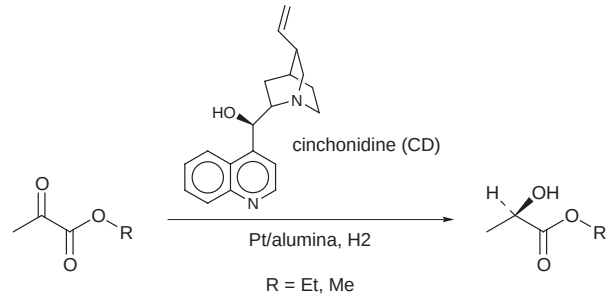
Solvent and substituent effects on the sense of the enantioselective hydrogenation of pyruvate esters catalysed by Pd and Pt in colloidal and supported forms

Paul J. Collier,[a] Tracey J. Hall,[b] Jonathan A. Iggo,*[a]† Peter Johnston,[b]‡ J. Anton Slipszenko,[b] Peter B. Wells*[b] and Robin Whyman*[a]

[a] *Department of Chemistry, University of Liverpool, PO Box 147, Liverpool, UK L69 7ZD*
[b] *Department of Chemistry, University of Hull, Hull, UK HU6 7RX*

The outcome of the enantioselective hydrogenation of pyruvate esters using cinchona alkaloid-modified palladium catalysts is dependent on the choice of solvent/substituent; the sense of the enantioselectivity can be switched from *S* to *R* whilst maintaining the magnitude of the enantiomeric excess.

The enantioselective hydrogenation of methyl pyruvate (MP) and ethyl pyruvate (EP) catalysed by Pt modified by the cinchona alkaloids cinchonidine (CD) and cinchonine (CN) has received much attention over the last decade as one of only a few effective heterogeneous enantioselective systems (Scheme 1).[1–4] It is generally accepted that the adsorption of such modifiers onto a Pt surface *via* the quinoline moiety[5] provides an adjacent site at which *selective enantioface adsorption* of pyruvate occurs and at which subsequent hydrogenation provides lactate product with one enantiomer formed in excess, cinchonidine favouring the *R*- and cinchonine the *S*-enantiomer (Table 1, entries 1 and 2). Concomitant with enantioselectivity is an increase in rate, the enantioselective reaction typically being 20 to 50 times faster than the reaction in the absence of alkaloid. The corresponding Pd-catalysed reactions have been less well studied.[6–9] Two distinctive features of the Pd-catalysed reaction are that (i) the sense of the enantioselectivity is reversed with respect to that of the Pt system (*i.e.* CD directs the reaction to the *S* product and CN to the *R* product), and (ii) there is no rate enhancement.[6–8] Deuterium tracer studies have shown that, over platinum, there is direct addition of two deuterium atoms across the carbon–oxygen double bond but over palladium the main product-forming route is *via* the enolate tautomer and carbon–carbon double bond hydrogenation.[8,10]



Scheme 1

Table 1 The catalytic enantioselective hydrogenation of pyruvate esters

Run	Catalyst	Reactant	Solvent/ substituent	Modifier	Pressure/bar	Initial rate[a]/ mmol s^{-1} mol_{metal}^{-1}	Ee[b] (%)
1	6.3% Pt/silica	MP	EtOH	CD	10	1550	70 (*R*)
2	6.3% Pt/silica	MP	EtOH	CN	10	1375	65 (*S*)
3	colloidal Pt/KD1	EP	MEK	CD	70	635	12 (*R*)
4	colloidal Pt/KD1	EP	MEK	CN	70	795	12 (*S*)
5	colloidal Pt/KD1	EP	MEK	none	70	35	0
6	colloidal Pt	EP	MEK	CD	70	1025	25 (*R*)
7	colloidal Pt	EP	MEK	CN	70	830	15 (*S*)
8	colloidal Pd/KD1	EP	MEK	CD	70	45	29 (*R*)
9	colloidal Pd/KD1	EP	MEK	none	70	< 5	0
10	colloidal Pd/KD1	EP	MEK	CN	70	5	12 (*S*)
11	5% Pd/alumina[c]	MP	THF	CD	10	15	10 (*S*)
12	5% Pd/alumina[c]	MP	THF	CN	10	25	12 (*R*)
13	5% Pd/alumina[c]	MP	EtOH	none	10	80	0
14	5% Pd/alumina[c]	MP	EtOH	CD	10	20	5 (*S*)
15	5% Pd/alumina[c]	MP	EtOH	CN	10	30	11 (*R*)
16	Pd/carbon[d]	MP	MeOH	CD	70	n/r	4 (*S*)
17	5% Pd/alumina[c]	MP	MEK	CD	70	30	7 (*S*)
18	5% Pd/alumina[e]	EP	MEK	CD	70	30	32 (*R*)
19	5% Pd/alumina[e]	EP	MEK	CN	70	15	7 (*S*)
20	5% Pd/alumina[c]	EP	MEK	CD	70	10	14 (*R*)
21	5% Pd/alumina[c]	EP	MEK	CN	70	5	1 (*R*)
22	5% Pd/alumina[c]	EP	EtOH	CD	70	10	8 (*R*)
23	5% Pd/alumina[c]	EP	THF	CD	10	20	15 (*R*)
24	Pd/carbon[f]	EP	EtOH	CD	70	n/r	14 (*S*)

[a] n/r = not reported. [b] Uncertainty ± 2%. [c] Johnson Matthey type 24C. Experiment performed in Hull. [d] Ref. 6. [e] Englehardt ESCAT14. Experiment performed in Liverpool. [f] Ref. 7.

We now report that the catalysis over palladium surfaces shows a more diverse chemistry than was hitherto suspected and that, depending on the choice of solvent/substituent, *each* alkaloid may give *either* enantiomer in excess.

Pt and Pd colloids stabilized with KD1, a proprietary protecting agent, were prepared by a metal vapour synthesis route[11]§ and used as catalysts in the enantioselective hydrogenation of EP.[12,13]¶ The Pt colloids gave the expected direction of enantioselectivity and rate enhancement on the basis of the known chemistry of supported platinum catalysts, *i.e.* CD and CN modification gave (*R*)- and (*S*)-lactate, respectively (Table 1, entries 3–5). The KD1 stabilizing agent was found to have only a marginal effect on the performance of the catalysts (Table 1, compare entries 3 and 4 with 6 and 7).

Surprisingly however, when modified by addition of a butan-2-one (MEK) solution of CD, the palladium colloids also gave (*R*)-lactate with ees of up to 30% in the hydrogenation of EP (entry 8), *i.e.* in the opposite sense to that previously reported for CD-modified Pd catalysts (*e.g.* entry 24).[6–8] In contrast to reactions using oxide-supported Pd catalysts these reactions also appear to show rate enhancement, the rate of the unmodified reaction being very slow (compare entries 8 and 9). The enantioselectivity induced by CN was more muted, in agreement with previous reports that CN is a less effective modifier than CD, and was in favour of (*S*)-lactate (entry 10). This is the *first* report of palladium emulating platinum in the sense of the enantioselectivity induced in pyruvate ester hydrogenation.

Previous studies of oxide-supported palladium catalysed reactions have used EtOH rather than MEK as the solvent[6,8] or have used the methyl rather than the ethyl ester as reactant.[7] In order to investigate the possibility of unprecedented solvent and/or substituent effects in Orito-type reactions, several oxide-supported palladium catalysts were modified either *in situ* or by the Orito procedure[14]‖ in EtOH, THF and MEK and used as catalysts in the hydrogenation of ethyl and methyl pyruvates. All these catalysts gave the expected[6–8] enantioselectivity, *i.e.* in the opposite sense to that observed for platinum catalysts, CD giving (*S*)- and CN (*R*)- product, and showed a reduced rate in MP hydrogenation, (entries 11–17). However, when used in ethyl pyruvate hydrogenation, CD modified catalysts gave (*R*)-lactate in substantial ee and CN modified catalysts (*S*)-lactate, (entries 18–23), *i.e. in the opposite sense to that previously reported*.[6–8] These results originate in independent studies in Liverpool (entries 18 and 19) and Hull (entries 20–23). Thus, this work is not only the *first* report of Pd following Pt in the sense of the observed enantioselectivity, but is also the *only* report, for *either* platinum or palladium, *of the direction of the enantioselectivity being solvent and/or substituent dependent.*

The mechanistic pathway of the palladium-catalysed reaction is not well-understood. Deuterium labelling experiments have shown that, in contrast to the case with Pt, over Pd the main product forming route is *via* the enol and carbon–carbon double bond hydrogenation.[8] Deuterium tracer experiments are in progress to test whether the palladium catalysed reaction in MEK also follows this mechanistic pathway.

These observations reveal that the palladium catalysed enantioselective hydrogenation of pyruvate esters is a much more complicated system than the analogous platinum-catalysed reaction and that coadsorption of solvent/substituent molecules on the Pd surface both during the modification procedure and thereafter during enantioselective hydrogenation is crucial in determining the stereochemical outcome of the reaction.

The authors thank the Catalysis Initiative of the EPSRC (J. A. I. and R. W.) and Johnson Matthey (P. B. W.) for financial support and the provision of studentships (P. J. C., T. J. H and J. A. S.).

Notes and References

† E-mail: iggo@liverpool.ac.uk
‡ Current address: Johnson Matthey PLC, Orchard Road, Royston, Herts, UK SG8 5HE

§ Colloidal metal solutions were prepared by metal vapour deposition in a Torrovap reactor. Typically 2.5 g of KD1, a proprietary protecting agent (ICI), was melted and dispersed onto the walls of the 5 l spherical chamber, after which the chamber was evacuated to 10^{-7} Torr and cooled in liquid nitrogen. 11.3 mmol of Pd was then evaporated over 2 h and co-condensed with 145 cm^3 of butan-2-one (MEK) which was simultaneously added to the vessel as vapour. After deposition the chamber was warmed to room temperature during which period a further 2.5 g KD1 in 60 cm^3 of MEK was added. Pt colloids were prepared by an analogous procedure. High resolution transmission electron microscopy showed the Pd colloids typically to have a particle size distribution ranging from 1.75 to 4.75 nm, with a maximum at 2.5 nm. After use in catalysis the particle size had increased to 2 to 9 nm with a maximum at 4 nm.

¶ A solution of the colloid containing 1 mg of Pd, modifier (6 mg, 2.0×10^{-5} mol), freshly distilled ethyl pyruvate (2.7 mg, 0.024 mol) (Aldrich)[15] and solvent/substituent (total reaction volume: 20 ml) was added to a Parr 4592 autoclave. The autoclave was sealed, purged three times with H_2 to 50 bar and then pressurized to 70 bar with H_2 and maintained at 25 ± 1 °C for 1 h.

‖ The reduced catalyst was first immersed in a solution of the alkaloid in the appropriate solvent and the slurry was then stirred in air for about 1 h before the catalyst was loaded into the high pressure reactor.

1 P. B. Wells and A. G. Wilkinson, *Top. Catal.*, in the press.
2 A. Baiker, *J. Mol. Catal. A,*, 1997, **115**, 473.
3 H-U. Blaser, H. P. Jalett, M. Muller and M. Studer, *Catal. Today*, 1997, **37**, 441.
4 R. L. Augustine and S. K. Tanielyan, *J. Mol. Catal. A*, 1997, **118**, 79.
5 G. Bond and P. B. Wells, *J. Catal.*, 1994, **150**, 329.
6 H-U. Blaser, H. P. Jallett, D. M. Monti, J. F. Reber and J. T. Wehrli, *Stud. Surf. Sci. Catal.*, 1988, **41**, 153.
7 H-U. Blaser, H. P. Jallett, M. Muller and M. Studer, *Catal. Today*, 1997, **37**, 441.
8 T. J. Hall, P. Johnston, W. A. H. Vermeer, S. R. Watson and P. B. Wells, *Stud. Surf. Sci. Catal.*, 1996, **101**, 221.
9 T. Mallat, S. Szabo, M. Schurch, U. W. Gobel and A. Baiker, *Catal. Lett.*, 1997, **47**, 221.
10 I. M. Sutherland, A. Ibbotson, R. B. Moyes and P. B. Wells, *J. Catal.*, 1990, **125**, 77.
11 R. W. Devenish, T. Goulding, B. T. Heaton and R. Whyman, *J. Chem. Soc., Dalton Trans.*, 1996, 673.
12 J. U. Kohler and J. S. Bradley, *Catal. Lett.*, 1997, **45**, 203.
13 H. Bonnemann and G. A. Braun, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 1992; H. Bonnemann and G. A. Braun, *Chem. Eur. J.*, 1997, **3**, 1200.
14 Y. Orito, S. Imai and S. Niwa, *Nippon Kagaku Kaishi*, 1979, 1118.
15 Impurities in the pyruvate reactant can have an effect on both the rate and ee in these reactions. Ethyl pyruvate was therefore distilled daily. The same batch of ethyl pyruvate was used in the comparative study. Ethyl pyruvate supplied by Aldrich has been reported as suffering fewest problems in this regard. H-U. Blaser, H. P. Jalett and F. Spindler, *J. Mol. Catal. A*, 1996, **107**, 85; T. Mallat, Z. Bodmer, B. Minder, K. Borszelay and A. Baiker, *J. Catal.*, 1997, **168**, 183.

Received in Cambridge, UK, 9th February 1998; revised manuscript received, 18th May 1998; 8/03901A