Improvement of the enantioselectivity in the enantioselective hydrogenation of ethyl pyruvate by addition of achiral tertiary amines

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In the asymmetric hydrogenation of ethyl pyruvate over the catalyst system cinchonidine–Pt/Al_2O_3 the enantioselectivity was significantly improved by addition of different achiral tertiary amines to the reaction mixture, however the effect appeared to be strongly solvent and concentration dependent.

The hydrogenation of α-keto esters and related compounds over cinchonidine–Pt/Al_2O_3 catalyst is of great scientific interest.[1] In these heterogeneous catalytic asymmetric hydrogenation reactions the enantioselectivity (ee) (ee = ([*R*] − [*S*])/([*R*] + [*S*])) appeared to be strongly solvent dependent.[2] In different solvents the ee increased in the following order: alcohols (ee = 0.70–0.75) < hydrocarbons (ee = 0.80–0.85) < acetic acid (ee = 0.92–0.95%).[2] In all solvents the ee depended strongly on the concentration of the modifier.[1,2] This effect was studied in detail in ref. 2, however neither the chemistry nor the surface phenomena responsible for the observed strong solvent effect could be explained. One of the most interesting observations is that in acetic acid (AcOH) ten times less cinchonidine is needed to obtain the maximum ee value than in toluene.[2]

We have also shown that the addition of small amounts of AcOH is sufficient to increase the ee value.[3] For instance, in EtOH at [AcOH] = 5 M the ee increased to 0.91 compared to 0.73 in its absence. In toluene, under similar conditions, the ee increased to 0.93 compared to 0.81 in its absence. Consequently, the above ee values were very close to those obtained in pure AcOH. However, it should be mentioned that the use of AcOH requires corrosion resistant stainless steel autoclaves and accessories, this fact strongly hinders its general use in academic research. Therefore, any new approach resulting in an increase in enantioselectivity in the absence of AcOH will be of great scientific and practical interest.

In this contribution we report that the addition of achiral tertiary amines (ACTAs) to the reaction mixture containing cinchonidine, substrate, solvent (*e.g.* toluene) and catalyst significantly increases both the rate and the enantioselectivity of the given asymmetric hydrogenation reaction. It is known that when the hydrogenation of ethyl pyruvate is carried out in the presence of ACTAs, *e.g.* triethylamine (TEA), quinuclidine (QN), pronounced rate acceleration is observed without asymmetric induction.[4–6] However, the rate acceleration was much less than in the presence of cinchona alkaloids.

In this study the modifier, either cinchonidine alone or its mixture with achiral tertiary amines, was injected by high pressure hydrogen at $t = 0$ into the reactor containing the catalyst, the substrate and toluene as solvent. Pseudo first order rate constants describing the kinetics for the first 6–10 min (k_1) and 10–40 min (k_2) were used to evaluate the effect of ACTAs. Details of the experimental method and the kinetic approach can be found elsewhere.[3,7,8]

Reaction kinetic data and enantioselectivities obtained in a series of experiments carried out at 20 °C either in the presence or absence of ACTAs are summarized in Table 1, while Fig. 1 shows the corresponding enantioselectivity *vs.* conversion dependencies. In these experiments the ACTAs : cinchonidine (CD) ratio was five and almost full conversion ($x < 0.99$) was achieved within 90 min. Thus, the addition of ACTAs did not result in any decrease in the rate of hydrogenation, moreover, as emerges from the data given in Table 1, the addition of ACTAs led to a considerable increase in both rate constants k_1 and k_2. The rate acceleration increased in the following order: TEA < DABCO < QN.

The enantioselectivity *vs.* conversion dependencies show a monotonic increase type. This form of ee–conversion dependency has been observed by different authors.[2,3,7–10] In the absence of ACTAs the enantioselectivity *vs.* conversion dependency passes through a maximum and decreases slightly above 0.5 conversion giving a final ee value (ee_{end}) around 0.71. Similar behaviour had been observed in our earlier work when $[CD]_0 < 5 \times 10^{-5}$ M.[3,8,11] Analogous results were obtained when TEA was added, however in this case both the ee_{max} and ee_{end} values increased quite substantially (see Table 1). The addition of quinuclidine or DABCO altered the character of the enantioselectivity *vs.* conversion dependency as the monotonic increase in ee was maintained up to 0.99 conversion. This type

Table 1 Influence of different achiral tertiary amines on the enantioselective hydrogenation of ethyl pyruvate in the presence of the cinchonidine–Pt/Al_2O_3 catalyst system[a]

ACTA	k_1/min^{-1}	k_2/min^{-1}	ee_{max}
—	0.0352	0.0465	0.750 (0.714)[b]
TEA[c]	0.0407	0.0676	0.841 (0.793)[b]
DABCO	0.0886	0.1588	0.915[b]
QN[c]	0.1289	0.1645	0.898[b]
QN[c]	0.1297	0.1757	0.909[b]

[a] Solvent: toluene; T = 20 °C; hydrogen pressure = 50 bar; $[Etpy]_0$ = 1.0 M (batch No. 1), $[CD]_0 = 1.2 \times 10^{-5}$ M, $[ACTA]_0 = 1.2 \times 10^{-5}$ M. Catalyst: 5 wt% Pt on Al_2O_3 (Engelhard, E4759), dispersion = 22%, amount = 0.125 g. [b] Measured at the end of reaction. [c] TEA = triethylamine, QN = quinuclidine.

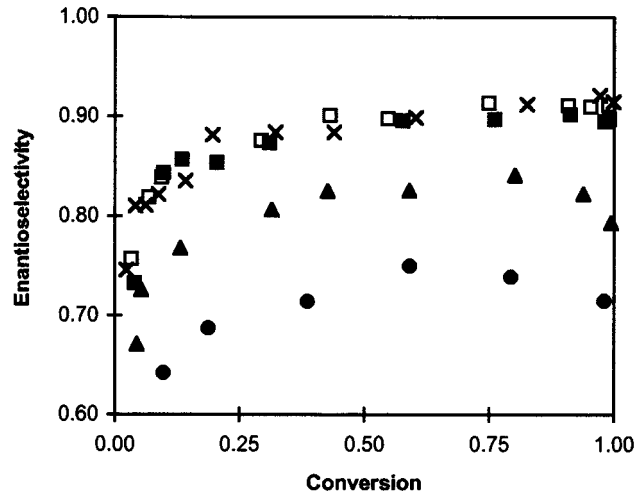

Fig. 1 Enantioselectivity *vs.* conversion obtained in the presence of different ACTAs. Experimental details and abbreviations are given in Table 1. (●) No ACTA, (▲) TEA, (X) DABCO, (■) and (□) QN.

Table 2 Influence of the concentration of quinuclidine (QN) on the enantioselective hydrogenation of ethyl pyruvate in the presence of the cinchonidine–Pt/Al_2O_3 catalyst system[a]

[QN]/M	k_1/min^{-1}	k_2/min^{-1}	ee[b]
0.0	0.0254	0.0065	0.775
1.2×10^{-6}	0.0273	0.0156	0.782
6.0×10^{-6}	0.0601	0.0932	0.910
1.2×10^{-5}	0.0832	0.1346	0.926
6.0×10^{-5}	0.1267	0.0371	0.936
1.2×10^{-4}	0.1219	n.m.[c]	0.946

[a] Solvent: toluene; T = 10 °C; hydrogen pressure = 50 bar; amount of catalyst = 0.125 g; $[Etpy]_0$ = 1.0 M (batch No. 1); $[CD]_0 = 1.2 \times 10^{-5}$ M. [b] Measured at the end of reaction. [c] n.m. = not measurable.

Table 3 Influence of the concentration of cinchonidine (CD) on the enantioselective hydrogenation of ethyl pyruvate in the presence of the cinchonidine–Pt/Al_2O_3 catalyst system[a]

Concentration of [CD]/M	k_1/min^{-1}	k_2/min^{-1}	ee_{max}[b]
0.0	0.0050	—	—
1.4×10^{-6}	0.0147	0.0109	0.216 (0.054)
6.8×10^{-6}	0.0273	0.0271	0.560 (0.334)
1.2×10^{-5}	0.0371	0.0413	0.646 (0.621)
3.4×10^{-5}	0.0823	0.1270	0.868
1.2×10^{-4}	0.1123	n.m.[c]	0.870

[a] Solvent: toluene; T = 20 °C; hydrogen pressure = 50 bar; amount of catalyst = 0.125 g; $[Etpy]_0$ = 1.0 M (batch No. 2). [b] Measured at the end of reaction. [c] n.m. = not measurable.

of enantioselectivity *vs.* conversion dependency was obtained[3,8,11] when $[CD]_0 > 5 \times 10^{-5}$ M. There was no measurable difference between quinuclidine or DABCO, however, the phenomena was well reproducible (see Table 1 and Fig. 1). In conclusion, results given in Table 1 and Fig. 1 precisely demonstrate that in the presence of ACTAs the final enantioselectivity (ee_{end}) increases from 0.71–0.72 to 0.91. This increase in enantioselectivity is considered to be a very pronounced selectivity improvement. Note that in toluene the highest ee value was 0.87 which was measured at $[CD]_0 = 6 \times 10^{-4}$ M. Similar ee values were reported in ref. 2. As emerges from data given in Fig. 1 the ability of ACTAs to increase the enantioselectivity increased in the following order TEA < DABCO = QN, *i.e.* the increase in ee is of a similar order as the rate acceleration effect. However, no measurable effect was induced by achiral tertiary amines when the concentration of CD increased to 10^{-4} M.

Analogous results were obtained in a series of experiments carried out at 10 °C. In these experiments quinuclidine was used as the ACTA and its concentration was varied. Related kinetic data and enantioselectivities are summarized in Table 2, which shows that the influence of ACTAs is strongly concentration dependent. These experiments indicate that the addition of quinuclidine (QN) in the given concentration range increases both the rate of the hydrogenation (rate constants k_1 and k_2) and the enantioselectivity. In these experiments, due to the decrease in the temperature, very high enantioselectivities were obtained. Table 2 shows the influence of ACTAs is already very pronounced at ACTA : CD = 0.5. The increase in the QN concentration resulted in a further increase in the k_1, k_2 and ee_{max} values. The increase in the rate constant k_1 and ee_{max} is gradual and levels off at ACTA : CD = 5–10, while the rate constant k_2 passes through a maximum. The enantioselectivities obtained in this series of experiments (ee_{max} = 0.93–0.94) are the highest values that have ever been obtained in this reaction in the absence of AcOH.

When EtOH was used as solvent no increase in ee was observed in the 10^{-5}–10^{-4} M concentration range of CD and at ACTA : CD = 1–5. No effect was observed in other alcohols, such as methanol or propanol. All of these results strongly indicate that the recognized effect induced by ACTAs depends on (i) the type of solvent used, (ii) the concentration of achiral tertiary amines, and (iii) the concentration of cinchonidine. Note that the observed effect appears at a very low concentration of cinchonidine (1.2×10^{-5} M), *i.e.* in the concentration range characteristic of enzyme catalytic reactions.

The observed increase of both the rate of hydrogenation and the enantioselectivity upon addition of ACTAs strongly resembles the influence of the initial concentration of cinchonidine on the kinetics and enantioselectivity.[2,3,8,11] Results obtained in this study indicated that addition of ACTAs would increase the amount of cinchonidine involved in the enantioselective hydrogenation. The above suggestion is strongly supported by results attained at difference concentrations of CD, but in the absence of ACTA. These results are summarized in Table 3. As emerges from the data in Tables 2 and 3, the increase in the concentration of both CD and ACTA resulted in similar changes in the reaction kinetics: (i) an increase of k_1, k_2 and ee_{max} values and (ii) alteration of the form of the enantioselectivity–conversion dependencies (see Fig. 1 in this paper and Fig. 2 in ref. 11).

The absence of any effect of ACTAs both at high concentrations of cinchonidine and in EtOH strongly resembles the solute–solute (alkaloid–alkaloid) interactions observed in the case of different dihydroquinines ((+)-DHQN and (−)-DHQN).[12] The (+)-alkaloid–(−)-alkaloid interaction was greatly reduced when an alcohol was used as solvent.[12] We propose that the alkaloid–alkaloid (cinchonidine–cinchonidine) interaction is not favourable for the given catalytic reaction as it reduces the amount of 'free alkaloid' required for asymmetric induction. It should be mentioned that in crystallographic form cinchonidine is stabilized by two hydrogen bonds between the OH group and the quinuclidine nitrogen,[13] consequently cinchonidine exists in the form of a cyclic 'dimer'. Based on the above literature analogy[12] we suggest that in the presence of ACTAs a new type of solute–solute interaction (*e.g.*, alkaloid–ACTA interaction) appears provided the concentration of the alkaloid is low and the solvent is not an alcohol. Due to the above interaction the amount of 'free alkaloid' required for asymmetric induction increases. Further studies are in progress in our laboratory to elucidate the character of interactions involved in the phenomena observed.

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