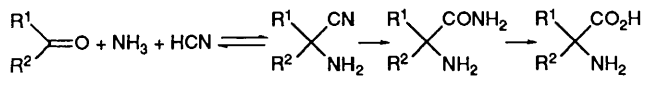
Enantioselective Hydration of α-Aminonitriles Using Chiral Carbonyl Catalysts

Z. Tadros, P. H. Lagriffoul, L. Mion, J. Taillades* and A. Commeyras

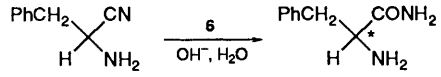
Laboratoire de chimie organique, associé au CNRS, USTL place Eugène Bataillon C17, 34060 Montpellier, France

(±)-α-Amino-β-phenylpropionitrile was hydrated enantioselectively, in a basic aqueous medium, using (−)-5β-(2-hydroxypropan-2-yl)-3α-cyano-2α-methylcyclohexanone as a chiral catalyst **6**, with 42% enantiomeric excess at half completion.

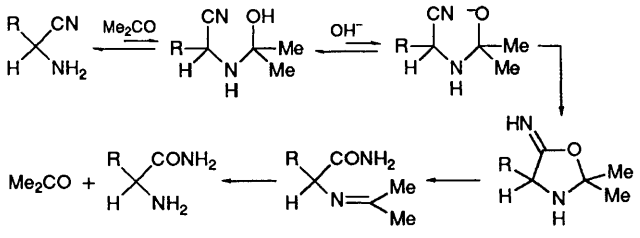
The Strecker reaction[1] allows a carbonyl derivative (aldehyde or ketone) to be converted into a racemic amino acid using HCN and NH_3 (Scheme 1). A racemic amino acid thus obtained or a derivative could be resolved classically to obtain an optically active amino acid. However, enzymatic resolution during the reaction itself may be feasible insofar as it is possible to isolate the reaction intermediates, α-aminonitriles and α-aminoamides. However, the lack of enantioselectivity using the known nitrilehydratase[2] allows, at the moment, only α-aminoamides to be resolved using an enantioselective



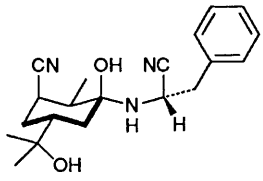
Scheme 1



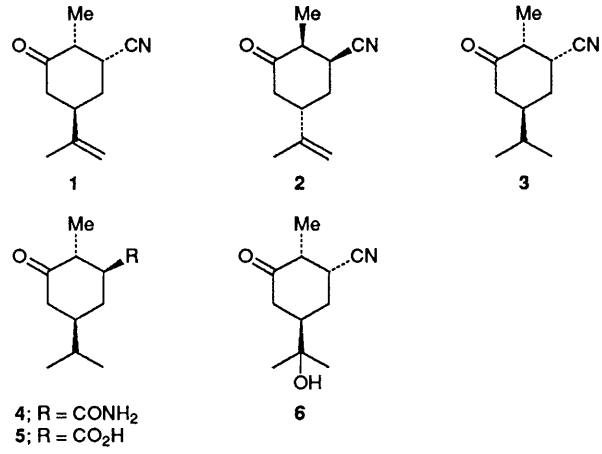
Scheme 2



Scheme 3



X



4; R = $CONH_2$
5; R = CO_2H

Table 1 Enantioselective hydration of the α-aminonitrile **A** using various catalysts in propan-2-ol–water[a]

Catalyst[b]	$[OH^-]$/ mol dm^{-3}	k/dm^6 mol^{-2} min^{-1}[c]	E.e. (%)[d] (config.)
1	0.23	0.20	15 (L)
2	0.23	0.20	15 (D)
3	0.45	0.10	12 (L)
4	0.45	0.21	14 (L)
5	0.45	0.041	0
6	0.23	0.20	16 (L)
6[e]	0.23	0.82	39 (L)
6[f]	0.23	1.14	42 (L)
Me_2CO	0.45	0.52	0
Me_2CO[f]	0.23	1.41	0

[a] At 10 °C; [**A**] = 0.017 mol dm^{-3}; Pr^iOH: H_2O 55:45 (v/v) unless otherwise noted. [b] [Catalyst] = 0.085 mol dm^{-3}. [c] $k = v_0$ $[OH^-]$-[nitrile]$_0$[catalyst]; see footnote †. [d] E.e. at half completion. [e] Pr^iOH: H_2O 25:75. [f] Pr^iOH: H_2O 10:90.

amidase[3] (pronase). Optically active amino acids could also be synthesised from their aldehyde precursors by an asymmetric synthesis of α-aminonitriles using a primary chiral amine[4] instead of NH_3.

In this work, we show that the use of a chiral carbonyl compound (catalyst **6**) allows enantioselective hydration [enantiomeric excess (e.e.) 42% at half completion] of α-amino-β-phenylpropionitrile **A** into L-α-amino-β-phenylpropionamide **B** at 10 °C with quantitative recovery of the chiral catalyst (Scheme 2).

The role of the carbonyl compound in the catalytic hydration of α-aminonitriles is similar to that in our previous work[5] using acetone as a catalyst (Scheme 3).

The slow step of this process is the formation of the imine of the α-aminoamide whose rate has a first-order dependence on the concentration of α-aminonitrile, carbonyl catalyst and hydroxide ions. The asymmetric induction depends on the relative stability of the aminoalcohol diastereoisomers and particularly on the cyclisation of the corresponding aminoalkoxides (in disfavoured rapid equilibrium with the α-aminonitrile). The transition state of the cyclisation, a 5-iminooxazolidine, requires the C–O and C–CN bonds to be in the same plane. It appears that the steric interactions between the benzyl group and the substituents in the 5-position of (−)-5β-(2-hydroxypropan-2-yl)-3α-cyano-2α-methylcyclohexanone **6** are minimised in the *S* enantiomer (structure **X**).

This work was carried out after several unsuccessful attempts in the choice of the chiral carbonyl compound (*e.g.* camphor, norcamphor, 3-methylcyclohexanone). The catalyst must be relatively stable in basic media, not racemisable, and, particularly, lead to catalytic activity similar to that with acetone as the catalyst. The last point is essential to avoid racemic hydration by the aldehyde arising from partial decomposition of the α-aminonitrile. These considerations led us to synthesise various catalysts starting from the (*R*)-(−)- and the (*S*)-(+)-carvone, whose stereochemistry was confirmed by 250 MHz NMR spectroscopy.[6]

Table 1† shows that, under the same experimental conditions (solvent particularly), the nature of the substituents in the 3-position [axial CN (**1–3**) or equatorial $CONH_2$ (**4**)] or the 5-position [$CMe{=}CH_2$ (**1,2**), Pr^i (**3–5**) or $C(OH)Me_2$ (**6**)] had little influence on the stereoselectivity; the acid **5**, a charged species in the basic medium, had very low catalytic activity. However, the catalyst **6** is reasonably soluble in water, which allows the use of a relatively low proportion of alcoholic cosolvent (propan-2-ol) and an increase in enantiomeric excess from 16% (55% propan-2-ol in water) to 42% (10% propan-2-ol) to be obtained. The solvation of the reaction site in the transition state, or rather of the 2-hydroxypropan-2-yl group in the 5-position, plays an important role in the stereoselectivity of the catalytic hydration.

† Reactions were monitored by HPLC by measuring the amounts of α-aminonitrile and α-aminoamide [eluent 0.05 mol dm^{-3} KH_2PO_4 (pH 6)–MeOH (70:30)]. The slope at the origin of a plot of α-aminonitrile concentration *vs.* time enables the rate constant $k = v_0/[OH^-][\text{nitrile}]_0[\text{catalyst}]$ to be evaluated.

The enantiomeric excess was evaluated after extraction of the amide at half completion, by measuring its optical rotation, or enzymatically using an enantioselective amidase (pronase) with determination of the L-phenylalanine formed.

Work is in progress in order to improve the enantioselectivity of these catalysts and to extend this study to other α-aminonitriles, trying to use sufficiently efficient catalysts to carry out this enantioselective hydration at a pH close to 9–10 for which the α-aminonitrile is in racemisation equilibrium *via* the aldehyde precursor.

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