Influence of a Hydroalcoholic Solvent on the Enantioselectivity of α-Amino nitrile Hydration Catalysed by Chiral Ketones

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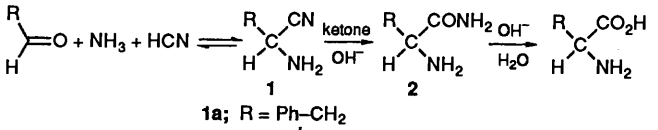
The enantioselective hydration of α-aminonitriles **1**, $RCH(CN)NH_2$ [**1a**: R = $PhCH_2$; **1b**: R = Pr^i; **1c**: R = Ph] has been achieved in an alkaline hydroalcoholic medium in the presence of chiral ketonic catalysts. Of the different ketones used, (−)-(5*R*,3*R*,2*R*)-5-(methylethenyl)-3-cyano-2-methylcyclohexanone (**8**) gives rise to significant enantioselectivity [*e.g.* for the substrate **1c**, k_D/k_L = 2.1; *T* = 10 °C; solvent, water–propan-2-ol (45:55,v/v)]. Although the structure of the catalyst could probably be improved, we show in this paper that the efficiency and especially the enantioselectivity of the catalyst are not only under steric control but also depend on the nature and composition of the hydroalcoholic solvent. Thus, for the three aminonitriles studied in the presence of the catalyst **8**, the increase in percentage of propan-2-ol favours the hydration of the D α-aminonitrile as shown for the hydration of **1c** for which the ratio k_D/k_L increases threefold when the percentage of propan-2-ol increases from 10 to 95%.

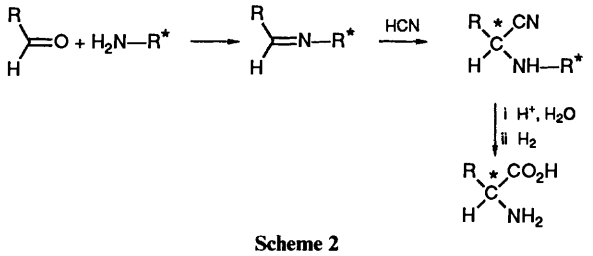
In recent years, major advances in the asymmetric synthesis of α-amino acids have been achieved.[1] The enantioselectivity of the process is generally controlled by the use of stoichiometric amounts of a chiral auxiliary. It should be noted that only a few examples of asymmetric synthesis using strictly catalytic amounts of the chiral auxiliary have been reported and these are generally limited to the use of transition metal complexes with chiral coordinates.[2–4] We have been working since 1970 on α-amino acid synthesis starting from aldehyde precursors in the presence of HCN and NH_3 by using what we have called 'Strecker's and related reactions'[6] where the α-aminonitrile **1** is the key compound (Scheme 1).



1a; R = Ph–CH_2
1b; R = Pr^i
1c; R = Ph

Scheme 1

On the basis of Prelog's work concerning cyanohydrin asymmetric synthesis,[6] attempts to prepare α-aminonitriles by asymmetric addition of HCN to the corresponding imine in the presence of alkaloid were unsuccessful.[7] Thus, Harada and co-workers[8] have shown that the use of a chiral primary amine instead of NH_3 allows stereoselective attack of HCN on the chiral imine intermediate (Scheme 2).



Scheme 2

Apart from the use of enzymes such as nitrile hydratase[9] or amidase[10] allowing, respectively, the hydration of α-aminonitriles and the hydrolysis of the α-aminoamide intermediates, no chemical chiral catalysis has been reported for the synthesis of D or L amino acids starting from their aldehyde precursors. Our previous work on the hydration of α-aminonitriles **1** in basic medium has shown that soluble ketones[11] or those immobilised on insoluble supports[12] catalyse this reaction efficiently in a pseudo-enzymatic process where the key step is intramolecular attack of the nitrile group on the labile addition compound between the α-aminonitrile and the ketone catalyst.

We show here that chiral ketone catalysts allow the enantioselective hydration of the α-aminonitriles **1a–c** which are, respectively, precursors of natural amino acids such as phenylalanine and valine or non-natural ones such as phenylglycine. After searching for a satisfactory chiral ketonic structure as regards its catalytic efficiency, we have ascertained the experimental conditions which optimise hydration enantioselectivity, particularly with respect to choice and proportion of the alcohol cosolvent.

Results

The hydration of α-aminonitriles **1** is efficiently catalysed in basic medium by the ketonic compounds. Without the use of a ketone catalyst, the hydration reaction is very slow and is accompanied competitively by substantial decomposition of the α-aminonitrile which in basic medium, leads to the aldehyde precursor and its degradation products. In this case, the formation of the α-aminoamide could result from hydration catalysis by the aldehyde arising from this decomposition in an 'autocatalytic' process.[13] Obviously, the enantioselective hydration of the α-aminonitrile could not be achieved unless the chiral ketone catalyst exhibits no racemisation, together with high chemical stability under the experimental conditions and sufficient efficiency to avoid both formation of racemic α-aminoamide by the autocatalytic process and also substantial decomposition of the α-aminonitrile.

Furthermore, the efficiency of this catalytic process and its negligible activation energy enables the hydration of the nitrile at low temperatures (*ca.* 10 °C), in the presence of a low concentration of hydroxide ion (0.25 mol dm^{-3}). These mild experimental conditions do not permit either racemisation of *e.g.*, L-α-aminophenylacetamide (**2c**) or that of its *N*-isopropylidene derivative, which is the intermediate in the hydration of α-aminophenylacetonitrile (**1c**) in the presence of acetone.

In general, the catalytic activity of the carbonyl compound is

Table 1 Catalytic efficiency (k_1) and enantioselectivity (k_D/k_L) calculated from the enantiomeric excess (ee) of the α-aminoamide formed at half completion for the different chiral ketone catalysts used in the hydration of **1c** in a H_2O–MeOH (50:50, v/v) medium

Catalyst	k_1/dm^6 mol^2 min^{-1}	% ee (Configuration)	k_D/k_L
4 (acetone)	0.7	0	1
5	0.026	0	1
6	0.23	3 (L)	0.91
7	0.96	1 (L)	0.97
8	0.14	15 (D)	1.55

determined from the initial rate p_0 of α-aminonitrile disappearance which is first order in concentration of α-aminonitrile $[RCN]_0$, carbonyl catalyst [CO] and hydroxide ion $[OH^-]$. Consequently, the rate constant of α-aminonitrile disappearance k_1 is given by eqn. (1).

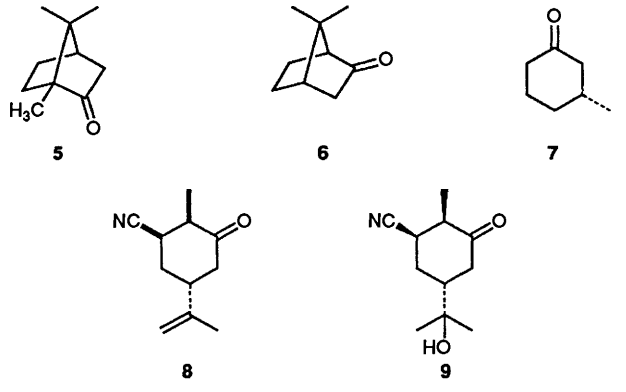
$$k_1 = p_0/([RCN]_0[CO][OH^-]) \quad (1)$$

The enantioselectivity of the catalyst is then determined by measuring the enantiomeric excess (ee) of the α-aminoamide formed at half completion. The ratio k_D/k_L of the hydration constants of the α-aminonitrile enantiomers is related to the experimental ee by eqns. (2) and (3).

$$k_D/k_L = \ln(0.5-0.5ee)/\ln(0.5 + 0.5ee) \quad (2)$$

$$k_D + k_L = 2k_1 \quad (3)$$

The hydration of the α-aminophenylacetonitrile **1c** was carried out in H_2O–MeOH (50:50, v/v) as solvent in the presence of chiral ketones such as 1-(*R*)-(+)-camphor (**5**), 3-(*R*)-(+)-methylcyclohexanone and (+)-(1*S*,4*R*)-2-norbornanone (**6**) which was obtained by the resolution of racemic norborneol followed by oxidation.[14] 1-(*R*)-(+)-Camphor (**5**) had very low activity (*ca.* 20 times less than that of acetone, **4**) which allows the autocatalytic hydration to become competitive leading consequently to the racemic α-aminophenylacetamide **2c** (Table 1).



5 **6** **7**

8 **9**

(+)-(1*S*,4*R*)-2-Norbornanone (**6**) and 3-(*R*)-(+)-methylcyclohexanone (**7**) have clearly higher catalytic activity comparable to that of acetone, arising from lower steric hindrance around the carbonyl group and giving rise to negligible enantioselective hydration.*

After these unsuccessful attempts, we turned our attention to derivatives of (−)-carvone, which is catalytically inactive. While the reduction of the α,β-unsaturated double bond of carvone leads to a catalyst having good efficiency, we preferred to carry out stereospecific addition of HCN to this double bond using a modification of Djerassi's experimental conditions[15] leading to 3(*R*)-cyanodihydrocarvone (**8**) whose stereochemistry has been established. The nitrile group, which is easily modifiable, allowed us subsequently[16] to immobilise the catalyst on an acrylic macromolecular support, in accordance with a technique described by us in the case of aminoketones such as piperidone.[17]

In basic medium, the ketone **8** is in rapid equilibrium leading to a mixture of two epimers with an axial:equatorial ratio of 23:77 as shown by NMR spectroscopy (^{1}H 250 MHz). Furthermore, under the experimental conditions used (10 °C, dilute NaOH), the coupling constants of H_3 with the neighbouring protons are not modified, showing that the carbon bearing the CN group is not epimerised conversely to the behaviour of **8** in a more basic medium and at higher temperatures.

The efficiency of the catalyst **8** in the hydration catalysis of α-aminophenylacetonitrile (**1c**) in water–MeOH (50:50, v:v) is 5 times lower than that for acetone but remains sufficient to supplant the autocatalytic process. α-Aminophenylacetamide (**2c**) is obtained in 15% enantiomeric excess at half completion corresponding to a slight but noticeable enantioselectivity of the catalyst since the ratio of the rate constants k_D/k_L in these conditions is 1.55.

Although it is clear that the structure of the chiral catalyst could surely be improved, it appears to us attractive to define first the nature and the proportion of the cosolvent used allowing optimisation of the catalyst.

The catalytic hydration of α-amino-β-phenylpropionitrile (**1a**) is very greatly reduced by the presence of a cosolvent, especially a non-hydroxylated one such as CH_3CN. The use of an alcoholic solvent allows the ketone catalyst activity to be conserved to an acceptable level. Particularly with the catalyst **8**, propan-2-ol gives rise to a threefold more rapid hydration of **1a** than that of MeOH, and twofold more rapid than that of EtOH.

The influence of the percentage τ of the cosolvent volume on the catalytic efficiency and the enantioselectivity of the ketonic catalyst had led us to use, in the case of low proportions of propan-2-ol, catalyst **9** instead of **8** which is clearly more soluble in water. For τ = 55%, these two catalysts give practically the same results concerning the efficiency and the enantioselectivity and could be recovered quantitatively at half completion with nearly 100% optical purity.

In water–alcohol medium at low proportions of propan-2-ol, the nitrile group of **9** is partially hydrated and 70% catalyst is recovered with 90% optical purity. The increase of τ from 10 to 80% significantly reduced (*ca.* 7 times) the catalyst activity in the hydration of **1a**. The rate constant decreased almost exponentially which seems to be general for all the ketone catalysts used. It is similar to that observed in the hydration of **1a** using acetone as catalyst in a medium with variable proportions of H_2OMeOH (Fig. 1).

The increase in the catalyst activity, for the three substrates used, at very high proportions of propan-2-ol, is connected to the demixing of the ternary H_2O–propan-2-ol–NaOH.[18] The presence of NaOH (0.23 mol dm^{-3}) in a propan-2-ol–H_2O medium (τ = 95%) leads to the formation of an aqueous phase with a small amount of propan-2-ol (<1%) and a high concentration in NaOH (>5 mol dm^{-3}), and a main alcoholic phase with a low concentration of NaOH.

Although the ketone catalyst is practically insoluble in the aqueous phase, the very high local concentration of NaOH is responsible for the unexpected increased efficiency of the hydration catalysis in this solvent which is poor in water.

* The catalyst **6** degrades in the reaction medium, even at 5 °C; the degradation products have not been identified.

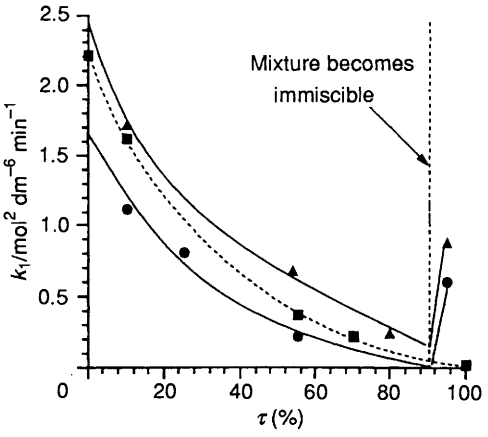


Fig. 1 Variation of the catalytic efficiency (k_1) *vs.* the cosolvent percentage τ. Hydration of **1c** (—▲—) and **1a** (—●—) in propan-2-ol–H_2O using **8** as catalyst. Hydration of **1a** (– – ■ – –) in H_2O–MeOH using acetone as catalyst.

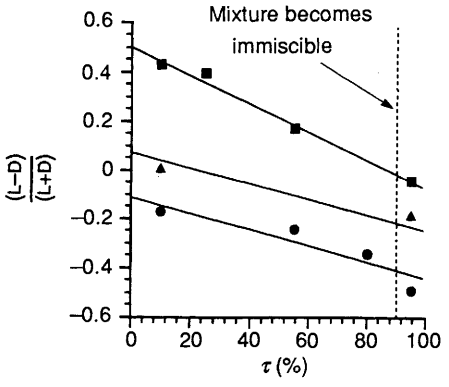


Fig. 2 Influence of the propan-2-ol percentage (τ) on the enantiomeric excess of L-α-aminoamide at half completion for the hydration of **1a** (—■—), **1b** (—▲—) and **1c** (—●—) using catalyst **8** *or* **9** at 10 °C. $[OH^-]$ = 0.25 mol dm^{-3}

The enantioselectivity of the hydration of α-aminonitriles **1a–c**, catalysed by **8** or **9**, is very sensitive to the composition of the water–alcohol solvent. In all cases, increasing τ favours the hydration of the D-α-aminonitriles (Fig. 2)

Thus, when τ passes from 10 to 95%, the enantioselectivity measured by the ratio k_D/k_L is doubled for the valine precursor **1b** and increases practically fourfold for the phenylalanine precursor **1a**. The phenylglycine precursor **1c** is situated at an intermediate level.

Conversely to the rate constant variation, the increase in catalyst enantioselectivity *vs.* the propan-2-ol proportion shows no discontinuity when τ reaches 95%.

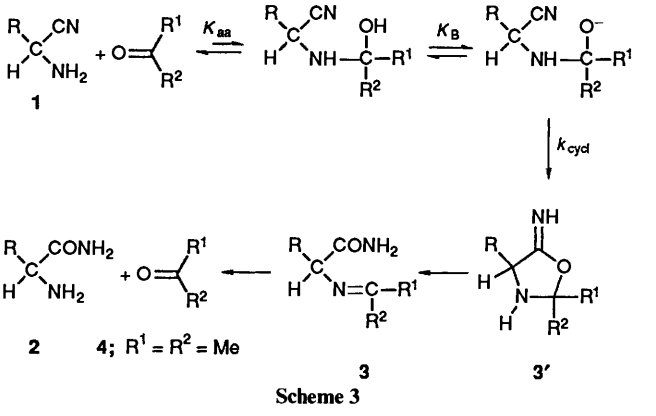
Under these experimental conditions, the use of (+)-(5*S*,3*S*, 2*S*)-5-(methylethenyl)-3-cyano-2-methylcyclohexanone, (+)-**8**, obtained from (+)-(*S*)-carvone allows preferential catalysis of the hydration of L-α-aminophenylacetonitrile with an enantioselectivity k_D/k_L close to 0.2.

The hydration of α-aminonitriles was also carried out in a two-phase medium using a more hydrophobic alcohol solvent such as *tert*-butyl alcohol (τ = 95%) allowing preferential hydration of D-α-aminophenylacetonitrile using the catalyst **8** with an enantioselectivity k_D/k_L of 3.3. In comparison with propan-2-ol, the decrease in this enantioselectivity could result from direct attack of OH^- on the CN which is facilitated in the heterogeneous *tert*-butyl alcohol–OH^- medium.[19] Lastly, we should point out that in octan-2-ol–NaOH where the two phases are not miscible, we have not been able to carry out the hydration of α-aminophenylacetonitrile even in the presence of a phase-transfer catalyst such as hexadecyltrimethylammonium chloride.

Discussion

In this work, the pseudoenzymatic nature of the hydration catalysis of α-aminonitriles by the carbonyl compounds, which has been reported[5,20] on the basis of kinetic criteria is accentuated by highlighting the enantioselectivity of the process in the presence of chiral ketones.

In order to understand the efficiency and the enantioselectivity of these catalysts, it is necessary to consider the mechanism of the catalytic hydration of α-aminonitriles in basic medium. This mechanism can be solved kinetically in two successive slow steps: the formation and the hydrolysis of the imine of the α-aminoamide[13] (Scheme 3).



Scheme 3

The first slow step results from the disfavoured formation of the aminoalcohol in rapid equilibrium (K_{aa}) followed by its cyclisation with a rate constant k_{cycl}. k_1 is connected to k_{cycl} and K_{aa} by eqn. (4) where K_B is the basicity constant of the aminoalkoxide.

$$k_1 = (K_{aa}k_{cycl})/K_B \quad (4)$$

In the particular case of the aminoalcohol arising from condensation of α-aminopropionitrile with isobutyraldehyde,[21] the rate constant of the cyclisation is very high and may be considered as being relatively independent of the catalyst used. The overall efficiency of the catalyst could be determined mainly by its capacity to stabilise the intermediate aminoalcohol.

In this work the importance of the solvation of the reaction site in the transition state appears when we use an aprotic solvent such as CH_3CN or an alcoholic one such as MeOH, EtOH, propan-2-ol. However, it is clear that the acid–base characteristics of the solvent must be taken into account. Thus, the limited decrease of the catalyst **8** activity could result from additional stabilisation of the aminoalkoxide in the presence of propan-2-ol which allows the use of more basic media than does MeOH or EtOH.[22]

In the hydration of **1a** or **1c** in the presence of the catalyst **8** or **9** the rate constant k_1 decreases continuously with the propan-2-ol proportion until the demixing of the reaction mixture which occurs around τ = 95%. The kinetic discontinuity and the significant increase in the catalytic activity may not result from the entry of the nitrile and the catalyst into the aqueous layer in which the concentration of NaOH is very high. In this case, we shall observe the same discontinuity for the enantioselectivity of the catalysis whereas the experimental enantiomeric excess for the substrate **1a** and **1c** varies continuously and independently of the demixing. Under these conditions, the increase in catalytic activity in this heterogeneous medium (H_2O–propan-2-ol) cannot result either from the direct

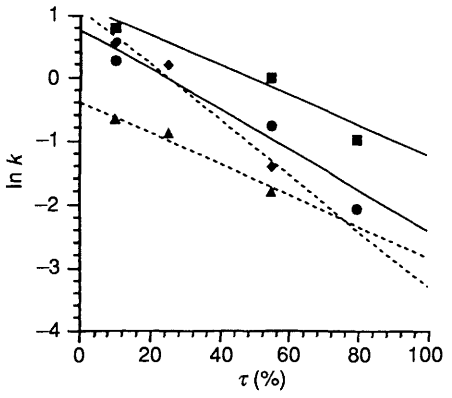


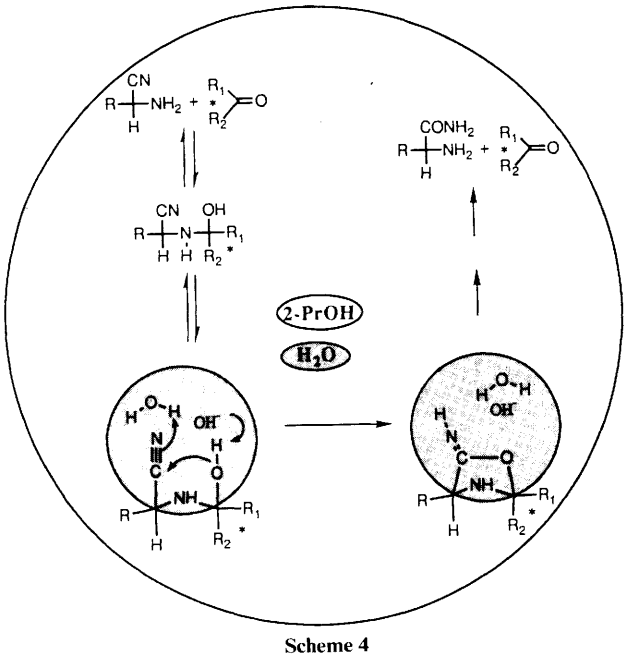
Fig. 3 Variation of $\ln k_D$ *vs.* τ for **1a** (– –▲– –), **1c** (—■—) and of $\ln k_L$ *vs.* τ for **1a** (– –◆– –) and **1c** (—●—) using the catalyst **8** or **9**

attack of the hydroxide ions on the substrate leading to a negligible enantioselectivity, or from a process catalysed by the ketone **8** in the aqueous layer leading to an enantioselectivity similar to that observed in media with large amounts of water.

The above results show that it seems possible, in this heterogeneous medium, to distinguish the parameters that determine the enantioselectivity of the catalyst and those that determine the activity of the catalysts.

(*a*) The formation of the aminoalcohol in the propan-2-ol layer and its solvation at the propan-2-ol–water interface determine the enantioselectivity.

(*b*) The trapping of the aminoalcohol at the interface which is facilitated by the high concentration (*ca.* 5 mol dm^{-3}) of the hydroxide ions and the cyclisation of the corresponding aminoalkoxide are responsible under these conditions for the increase in catalytic activity (Scheme 4).



Scheme 4

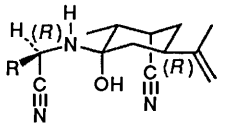
The schematic simplification of the above results in heterogeneous medium may serve as a model to discuss the hydration of the nitriles **1a–c** in homogeneous phase according to the propan-2-ol percentage (τ) in the solvent. For the three compounds, the catalytic hydration of the D-α-aminonitrile is favoured when τ increases. This behaviour may be rationalised by considering the exponential decrease of the rate constants k_D and k_L *vs.* τ which can be written as given in eqns. (5) and (6).

$$\ln k_D = p_1(100 - \tau)/100 + \ln k_{D(\tau=100)} \quad (5)$$

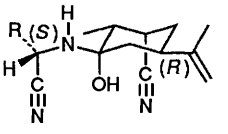
$$\ln k_L = p_2(100 - \tau)/100 + \ln k_{L(\tau=100)} \quad (6)$$

The extrapolation of these curves (Fig. 3) to $\tau = 100\%$ should lead in this non-aqueous medium to a more important virtual reactivity of the D enantiomer with a deviation between $\ln k_{D(\tau=100\%)}$ and $\ln k_{L(\tau=100\%)}$ about threefold greater for **1c** (R = Ph) than for **1a** (R = Ph-CH_2). Thus, it seems that the extrapolated reactivity at $\tau = 100\%$ is mainly under steric control without solvation phenomena. The phenyl substituent which leads to a more important steric hindrance in the aminoalcohol allows better differentiation of the reactivity of the two enantiomers.

In the case of the catalysts **8** and **9**, the two aminoalcohols **A** and **B** with the aminonitrile group in an equatorial position are thermodynamically more stable. Although the epimerisation of the methyl group α to the CO group is rapid under the experimental conditions used it seems, however, that the ketone with an equatorial methyl group is more reactive and leads to the aminoalcohols **A** and **B** with an *R* configuration for the carbon bearing the methyl group. Furthermore, among the possible conformations, we consider only the aminoalcohols where the C–CN and C–OH bonds are in the same plane allowing the cyclisation into the iminooxazolidine **3′**. Thus, it appears that the steric interactions between the benzyl or the phenyl and the methyl group in the 2-position are minimised in the diastereoisomer **A** where the α-aminonitrile has the *R* configuration.



A



B

When τ varies, the enantioselectivity of the hydration is not only under an intrinsic steric control, but the solvation of the reaction site by the molecules of water should also be taken into account. It is striking that the slope p_1 of the straight line $\ln k_D = f(\tau)$ is practically the same for **1a** and **1c** and is similar to that obtained with an achiral catalyst such as acetone (Table 2).

Thus, when the steric hindrances between the substrate and the catalyst are minimised (R and CH_3 are on opposite sides of the middle plane of the diastereoisomer **A**) the influence of the solvent composition on the reactivity is simply expressed in terms of concentrations of the reactive species H_2O, independently of the catalyst used. Conversely, the reactivity of the enantiomer L is very sensitive to the solvent composition and shows a diastereospecific solvation effect, particularly in the case of **1a** ($p_2 = 4.2$) and slightly less for **1c** ($p_2 = 3.25$).

In the aminoalcohol diastereoisomer **B** where the hydrophobic groups are pushed back to the same side of the middle plane of the molecule, the solvation of the reactional site by water is facilitated. In the case of **1a**, this positive effect can overcome the negative steric hindrance effect between the Ph-

Table 2 Slopes of the straight lines $\ln k = f(\tau)$ for the hydration of **1a** and **1c** using the catalyst **8** or **9** and for the hydration of **1a** in the presence of acetone

Catalyst	Substrate	p_1	p_2
8 or **9**	**1a**	2.55	4.2
8 or **9**	**1c**	2.35	3.25
4	**1a**	2.2	2.2

CH_2 and CH_3 groups. Conversely, when R = Ph, the reactivity remains globally under steric control, *e.g.* the inversion of the reactivity of the D and L enantiomers cannot be observed, even in the absence of propan-2-ol.

Conclusions

The α-aminonitriles are hydrated enantioselectively under mild basic conditions in a hydroalcoholic medium in the presence of chiral ketonic catalysts. This enantioselective catalysis is very sensitive to the experimental conditions and particularly to the solvent composition.

A preliminary study has shown that the nature and the configuration of the substituent β to the CO group of the catalyst **8** obtained from the (*R*)-(−)-carvone has little influence on the performances of the catalyst.[23] It is clear that a stereospecific disubstitution at the α position of the CO group will enhance its enantioselectivity providing that the autocatalytic process does not supplant the catalysis by this kind of unreactive carbonyl compound. In this connection it is essential to define the experimental conditions limiting the decomposition of the substrate. The enantioselective catalysis of α-aminonitriles emphasized in this paper in a heterogeneous medium (H_2O–NaOH–propan-2-ol) poor in water seems to provide an answer to this problem.

Experimental

M.p.s were determined on a Büchi 520 apparatus and are uncorrected. IR spectra were recorded using a Perkin-Elmer 1420 spectrophotometer. ^1H NMR spectra were recorded at 60 MHz on a Varian EM 360 with Me_4Si as internal standard and at 250 MHz using a Bruker AC 250. Chemical shifts are given in ppm and all *J* values are in Hz. Optical rotations were measured using a Perkin-Elmer 241 polarimeter. Analytical HPLC was carried out on a Varian liquid chromatograph equipped with a Varian 2550 UV detector (254 nm) for **1a** and **1c** or a RID-6A Shimadzu refractive index detector for **1b**, a Varian 2510 pump and a Varian 4290 integrator. The column used was a 150 × 6 mm C18 (Nucleosil 5 μm). Column chromatography was carried out on Merck Kieselgel 60 (230–400 mesh). TLC was carried out on Merck Kieselgel 60 GF 254 plates coated to a thickness of 0.2 mm. Ether refers to diethyl ether.

α-Amino-β-phenylpropionitrile (**1a**).—A solution of phenylacetaldehyde (13.94 g, 116 mmol) in ethanol (50 cm^3) was added with a flow of 0.3 cm^3 min^{-1} to stirred solution of KCN (9.26 g, 142 mmol) and NH_4Cl (12.35 g, 230 mmol) in 33% ammonia (125 cm^3). The reaction medium was left for 1 h at room temperature. The salts were collected by filtration and the mixture NH_3–MeOH was removed under reduced pressure. The aqueous layer was extracted with ether. The organic layer was dried on Na_2SO_4 and removed under reduced pressure. The oily product obtained crystallises in ether at −20 °C. Yield 76%, m.p. 39.5–40.5 °C; $\nu_{max}(CCl_4)/cm^{-1}$ 3320–3390 (NH_2) and 2220 (CN); δ_H(60 MHz, $CDCl_3$) 1.65 (s, 2 H, NH_2), 3.0 (d, 2 H, CH_2), 3.91 (t, 1 H, CH) and 7.33 (s, 5 H, Ph).

α-Amino-β-methylbutyronitrile (**1b**).—To a solution of KCN (11.3 g, 173 mmol) and NH_4Cl (14.7 g, 274 mmol) in 33% ammonia (170 cm^3) was added at room temperature, dropwise over 1 h, a solution of isobutyraldehyde (10 g, 139 mmol) in methanol (50 cm^3). After further 1 h at 20 °C, the salts were collected by filtration and the mixture NH_3–MeOH was removed under reduced pressure. The aqueous layer was extracted with ether and the organic layer dried on Na_2SO_4 and removed under reduced pressure to give the α-aminonitrile **1b** in 89% yield; $\nu_{max}(CCl_4)/cm^{-1}$ 3390–3320 (NH) and 2230 (CN); δ_H(60 MHz, $CDCl_3$) 1.1 [d, 6 H, $(CH_3)_2$–C], 1.9 (s, 2 H, NH_2), 1.5–2.1 (m, 1 H, $CHMe_2$) and 3.6 (d, 1 H, CH–CN).

α-Aminophenylacetonitrile (**1c**).—To a solution of KCN (7.7 g, 118 mmol) and NH_4Cl (10 g, 187 mmol) in 33% ammonia (115 cm^3) was added, with a flow of 0.3 cm^3 min^{-1}, a solution of freshly-distilled benzaldehyde (10 g, 94 mmol) in methanol (50 cm^3). At the end of the addition, stirring was continued for 1 h at room temperature. The salts were collected by filtration whereupon the mixture NH_3–MeOH was removed under reduced pressure. The aqueous layer was extracted with ether and the organic layer was dried on Na_2SO_4 and removed under reduced pressure leading to the α-aminonitrile which crystallises in ether to give 11.2 g of **1c**. Yield 90%; m.p. 55–56 °C; $\nu_{max}(CCl_4)/cm^{-1}$ 3390–3320 (NH) and 2220 (CN); δ_H(60 MHz, $CDCl_3$) 2.0 (s, 2 H, NH_2), 4.96 (s, 1 H, CH) and 7.5 (m, 5 H, C_6H_5).

(−)-(*R*)-*Methylphenylglycinate Hydrochloride Salt*.—Thionyl chloride (7.2 cm^3) was added dropwise to cooled methanol (250 cm^3) (0 °C). The solution was allowed to warm to 20 °C whereupon (*R*)-(−)-phenylglycine (5 g) was added. The mixture was refluxed for 3 h and the solvent removed under reduced pressure. The residue obtained was dissolved in a minimum of methanol and the hydrochloride salt was precipitated in ether (200 cm^3). Yield 92%; m.p. 202 °C; $[\alpha]_D^{20}$ −122° (*c* 0.1, H_2O); δ_H(60 MHz, $CDCl_3$) (methylphenylglycinate) 2.07 (s, 2 H, NH_2), 3.73 (s, 3 H, OCH_3), 4.67 (s, 1 H, CH) and 7.42 (m, 5 H, Ph).

(−)-(R)-α-*Aminophenylacetamide* (**2c**).—The previous hydrochloride salt was dissolved in methanol saturated with ammonia under pressure. After the disappearance of the ester [TLC, eluent propan-1-ol–NH_4OH (32%), 7:3 (v/v), Ninhydrin] the salts were collected by filtration and the solvent NH_3–MeOH removed under reduced pressure. The pH of the medium was raised to 11 by addition of NaOH and compound **2c** was extracted with dichloromethane and then crystallised in ethanol, 95 °C. Yield 80%; $[\alpha]_D^{20}$ −100° (*c* 0.8; 1 mol dm^{-3} HCl); $\nu_{max}(CHCl_3)/cm^{-1}$ 3500–3340 (NH) and 1685 ($CONH_2$); δ_H(60 MHz, $CDCl_3$) 1.85 (s, 2 H, NH_2), 4.5 (s, 1 H, CH), 5.9 (and 6.8 (m, 2 H, $CONH_2$) and 7.5 (m, 5 H, Ph).

(−)-(R)-N-*Isopropylidene-α-aminophenylacetamide* (**3**).—(*R*)-(−)-α-Aminophenylacetamide (500 mg) was added to a stirred suspension of Na_2CO_3 (6.5 g) in acetone (35 cm^3). The mixture was heated to reflux for 3 h. The salts were collected by filtration and the solvent was removed under reduced pressure to give the corresponding imine **3** in 95% yield. δ_H(60 MHz, $CDCl_3$) 1.85 (s, 3 H, CH_3), 2.15 (s, 3 H, CH_3), 4.96 (s, 1 H, CH), 6.0 (m, 2 H, $CONH_2$) and 7.4 (m, 5 H, Ph).

(+)-(1S,4R)-2-*Norbornanone* (**6**).—This was prepared from the resolution of the *exo*-norborneol following the procedure described by Irwin and co-workers.[15]

(−)-(5R,3R,2R)-5-(*Methylethenyl*)-3-*cyano*-2-*methylcyclohexanone* [(−)-**8**].—A solution of KCN (3 g, 46 mmol) in water (7 cm^3) was added to a solution of (*R*)-(−)-carvone (5 g, 33 mmol) in ethanol (16 cm^3). The mixture was cooled to 0 °C and acetic acid (2 cm^3) was added dropwise over 10 min. After 16 h, the crystals were collected and washed with water. The raw product was dried *in vacuo* and then recrystallised from ethanol, 95 °C. Yield 90%; m.p. 92.5–93.5 °C; $[\alpha]_D^{20} = -5.36°$ (*c* 1.1, EtOH 100°); $\nu_{max}(CHCl_3)/cm^{-1}$ 3080 (CH_2=CH) 2240 (CN), 1720 (C=O) and 1640 (C=C); δ_H(250 MHz, $CDCl_3$) 1.23 (d, *J* 6.71, 3 H, CH_3–C–CO), 1.76 (s, 3 H, CH_3–C=C), 1.96 (m, 1 H, H_{4ax}), 2.28 (m, 2 H, H_{6ax} and H_{4eq}), 2.59 (m, 2 H, H_{2ax} and H_{6eq}), 2.77 (m, 1 H, H_{5ax}),

3.34 (m, 1 H, J_{H3H2} 5.9, J_{H3H4eq} 3.45, J_{H3H4ax} 4.03, H_{3eq}), 4.82 (d, 2 H, CH_2=C) (Found: C, 74.8; H, 8.7; N, 7.9. $C_{11}H_{15}ON$ requires C, 74.54; H, 8.53; N, 7.9%). ^1H NMR 250 MHz (CD_3OD/CD_3ONa) δ: 1.17 (d, 3 H, $-CO-C-CH_{3ax}$), and 1.11 (d, 3 H, $CO-C-CH_{3eq}$).

(+)-(5S,3S,2S)-(*Methylethenyl*)-3-*cyano*-2-*methylcyclohexanone* [(+)-**8**].—This was prepared following the same procedure described for (−)-**8**, starting from the (*S*)-(+)-carvone. Yield 81%; m.p. 91–92 °C; $[\alpha]_D^{20}$ +5.65° (*c* 1.1; EtOH 100 °C); IR and NMR are the same as for (−)-**8**.

(−)-(5R,3R,2R)-5-(1-*Hydroxy*-1-*methylethyl*)-3-*cyano*-2-*methylcyclohexanone* [(−)-**9**].—(−)-**8** (20 g, 113 mmol) was added to a cold solution of sulfuric acid (200 g) in water (200 cm^3). The reaction mixture was stirred until complete dissolution of the product. The starting material which had not reacted was extracted with ether (100 cm^3) and the product was extracted with dichloromethane (6 × 150 cm^3). The organic layer was dried on Na_2SO_4 and evaporated under reduced pressure to give (−)-**9** (19.3 g, 87%); m.p. 76–79 °C (*c* 1, EtOH 100 °C); $\nu_{max}(CHCl_3)/cm^{-1}$ 3600–3400 (OH), 2230 (CN) and 1709 (C=O); δ_H(250 MHz, $CDCl_3$) 1.13 (d, 3 H, $CH_3-C-C=O$), 1.21 (s, 6 H, $(CH_3)_2-C-O$), 1.67 (s, 1 H, OH), 1.5–3 (m, 6 H, H cycle) and 3.33 (m, 1 H, H–C–CN).

Kinetics of Hydration of α-Aminonitriles Catalysed by Chiral Ketones.—The advancement of the hydration of α-aminonitriles was monitored by HPLC [eluent 0.05 mol dm^{-3} KH_2PO_4 (pH 6)–MeOH 70:30 v/v)] using phenol as internal standard. The ketonic catalyst (85 mmol) and the α-aminonitrile (17 mmol) were dissolved prior to $t = 0$ in the alcoholic cosolvent at 10 °C and the necessary amount of NaOH was added at $t = 0$. The advancement of the reaction is evaluated from the analysis of 0.1 cm^3 from the reaction mixture diluted in 1 cm^3 of the HPLC eluent. The retention volumes of the different species are V_r(phenol) 10.6 cm^3; V_r(**1a**) 12.5 cm^3; V_r(**2a**) 4.2 cm^3; V_r(**1b**) 6.0 cm^3; V_r(**2b**) 2.9 cm^3; V_r(**1c**) 9.3 cm^3; V_r(**2c**) 3.1 cm^3.

Evaluation of the Enantiomeric Excess.—The hydration reaction of α-aminonitriles catalysed by the chiral ketones was stopped at half completion by acidification of the medium with hydrochloric acid to pH 1 allowing a minimisation of the decomposition of the α-aminonitrile. The cosolvent was evaporated under reduced pressure and the ketonic catalyst was extracted with dichloromethane. The pH of the aqueous phase was raised to 6 and the α-aminonitrile which had not reacted was extracted with CCl_4. The α-aminoamide was then extracted at pH 11 with dichloromethane and purified on a silica gel column with ethyl acetate–MeOH (7:3) as eluent. The enantiomeric excess of the α-aminoamide obtained was evaluated by measuring its rotatory power $[\alpha]_D^{20}$ +13.3° (*c* 1, MeOH) for **2a**; $[\alpha]_D^{20}$ +27.1° (*c* 1, H_2O) for the hydrochloric acid salt of **2b**; $[\alpha]_D^{20}$ −100.8° (*c* 0.8, H_2O) for the hydrochloric acid salt of **2c** or enzymatically using an enantiospecific amidase (pronase: Boehringer Manheim no. 165921) for **2a** and the leucine amino peptidase (LAP: Sigma no. L9876) for **2c**.

Pronase (5 mg) was added to a buffer aqueous solution (3 cm^3) of glycinate (0.05 mol dm^{-3}, pH 9.6) with 2 cm of an aqueous solution of **2a** (8.3 mmol dm^{-3}). The advancement of the enzymatic hydrolysis of the L amide was monitored by HPLC on a sample of 1 cm^3 diluted with 1 cm^3 of the HPLC eluent containing 0.04 mg of phenol. At the end of the reaction, the proportion of the non-active amide (x) allowed the evaluation of the enantiomeric excess of the α-aminoamide obtained from the enantioselective hydration of **1a** [ee = $\pm(1 - 2x)$].

In the same way, 12.5 mg of **2c** were dissolved in 2.5 cm^3 of an aqueous solution of borax at pH 8.5 and hydrolysed enzymatically with 20 mg^3 of LAP in suspension in the presence of 1 mg of $MnSO_4$ 1.9 mg, of enzyme cm^{-3} of the suspension solution (210 units mg^{-1}).

Appendix

Advancement of the Enantiomeric Excess during the Hydration Reaction.—The global rate V of the α-aminoamide formation is given by eqn. (i),

$$V = k_D[Nit_D] + k_L[Nit_L] \quad (i)$$

where $[Nit_D]$ and $[Nit_L]$ are the concentrations of the two α-aminonitrile enantiomers leading, with an apparent constant rates k_D and k_L, to the corresponding α-aminoamide enantiomers with a concentration $[Am_D]$ and $[Am_L]$. This rate is only first-order dependence according to the total concentration of the α-aminonitrile at $t = 0$ of the kinetic where $[Nit_D] = [Nit_L] = [RCN]_0/2$.

The progress of the α-aminoamide concentrations Am_D and Am_L *vs.* time is given by eqns. (ii) and (iii).

$$[Am_D] = 0.5[RCN]_0[1 - e^{-k_D t}] \quad (ii)$$

$$[Am_L] = 0.5[RCN]_0[1 - e^{-k_L t}] \quad (iii)$$

The constant rates k_D and k_L can be evaluated from the eqns. (iv) and (v),

$$e^{-k_D t} = (1 - y) - y \cdot ee \quad (iv)$$

$$e^{-k_L t} = (1 - y) + y \cdot ee \quad (v)$$

where y is the global transformation rate $y = ([Am_D] + [Am_L])/[RCN]_0$ and ee the enantiomeric excess of the α-aminoamide D.

Explicitly, the enantioselectivity of the catalyst measured by the ratio k_D/k_L is connected to y by eqn. (vi).

$$k_D/k_L = \ln[(1 - y) - y \cdot ee]/\ln[(1 - y) + y \cdot ee] \quad (vi)$$

which is reduced for $t = 0$ to eqn. (vii).

$$(ee)_{y=0} = [1 + k_D/k_L]/[1 - k_D/k_L] \quad (vii)$$

This expression is also valid if the α-aminonitrile is held, in the course of its hydration, in racemisation equilibrium.

Under the general experimental conditions used for the evaluation of the catalyst enantioselectivity, *e.g.* at half completion ($y = 0.5$), eqn. (vi) is reduced to eqn. (viii).

$$k_D/k_L = \ln(0.5 - 0.5ee)/\ln(0.5 + 0.5ee) \quad (viii)$$

Fig. 4 gives the calculated curves from eqn. (vi) for the ee

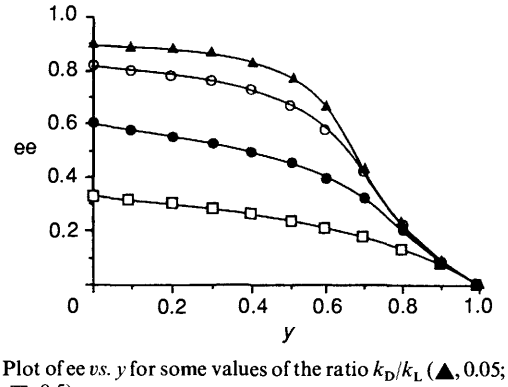


Fig. 4 Plot of ee *vs.* y for some values of the ratio k_D/k_L (▲, 0.05; ○, 0.1; ●, 0.25; □, 0.5)

progress *vs.* the advancement of the reaction y for some values of the ratio k_D/k_L.

Acknowledgements

We thank *Rhône Poulenc Nutrition Animale* for financial support of this work.

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Paper 2/00122E
Received 10*th January* 1992
Accepted 15*th April* 1992