New Chiral Modifiers for the Enantioselective Hydrogenation of Ethyl Pyruvate over Pt/Al2O3 Catalysts

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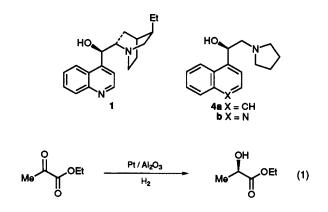
Catalytic quantities of structurally simple chiral amino alcohols such as 2-(1-pyrrolidinyl)-1-(1-naphthyl)ethanol can induce enantioselectivities of up to 75% e.e. in the hydrogenation of ethyl pyruvate over Pt/Al2O3 catalysts.

Modification of metal surfaces by chiral additives is an attractive concept in asymmetric heterogeneous catalysis.[1] Two efficient enantioselective processes based on this principle have been reported so far: the hydrogenation of β-ketoesters with nickel catalysts modified by tartaric acid,[2] and the hydrogenation of α-ketoesters on platinum using cinchona alkaloids as chiral modifiers.[3] Although enantiomeric excesses as high as 90–95% have been achieved with these catalysts, their application range is rather limited. Moreover, very little is known about the catalyst structure and the function of the modifier.

Intrigued by the remarkable properties of the Pt–dihydrocinchonidine system, we decided to examine structurally simple chiral amino alcohols as possible substitutes for dihydrocinchonidine 1 in order to learn more about the structural requirements for the modifier and the mechanism of enantioselection. We hope that the information gained from such studies will eventually lead to useful catalyst systems for other substrates and reactions.
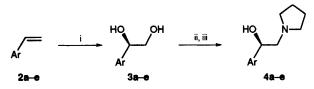
Using the Sharpless asymmetric dihydroxylation[4] as the key-step, a series of enantiomerically pure 2-hydroxy-2-arylethylamines 4 was synthesized (Scheme 1) and tested in the hydrogenation of ethyl pyruvate over Pt/alumina catalysts [Eqn. (1) and Table 1]. The naphthalene derivative 4a proved to be a remarkably efficient modifier inducing enantiomeric excesses as high as 75%. At hydrogen pressures between 1–10 bar, the enantioselectivities are in the same range as with dihydrocinchonidine 1. In contrast to 1 which is more effective at high pressures (under optimum conditions up to 90–95% e.e. in AcOH at 100 bar),[1c,5] the enantioselectivity induced by 4a decreases with increasing hydrogen pressure. This negative pressure effect is probably due to partial hydrogenation of the naphthalene ring observed under these conditions. Accordingly, prehydrogenation of the modifier before adding the substrate results in considerably lower e.e.

At low pressure, the corresponding quinoline derivative 4b is inferior to 4a. Interestingly, with 4b the enantioselectivity increases at higher pressure as reported for the cinchona-based catalysts. Analogous naphthalene-derived modifiers containing more bulky amino groups [–N(Bu^i)$_2$, –NHBu^t] induce markedly lower enantioselectivities (49 and 30% e.e. at 1 bar, respectively). The structurally related diol 3a, as well as the benzene and pyridine derivatives 4c and 4d are

ineffective (<5% e.e.). With the 2-naphthyl-substituted amino alcohol 4e, e.e. range between 28–42%.

The most efficient modifier in this series, 4a, was studied in more detail. Typically, 100 mg of 5% m/m Pt–Al2O3 (Engelhard 4759; freshly reduced in flowing H2 at 400 °C for 1.5 h) was transferred under argon into 20 ml of AcOH containing 6.2 μmol of modifier. Then 90 mmol of ethyl pyruvate was added. Kinetic analyses were based on measuring H2 consumption in an autoclave with a glass–PTFE liner (standard conditions: 10 bar, 25 °C). Both the initial rate and the enantioselectivity show the same characteristic dependence on the modifier concentration as observed for the Pt–cinchona system (Fig. 1).[5] A similar curve was obtained by measuring the rate and e.e. vs. catalyst concentration at constant modifier : catalyst ratio (0.015). Interestingly, the best selectivity (75% e.e.) was observed at high catalyst loading. At low H2 pressures of 1–10 bar, the rate increased sharply with augmenting pressure, while the enantioselectivity remained constant. Above 10 bar, the e.e. dropped significantly (55%

a: Ar = 1-naphthyl, b: Ar = 4-quinolyl, c: Ar = phenyl,
d: Ar = 4-pyridyl, e: Ar = 2-naphthyl.

Scheme 1 Reagents and conditions: i, AD-mix-β,[4] Bu^{t}OH : H2O 1 : 1, 0 °C (70–90%); 3a: 98% e.e., after recrystallisation from Et2O–hexane >99.5% e.e.; ii, 1.05 equiv. TsCl, 1.5 equiv. NEt3, CH2Cl2, 5 °C (50–80%); iii, pyrrolidine, 23 °C (60–80%)

Table 1 Enantioselective hydrogenation of ethyl pyruvate [Eqn. (1)][a]

Modifier	H2 Pressure/ bar	t/h	Conversion (%)[b]	E.e. (%)[b]
1	1	1.0	100	73
	75	0.5	100	87
4a	1	1.0	100	68
	10	0.2	100	75^c
	25	1.0	99	47
	75	0.5	100	46
4b	1	1.0	100	48
	25	0.5	98	55
	75	0.5	100	66
4c	25	2.0	50	0
4d	1	4.0	100	0
	75	1.0	30	0
4e	1	2.0	79	42
	75	1.0	44	28

4a X = CH
b X = N

$$ \text{(1)} $$

[a] Reactions were performed on a 10 mmol scale in 2 ml of AcOH at 23 °C. Hydrogenations at 1 bar: 50 mg of 5% m/m Pt/Al2O3, [substrate]/[modifier] = 300; at 25 and 75 bar: 10 mg of 5% m/m Pt/Al2O3, [substrate]/[modifier] = 1500. [b] Determined by GC analysis (permethylated β-cyclodextrin). [c] 800 mg of 5% m/m Pt/Al2O3, 20 ml of AcOH, 91 mmol of substrate, [substrate]/[modifier] = 1800, 25 °C.

e.e. at 40–70 bar), whereas the rate steadily increased reaching a maximum at 40 bar. In toluene and AcOH the highest enantioselectivity was obtained at 0–5 °C; above 30 °C the e.e. declined sharply. Both the rate and enantioselectivity decrease with increasing solvent polarity, reaching a minimum of 12% e.e. in water. As reported for the Pt–cinchona system,[6] acetic acid is an exceptional solvent giving rise to much higher e.e. than would be expected from its polarity. This is likely due to protonation of the amino function of the modifier, as suggested by MO calculations of possible transition states for the methyl pyruvate–cinchonidine system.[7]

In summary, we have shown that structurally simple, readily available amino alcohols containing a naphthalene or quinoline ring can induce substantial levels of enantioselectivity in the hydrogenation of ethyl pyruvate over Pt catalysts. The ineffectiveness of analogous benzene and pyridine derivatives demonstrates that an extended aromatic π-system is necessary for the function of the modifier. This is consistent with the hypothesis that the quinoline ring of the cinchona alkaloids serves as a binding site for the catalyst surface.[8] In view of the results obtained with the naphthalene derivative 4a, the quinoline N atom does not seem to be essential, indicating that the aromatic π-system rather than the quinoline N atom is involved in the adsorption process. As can be seen from our data, the enantioselectivity of the reaction crucially depends on the amino group of the modifier, in line with previous studies of the Pt–cinchona system which led to the conclusion that the enantioselectivity is determined primarily by the interaction of the quinuclidine part with the substrate.[7,8]
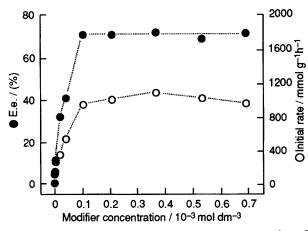
Footnote

† All compounds gave correct elemental analyses. Analytical data of 4a; MP 78–79 °C (recryst. from Et$_2$O–hexane). $[\alpha]_D = -116$ (c. 1.3, CHCl$_3$, 23 °C); >99.5% e.e. (HPLC analysis of the corresponding acetate on a Daicel–Chiralcel OD column, hexane : Pr^{i}OH 95 : 5). ^{1}H NMR (CDCl$_3$): 8.05 (m, 1H), 7.84 (m, 1H), 7.77 (m, 2H), 7.48 (m, 3H), 5.55 (dd, 1H, $J = 10.2, 3.0$ Hz), 5.0–3.0 (br. s, 1H, OH), 2.82 (m, 4H), 2.62 (m, 2H), 1.86 (m, 4H). ^{13}C NMR (CDCl$_3$): 138.0 (C), 133.6 (C), 130.4 (C), 128.8 (CH), 127.6 (CH), 125.7 (CH), 125.6 (CH), 125.2 (CH), 122.9 (CH), 122.8 (CH), 67.6 (CH), 63.2 (CH$_2$), 53.9 (CH$_2$), 23.6 (CH$_2$).

Fig. 1 E.c. and initial rate as a function of the concentration of modifier 4a (AcOH, reaction conditions: see text)

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