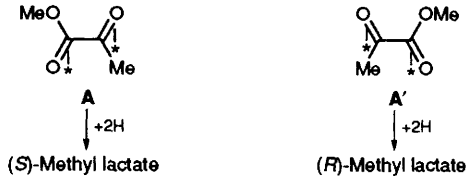

Fig. 1 The conversion of adsorbed methyl pyruvate (A and its mirror image A′) by hydrogen addition to the two enantiomers of methyl lactate

Table 1 Enantioselective hydrogenation of methyl pyruvate to (*S*)-methyl lactate **A** and of butane-2,3-dione to (*S*)-3-hydroxybutan-2-one **B** at 10 bar hydrogen pressure and 298 K, catalysed by 6.3% Pt/silica reduced at 393 K, modified by various alkaloids

	Catalyst Modification				
Entry	Alkaloid[a] (μmol)	Solvent (volume/ml)	Reactant[b]	Max. rate/ mmol $g_{cat}^{-1} h^{-1}$	E.e. (%)
1	none	EtOH (40)	**A**	50	0
2	**1** (680)	EtOH (40)	**A**	1100	65–80[c,d]
3	**1** (680)	CH_2Cl_2 (40)	**A**	1100	70[c]
4	**2** (670)	EtOH (20)	**A**	90	3
5	**2** (670)	EtOH (40)	**A**	260	3
6	**2** (310)	EtOH (70)	**A**	310	3
7[e]	**2** (310)	EtOH (70)	**A**	330	3
8	**2** (66)[f]	EtOH (20)	**A**	80	4
9	**2** (53)[f]	EtOH (20)	**A**	60	3
10	**2** (670)	CH_2Cl_2 (20)	**A**	70	4
11	**2** (60)[f]	CH_2Cl_2 (20)	**A**	70	4
12	**3** (660)	EtOH (20)	**A**	80	3
13[e]	**4** (380)	EtOH (40)	**A**	210	12
14[e]	**4** (260)	EtOH (70)	**A**	190	10
15[e]	**5** (300)	EtOH (70)	**A**	110	2
16	none	EtOH (40)	**B**	180	0
17	none	CH_2Cl_2 (40)	**B**	180	0
18	**1** (680)	EtOH (40)	**B**	1650	8[g]
19	**1** (680)	CH_2Cl_2 (40)	**B**	1650	21[g]
20	**2** (670)	EtOH (40)	**B**	2340	1
21	**2** (670)	CH_2Cl_2 (40)	**B**	2410	1
22[e]	**4** (380)	EtOH (40)	**B**	600	1

[a] **1** = cinchonidine, **2** = codeine, **3** = 7,8 dihydrocodeine, **4** = brucine, **5** = strychnine. [b] Conversions >50%. [c] (*R*)-methyl lactate formed. [d] Reference 10. [e] Reduced at 723 K. [f] Modification in autoclave. [g] (*R*)-(−)-3-hydroxybutan-2-one formed, ref. 11.

curs (*i.e.* as **A** rather than **A'**, Fig. 1) leading, on H-atom addition, to an excess of the (*S*)-product. Preliminary molecular modelling suggests that adsorption in the vicinity of the ring-*O* and the 6-hydroxy substituent of codeine may result in configurational selection for methyl pyruvate in the observed sense, but not for the butane-2,3-dione.

An enhanced rate is of great value where the only process being accelerated is that which gives rise to the e.e. Such is the case with cinchonidine as modifier with Pt catalysts. Codeine modification for butane-2,3-dione hydrogenation provides a substantial rate enhancement but the value of the e.e. suggests that both the racemic reaction and the enantioselective reaction are equally enhanced, and hence no benefit in respect of the enantiomeric excess is obtained. By contrast, the result for methyl pyruvate hydrogenation over brucine-modified Pt indicates that the more modestly enhanced rate may have been restricted largely or wholly to the enantioselective reaction.

The morphology of the Pt surface is also expected to influence the e.e. obtained. EUROPT-1 contains Pt particles having an average size of 18 Å capable of showing preferential (111)-orientation and a raft-like morphology.[12] This surface is well suited for cinchonidine adsorption but molecular modelling suggests that stepped surfaces may be more appropriate for adsorption of the morphine and strychnos alkaloids *via* their aromatic moeity. The breakthrough represented by the observation that morphine and strychnos alkaloids are capable of inducing enantioselectivity now invites optimisation of the catalyst morphology and enantiomeric excess in this reaction and warrants further investigation in the search for improved alternative modifiers.

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