Catalysis Letters Vol. 103, Nos. 1–2, September 2005 (© 2005)
DOI: 10.1007/s10562-005-6512-8

Unexpected inversion in enantioselectivity in the hydrogenation *N*-acetyl dehydrophenylalanine methyl ester using cinchona-modified Pd/Al_2O_3 catalyst

Nichola J. Colston[a], Richard P. K. Wells[a,b], Peter B. Wells[a], and Graham J. Hutchings[a,*]

[a]*School of Chemistry, Cardiff University, P.O. Box 912, Cardiff, CF10 3AT, UK*
[b]*Department of Chemistry, College of Physical Sciences, University of Aberdeen, Meston Walk, Aberdeen, AB24 3UE, UK*

Received 29 April 2005; accepted 5 May 2005

The enantioselective hydrogenation of *N*-acetyl dehydrophenylalanine methyl ester (NADPME) to *N*-acetyl phenylalanine methyl ester is investigated using cinchona-modified Pd/Al_2O_3 catalysts. The catalyst was prepared using deposition-reduction and was evaluated for the reaction using methanol as solvent with various cinchonine alkaloid/NADPME molar ratios. Enantioselectivity was sensitive to this ratio. For cinchonine at low cinchonine:NADPME molar ratios the *S*-*N*-acetyl phenylalanine methyl ester was formed with low enantioselection, and as the cinchonine:NADPME ratio was increased the reaction became less enantioselective. In the extreme the solubility of cinchonine limited the extent of the experimental conditions that could be explored. As expected cinchonidine modified Pd/Al_2O_3 initially gave *R*-*N*-acetyl phenylalanine methyl ester, again with low enantioselection. However, as the cinchonidine:NADPME molar ratio was increased the reaction initially became racemic and then was selective to the formation of *S*-*N*-acetyl phenylalanine methyl ester. This unexpected inversion in the sense of enantioselection was observed in a range of solvents.

KEY WORDS: enantioselective hydrogenation; *N*-acetyl dehydrophenylalanine methyl ester; cinchonina-modified Pd catalyst; inversion in enantioselectivity.

1. Introduction

Enantioselective hydrogenation remains one of the most intensely studied fields of research in catalysis, particularly for the synthesis of pharmaceuticals and agrochemicals [1–4]. One reaction for which homogeneous catalysts are very effective but, to date, there has been no success with the identification of a heterogeneous counterpart is the hydrogenation of prochiral carbon carbon double bonds in esters. An example of this class of reactions is the enantioselective hydrogenation of *N*-acetyl dehydrophenylalanine methyl ester (NADPME) to *N*-acetyl phenylalanine methyl ester. This type of reaction, i.e. the hydrogenation of an enamide, is relevant to the synthesis of homochiral natural and non-natural amino acids, and represents a challenging problem. At present, the enantioselective hydrogenation of NADPME and related prochiral molecules has been achieved homogeneously using chiral rhodium complexes [5–8], most notably using BINAP as the ligand [4]. The immobilisation of chiral rhodium diphosphine complexes has been intensely studied and has met with some success with relatively simple reactants. However, for many complex reactants, such as enamides, these immobilised catalysts tend to be unstable and leach rhodium rapidly during reaction. For this reason we have investigated catalysts for the hydrogenation of NADPME based on the modification of nanocrystalline palladium catalysts using chiral alkaloids. This approach has been found to be effective for heterogeneous enantioselective hydrogenation of prochiral ketones, particularly using cinchona-modified supported Pt catalysts [9–12].

There has been significant progress in the use alkaloid-modified supported palladium catalysts for the hydrogenation of prochiral carbon–carbon double bonds in acids [5,13–17]. Enantioselective hydrogenation of the corresponding esters has not met with success. In this paper we present some initial results for the enantioselective hydrogenation of NADPME using cinchona-modified Pd/Al_2O_3 and in particular report an unexpected inversion in the sense of enantioselectivity for cinchonidine-modified catalysts.

2. Experimental

2.1. Preparation of materials

Preparation of dehydrophenylalanine azlactone. Benzaldehyde (55 g), *N*-acetylglycine (61 g) and sodium acetate (43 g) were suspended in ethyl acetate (125 mL), acetic anhydride (36 g) was added and the mixture was heated (85–90 °C) with stirring for 20 h. The resultant

* To whom correspondence should be addressed.
E-mail: hutch@cardiff.ac.uk

solution was cooled to 50 °C and deionised water (382 mL) was added to precipitate the product. The mobile slurry was stirred at 30–35 °C for 0.5 h and then cooled to 0–5 °C for 1 h. The product was recovered by vacuum filtration and washed with deionised water. The product was characterised by ^{1}H NMR (CD_3OD, 400 MHz), δ: 2.2, (singlet, 3H), 6.9 (singlet, 1H) 7.3 (multiplet, 3H), 7.9 (multiplet, 2H).

Preparation of (E)-NADPME. Dehydrophenylalanine azlactone (15 g) was slurried in methanol (50 mL) at 25 °C for 1 h, 25% sodium methoxide in methanol was slowly added to form a brown solution which was stirred for 1 h. The product was recovered by vacuum filtration and dried (50 °C, 16 h) and characterised by ^{1}H NMR (CD_3OD, 400 MHz), δ: 2.2, (singlet, 3H), 3.9 (singlet, 3H) 7.0 (singlet, 1 H), 7.5 (multiplet, 6 H).

Catalyst preparation. 5% Pd/Al_2O_3 was prepared using a deposition-reduction method.

Alumina (2 g, γ-Al_2O_3, Sasol, 148 m^2 g^{-1}) was added to distilled water (30 mL). An appropriate amount of potassium tetrachloropallidite (K_2PdCl_4, Johnson Matthey) was added to this suspension and was maintained at pH 11 by the addition of solid KOH. The suspension was refluxed for 1 h, and sodium borohydride (ca. 3 times the stoichiometric requirement) was added. After 0.5 h the mixture was cooled and the catalyst recovered by filtration.

2.2. Hydrogenation reactions

A standard procedure was adopted for the hydrogenation of NADPME as follows. NADPME (100 mg, 0.46 mol) and cinchonine or cinchonidine (Fluka) were dissolved in methanol (10 mL) and added to the catalyst (50 mg) in a Parr autoclave (50 mL reactor volume) and the reactor was closed. Various amounts of cinchonine were used to investigate the effect of the cinchonine:NADPME molar ratio on enantioselectivity. The reactor was purged twice with He and then twice with H_2 (3 bar) to remove residual air from the reactor. The reactor was pressurised to 10 bar and stirring started (1000 rpm) and maintained at 25 °C for 3 h to achieve complete conversion; all results are quoted at 100% conversion unless stated otherwise. Products were analyzed using chiral gas chromatography after the catalyst was removed by filtration. Experiments were carried out in triplicate and the average results are presented in this study. Detailed calibration of the gc method showed that the ee could be determined with an accuracy of ±0.7%.

3. Results and discussion

The 5% Pd/Al_2O_3 catalyst was investigated for the enantioselective hydrogenation of NADPME and the results as a function of the alkaloid:NADPME molar ratio are shown in table 1. Using cinchonine as modifier leads to the formation of a small ee to *S*-*N*-acetyl phenylalanine methyl ester. As the concentration of cinchonine is increased the ee decreases and the reaction becomes racemic. At the higher cinchonine:NADPME molar ratios the methanol solution becomes saturated and conversion decreases. With cinchonidine there were no solubility problems and the full range of ratios could be explored. As expected, at low concentration use of cinchonidine gave the opposite sense of enantioselection to that observed with cinchonine and a low ee was observed to *R*-*N*-acetyl phenylalanine methyl ester. However, as the concentration of cinchonidine was increased the reaction became initially racemic and then gave an increasing ee to *S*-*N*-acetyl phenylalanine methyl ester, i.e. the same enantiomer formed preferentially from the cinchonine-modified catalyst. The trends are shown in figure 1 and it is clear how the changing alkaloid concentration has opposite effects on enantioselection with cinchonine and cinchonidine.

As the effect was limited with cinchonine due to its limited solubilit, we investigated the effect further using cinchonidine as modifier with a range of solvents. The results (table 2) show that the inversion in enantioselection is observed when primary alcohols are used as solvents but not for secondary alcohols. For all solvents tested the highest ee was for the *S*-enantiomer at the highest ratio of cinchonidine:NADPME investigated. The order observed for the highest ee was:

$$\mathrm{DMF} \sim \mathrm{methanol} > \mathrm{ethanol} > \mathrm{propan-2-ol} \sim \mathrm{propan-1-ol} > \mathrm{DCM} > \mathrm{THF}$$

This sequence correlates well with the sequence of the dielectric constants of these solvents, a correlation that has been previously observed for the hydrogenation of pyruvate esters with cinchona-modified Pt catalysts [9–12].

The inversion in enantioselectivity was probed further using mixed acetic acid-solvent systems (table 3). Addition of acetic acid to methanol and ethanol

Table 1
Effect of alkaloid: NADPME ratio on the enantiomeric excess in reactions over cinchonine- and cinchonidine-modified 5% Pd/γ–Al_2O_3

Alkaloid: NADPME mol ratio	Cinchonine, ee (*S*)/%	Cinchonidine, ee/%
0.006	10	3.4 (*R*)
0.01	9.5	3.0 (*R*)
0.02	9.0	3.0 (*R*)
0.03	9.5	0
0.07	7.5	1.0 (*S*)
0.14	6.0	2.0 (*S*)
0.20	5.5	2.5 (*S*)
0.40	4.0[a]	8.0 (*S*)
0.60	3.0[a]	16.5 (*S*)
1.00	2.0[a]	21.5 (*S*)
2.00	0[a]	18.0 (*S*)

[a]Saturated solutions, conversion 0% for cinchonine:NADPME mol ratio 2.0.

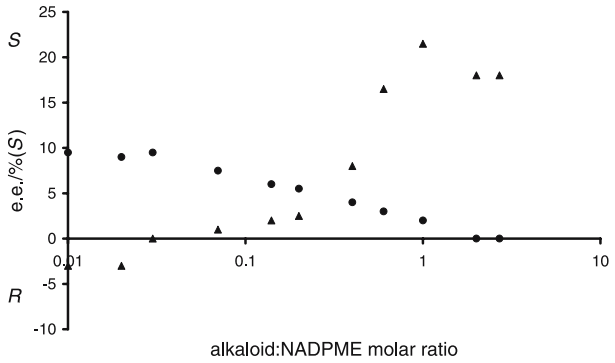

Figure 1. Semi-logarithmic presentation of the variation in enantiomeric excess with modifier:NADPME molar ratio: ●, cinchonine-modified reactions (open circles represented saturated solutions); ▲, cinchonidine-modified reactions.

Table 2
Variation of the sense and magnitude of the enantiomeric excess with cinchonidine concentration as a function of solvent

Solvent[a]	Cinchonidine:NADPME mol ratio (ee/%)				
	0.006	0.03	0.14	0.40	1.0
Methanol	3.4 (*R*)	0	2.0 (*S*)	8.0 (*S*)	21.5 (*S*)
Ethanol	2.0 (*R*)	0	3.0 (*S*)	7.0 (*S*)	14.0 (*S*)
Propan-1-ol	1.5 (*R*)	0	2.5 (*S*)	4.0 (*S*)	9.5 (*S*)
Propan-2-ol	5.0 (*S*)	6.0 (*S*)	7.0 (*S*)	7.0 (*S*)	10.0 (*S*)
DMF	0	7.0 (*S*)	12.0 (*S*)	17.0 (*S*)	22.0 (*S*)
DCM	4.0 (*S*)	5.0 (*S*)	8.0 (*S*)	8.0 (*S*)	8.5 (*S*)
THF	2.5 (*S*)	2.0 (*S*)	2.5 (*S*)	3.0 (*S*)	3.0 (*S*)

[a]DMF *N*,*N* dimethylformamide, DCM dichloromethane, THF tetrahydrofuran.

suppressed the ee, but the inversion in enantioselection was still apparent at higher cinchonidine:NADPME molar ratios (figure 2). In contrast addition of acetic acid to dichloromethane increased the ee to the *S*-enantiomer.

As noted the enantioselective hydrogenation of pyruvate esters has been extensively studied using cinchona-modified catalysts. In these earlier studies it has been well established that, with cinchonidine- and quinine-modified platinum catalysts, the reaction proceeds to form (*R*)-ethyl lactate predominantly, whereas with cinchonine- and quinidine-modified platinum catalysts the reaction forms (*S*)-ethyl lactate preferentially. In the present study it is clear that cinchonine and cinchonidine at low concentrations also direct the enantioselection in opposite directions. Considerable effort has been focussed on the mechanism of the enantioselective hydrogenation of pyruvate esters, and three structural features of the cinchona and related modifiers that ensure they are effective in enantiodirection have been identified, namely (a) an aromatic moiety that enables adsorption on the platinum surface, (b) the absolute configuration at C(8) which controls the sense of the enantioselectivity, and (c) a basic nitrogen which is considered to interact with the substrate resulting is a 1:1 complex that is hydrogenated enantioselectively [18]. The reaction is, however, complicated by effects observed in the early part of the reaction where enantioselection increases with conversion [19–22]. However, recently, Baiker and co-workers [23–25] and Bartók

Table 3
Variation of the sense and magnitude of the enantiomeric excess with cinchonidine concentration for reactions in three mixed solvents[a]

Solvent[a]	Cinchonidine:NADPME mol ratio (ee/%)				
	0.006	0.02	0.40	0.60	1.0
Methanol/acetic acid	8.0 (*R*)	5.5 (*R*)	1.0 (*R*))	3.0 (*S*)	5.5 (*S*)
Ethanol/acetic acid	5.5 (*R*)	3.0 (*R*)	0	2.0 (*S*)	4.0 (*S*)
DCM/acetic acid	7.0 (*S*)	14.0 (*S*)	14.0 (*S*)	14.5 (*S*)	14.0 (*S*)

[a]Methanol, ethanol, dichloromethane (9.95 mL), acetic acid (0.05 mL).

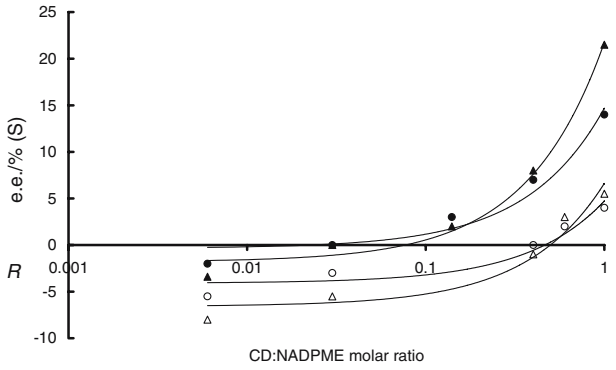

Figure 2. Semi-logarithmic presentation of the effect of the solvent on the variation of both the sense and magnitude of the enantiomeric excess with increasing cinchonidine:NADPME molar ratio: ▲, methanol; ●, ethanol; Δ, methanol/acetic acid; ○, ethanol/acetic acid.

et al. [26] have shown a further intriguing aspect of this reaction, namely that the sense of the enantioselection can be inverted for specific modifiers by changing the extent of reaction [23], the solvent [26] or the substituent at C(8) position [24,25]. In all these cases the effect is induced by changes in the reaction conditions. We have now shown a further example of enantioinversion, but in this case the effect is induced solely by changing the concentration of the modifier. We consider the effect may be due to an interaction of the modifier with specific Pd sites at low modifier concentrations. The observation that acetic acid addition affects the concentration of cinchonidine at which the effect is observed (figure 2) is evidence that the effect is related to the conformation of the cinchonidine which in acid solutions is known to favour the open-3 conformer [13]. The effect is, however, intriguing and may be a key factor in the enantioselective hydrogenation of NADPME using alkaloid modified catalysts and helps to explain why low enantioselection is typically observed.

4. Conclusions

Cinchona-modified Pd/Al_2O_3 catalysts can be effective for the enantioselective hydrogenation of NADPME to the *N*-acetyl phenylalanine methyl ester. At low alkaloid:NADPME molar ratios cinchonine gave *S*-*N*-acetyl phenylalanine methyl ester and cinchonidine the *R*-*N*-acetyl phenylalanine methyl ester. However, at higher alkaloid concentrations the sense of enantioselectivity inverted for cinchonidine, representing one of the first examples of this type of behaviour.

Acknowledgments

We thank the EPSRC and Robinson Brothers for financial support.

References

[1] P. McMorn and G.J. Hutchings, Chem. Soc. Rev. 33 (2004) 108.
[2] L.-X. Dai, Angew. Chem. Int. Ed. 43 (2004) 5726.
[3] S.A. Raynor, J.M. Thomas, R. Raja, B.F.G. Johnson, R.G. Bell, and M.D. Mantle, Chem. Commun. (2000) 1925.
[4] G.J. Hutchings, Chem. Commun. (1999) 301.
[5] U. Nagel and J. Albrecht, Top. Catal. 5 (1998) 3.
[6] B.R. James, A. Pacheco, S.J. Rettig, I.S. Thorburn, R.J. Ball and J.A. Ibers, J. Mol. Catal. 41 (1987) 147.
[7] W.S. Knowles, M.J. Sabacky and B.D. Vineyard, J. Am. Chem. Soc. 97 (1995) 2567.
[8] W.S. Knowles, M.J. Sabacky, and B.D. Vineyard, J. Chem. Soc., Chem. Commun. (1992) 10.
[9] A. Baiker, J. Mol. Catal. A 163 (2000) 205.
[10] H.U. Blaser, J.P. Jalett, M. Müller and M. Studer, Catal. Today 37 (1997) 441.
[11] P.B. Wells and A.G. Wilkinson, Top. Catal. 5 (1998) 39.
[12] M. von Arx, T. Mallat and A. Baiker, Top. Catal. 19 (2002) 75.
[13] T. Burgi and A. Baiker, J. Am. Chem. Soc. 120 (1998) 12920.
[14] T. Burgi, F. Atamny, A. Knop-Gericke, M. Havecker, T. Schedel-Niedrig, R. Schögl and A. Baiker, Catal. Lett. 66 (2000) 109.
[15] K.E. Simons, P.A. Meheux, S.P. Griffiths, I.M. Sutherland, P. Johnston, P.B. Wells, A.F. Carley, M.K. Rajumon, M.W. Roberts and A. Ibbotson, Recl. Trav. Chim. Pays-Bas 113 (1994) 465.
[16] A. Baiker, T. Mallat, B. Minder, O. Schwalm, K.E. Simons and J. Weber, in: *Chiral Reactions in Heterogeneous Catalysis*, eds. G. Jannes and V. Dubois (Plenum Press, New York, 1995) p. 95.
[17] R. Augustine and S. Tanielyan, J. Mol. Catal. A 112 (1996) 93.
[18] H.U. Blaser, Chem. Commun. (2003) 293.
[19] T. Mallat, Z. Bodnar, B. Minder, K. Borszeky and A. Baiker, J. Catal. 168 (1997) 183.
[20] D.G. Blackmond, J. Catal. 176 (1998) 267.
[21] T. Mallat and A. Baiker, J. Catal. 176 (1998) 271.
[22] X. Li, R.P.K. Wells, P.B. Wells and G.J. Hutchings, J. Catal. 221 (2004) 653.
[23] M. von Arx, T. Mallat and A. Baiker, Angew. Chem. Int. Ed. 40 (2001) 2302.
[24] R. Hess, A. Vargas, T. Mallat, T. Bürgi and A. Baiker, J. Catal. 222 (2004) 117.
[25] S. Diezi, A. Szabo, T. Mallat and A. Baiker, Tetrahedron Asymm. 14 (2003) 2573.
[26] M. Bartók, M. Sutyinski, K. Felföldi and Gy. Szöllósi, Chem. Commun. (2002) 1130.