DOI: 10.1002/ejoc.200600294

Regioselective Hydration and Deprotection of Chiral, Dissymmetric Iminodinitriles in the Scope of an Asymmetric Strecker Strategy

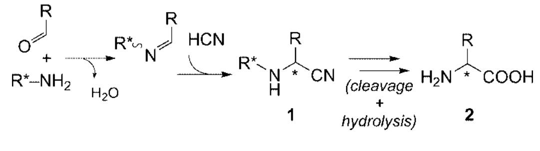
Jean-Christophe Rossi,*[a] Marc Marull,[b] Laurent Boiteau,[a] and Jacques Taillades[a]

Keywords: Iminodinitriles / Chiral α-aminonitriles / α-Amino acids / Regioselective hydration / Asymmetric Strecker synthesis

The controlled, selective decomposition of dissymmetric iminodinitriles (DIDN) of formula RCH(CN)–NH–C(CN)R′R′′ (considered as *N*-protected alpha-aminonitriles), is a critical issue for an original asymmetric Strecker strategy previously outlined by us for the enantioselective synthesis of amino acids. This strategy, derived from Harada's work, involves a double sequence of (*i*) stereoselective Strecker condensation of a chiral ketone R′R′′CO with NH_3 and HCN, followed by (*ii*) stereoselective Strecker condensation with an aldehyde RCHO and HCN, then (*iii*) regioselective retro-Strecker decomposition of the DIDN intermediate to release the target alpha-aminonitrile. In addition to the use of quite simple, cheap cyclic ketones (e.g. carvone derivatives) as chiral auxiliaries, another great advantage of this strategy is that step (*iii*) enables the recovery of the chiral ketone and hence its reuse. While our previous investigations on step (*iii*) under various conditions, either preceded or followed by the hydration of the secondary nitrile group RH(CN)- into an amide, had shown insufficient selectivity, we succeeded in the regioselective hydration of the secondary nitrile of DIDN without significant racemisation, by using a large excess of hydrogen peroxide in methanolic/aqueous ammonia (pH 12.5) at low temperature. The resulting imino nitrile/amide compound was then classically decomposed in acidic medium through a retro-Strecker reaction, affording the chiral alpha-amino amide. Alternately, the regioselective retro-Strecker decomposition of the tertiary moiety of the DIDN was achieved by reaction with silver cation in aqueous nitric acid, also without significant racemisation, thus establishing an original, enantioselective synthesis of alpha-aminonitriles. In both reactions, the chiral ketonic auxiliary resulting from DIDN decomposition was recovered in good yields.

Introduction

Asymmetric Strecker synthesis is an interesting route for the stereoselective preparation of non-natural amino acids and derivatives, such as D-amino acids. Its principle, initially proposed in 1963 by Harada,[1] derives from the Strecker reaction[2] and involves the stereoselective addition of hydrogen cyanide to a chiral imine derived from the condensation of an aldehyde with a chiral, primary amine followed by the selective cleavage of the *N*-substituted aminonitrile intermediate **1** (Scheme 1). Since then, besides the use of various hydrocyanating agents such as α-hydroxyisobutyronitrile $Me_2C(CN)OH$, trimethylsilylcyanide (TMSCN) Me_3SiCN,[3] diethylaluminium cyanide $(C_2H_5)_2AlCN$,[4] or diethyl phosphorocyamidate[5] instead of HCN itself, asymmetric Strecker synthesis was subject to numerous investigations and extensions such as the recent cyanosilylation of α-sulfinyl ketimines.[6] Most methods developed since Harada's work involve the use of a chiral auxiliary usually covalently bound to the amine moiety.[7] Besides, catalytic Strecker reactions have been more recently developed,[8] some of which show high efficiency in terms of both yield and stereoselectivity (e. g. those involving Jacobsen organocatalysts), in spite of generally involving either sophisticated substrates or multistep synthetic routes.



Scheme 1.

In the scope of Harada's principle, however, it would be highly profitable to develop an asymmetric Strecker synthesis involving only simple, easily accessible compounds and one-pot processes, with the possibility of recycling the chiral auxiliary. Following our previous investigations on the mechanism of the Strecker reaction,[9,10] we already outlined a promising case where the chiral amine is a tertiary α-aminonitrile **4** derived from the Strecker reaction of a chiral ketone **3** with hydrogen cyanide and ammonia.[11a] The key asymmetric intermediate is then a dissymmetric iminodinitrile **6**, obtained by the subsequent Strecker reaction of **4** with an aldehyde RCHO and HCN. The diastereoselectivity of the addition of HCN on the prochiral imine **5** depends

---

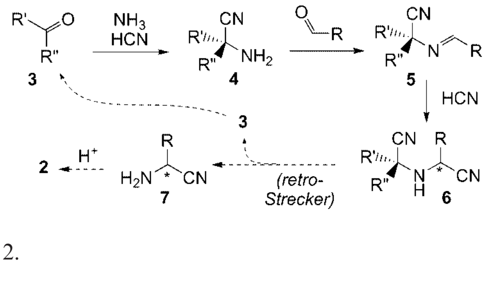
[a] Dynamique des Systèmes Biomoléculaires Complexes, UMR 5073 CNRS, Université Montpellier II,
Place Eugène Bataillon, 34095 Montpellier Cedex 5, France
[b] Institut de Chimie Moléculaire et Biologique, BCh, Ecole Polytechnique Fédérale,
Lausanne, Switzerland

both on the nature of the substituents R, R′, R′′, on the HCN donor and on the reaction conditions.[11b] In the investigated cases where **3** is a substituted cyclohexanone, the most stable β configuration of the pericyclic nitrile favours an eclipsed imine–nitrile configuration in **5**.[11a]

The main advantage of this pathway is the possibility of easily and selectively decomposing **6** through a retro-Strecker process, either before or after regioselective hydration of the secondary nitrile group, thus enabling the recovery of the starting chiral ketone **3**. Indeed, our previous investigations on the reactivity of α-aminonitriles **4** and **7** in aqueous solution[10] showed that they are subject to two competing processes: (*i*) decomposition into aldehyde/ketone, through elimination of HCN followed by NH_3 (retro-Strecker) and (*ii*) hydration of the nitrile group into an amide. The most important parameter for the selectivity of this reaction is the tertiary (faster decomposition) or secondary (faster hydration) nature of the α-aminonitrile. In addition, in moderately alkaline media, α-aminonitrile hydration is often subject to autocatalysis by either the ketone or the aldehyde released by the decomposition of the substrate.[10]

The reactivity of iminodinitriles in aqueous solution is in theory subject to the same kind of selectivity: faster hydration of secondary nitrile groups and faster decomposition of tertiary nitrile groups. However, the higher steric hindrance and the presence of both secondary and tertiary nitriles on the same substrate require the experimental validation of this relation to dissymmetric iminodinitrile reactivity. The main concern addressed in this paper is thus the controlled decomposition of iminodinitrile **6** to release the targeted α-amino acid **2** (or nitrile **7** or amide **10**) without loss of chirality and with good recovery of the chiral auxiliary.

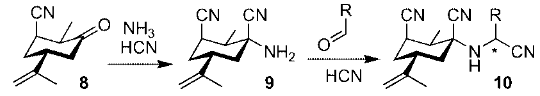
Fulfilling this requirement would lead to further interesting developments of this synthetic pathway including the covalent binding of the chiral ketone **3** onto a polymer resin to facilitate its recycling (a method already described elsewhere[12] for other purposes), or the enantioselective synthesis of non-proteogenic amino acids (e.g. α-methylated amino acids, by replacing the aldehyde RCHO in Scheme 2 by a methyl ketone, as it seems possible on the basis of preliminary experiments). Moreover, it will also be valuable to extend this synthetic scheme to the preparation of chiral α-aminophosphinic acids, known for their antibacterial properties as mimics of α-amino acids or for their antitumour or herbicidal properties.[13]



Scheme 2.

Results and Discussion

The investigated iminodinitriles **10a**–**d** (with R = Me, *i*Pr, *i*Bu, Bn respectively, Scheme 3) were prepared according to our previously described procedure,[11a] starting from enantiopure 1*R*,2*R*,3*R*,5*R*(–)-3-cyanodihydrocarvone **8** obtained by straightforward, stereoselective hydrocyanation of (–)-carvone. The presence of the 3-cyano group on **8** providing an anchor for easy chemical transformation (through its reduction into an amine), was chosen in view of prospective covalent binding of this chiral auxiliary onto a polymer resin. Isolation of the intermediate tertiary α-aminonitrile **9** was not necessary (whether **9** was isolated or not, overall yields and stereoselectivities for **10** were identical in all cases). Separation of diastereoisomer pairs **10**-*R* and **10**-*S* (obtained in a ratio of ca. 4:1) was carried out by liquid chromatography. In this paper, stereoisomers of either one of **2**, **7**, **10**–**14**, will be referred to after the configuration of the stereogenic centre of the target amino acid or derivative (the carbon-atom-bearing substituent R), e.g. **2**-*R*, **10a**-*S*.

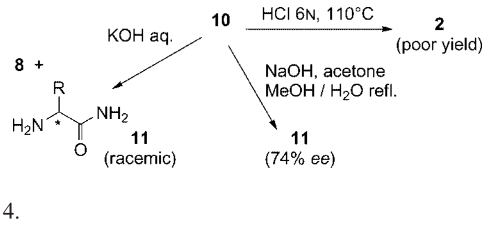


Cpd.	R	Amino Acid
10a	Me	D/L-Ala
10b	*i*Pr	D/L-Val
10c	*i*Bu	D/L-Leu
10d	Bn	D/L-Phe

Scheme 3.

Strong conditions, either alkaline or acidic, are inappropriate, because of the lability of the secondary nitrile group or the high sensitivity toward racemisation of the compounds involved (Scheme 6). Hydrolysis of **10b** (either-*R* or -*S*) with KOH in either aqueous or *tert*-butyl alcohol solution affords the fully racemised amino amide **11b**. The catalysis of nitrile hydration with acetone under alkaline conditions developed by us[14] is poorly efficient with iminodinitrile **10** because of the difficulty of formation of the key intermediate by addition of acetone on the hindered secondary amine. The need for high temperature then results in both the partial racemisation of **11** and the degradation of the chiral auxiliary **8**.

Although the hydrolysis of symmetrical secondary iminodinitriles (**10** with R′ = R and R′′ = H) in sulfuric acid yields the corresponding imino diacids,[15] our investigation on acidic hydrolysis/decomposition of iminodinitriles **10**[11a] did not provide good results because of the competing decomposition reaction. Hydrolysis of iminodinitriles **10a**–**d** (either -*R* or -*S*) at 110 °C in 6 N HCl afforded the expected



Scheme 4.

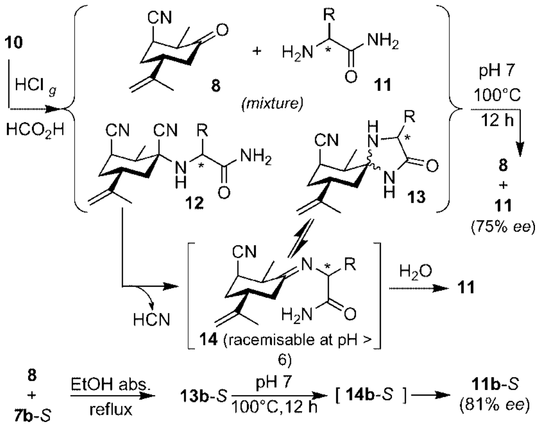
Table 1. Yields and optical purity of α-amino acids or derivatives and recovery of chiral ketonic auxiliary **8** under various conditions: *ee* measured by GC analysis of the (–)-menthyloxycarbonyl derivative of amino acids **2**[22] (entries 1–8 and 14–16 after HCl hydrolysis of **7**) or by polarimetry (entries 9–13). Experimental conditions are detailed in the text.

Entry	Substrate	R	Conditions	Product	AA	Yield (%)	*ee* (%)	Recovered **8** (%)
1	**10a**-*R*	Me	HCl 110 °C	**2a**-*R*	D-Ala	37	97.8	–
2	**10a**-*S*	Me	HCl 110 °C	**2a**-*S*	L-Ala	54	99.0	–
3	**10b**-*R*	*i*Pr	HCl 110 °C	**2b**-*R*	D-Val	23	98.2	–
4	**10b**-*S*	*i*Pr	HCl 110 °C	**2b**-*S*	L-Val	62	97.0	–
5	**10c**-*R*	*i*Bu	HCl 110 °C	**2c**-*R*	D-Leu	17	81.2	–
6	**10c**-*S*	*i*Bu	HCl 110 °C	**2c**-*S*	L-Leu	52	95.1	–
7	**10d**-*R*	Bn	HCl 110 °C	**2d**-*R*	D-Phe	41	96.4	–
8	**10d**-*S*	Bn	HCl 110 °C	**2d**-*S*	L-Phe	57	97.0	–
9	**10d**-*R*	Bn	HCl/HCO_2H	**11d**-*R*	(D-Phe)	78	77.3	–
10	**13b**-*S*	*i*Pr	H_2O 100 °C	**11b**-*S*	(L-Val)	71	81.0	–
11	**10b**-*R*	*i*Pr	H_2O_2/NH_3/HCl 50 °C[a]	**11b**-*R*	(D-Val)	50[b]	95.6[b]	37[c]
12	**10c**-*R*	*i*Bu	H_2O_2/NH_3/HCl 50 °C[a]	**11c**-*R*	(D-Leu)	72[b]	93.8[b]	75[c]
13	**10d**-*R*	Bn	H_2O_2/NH_3/HCl 50 °C[a]	**11d**-*R*	(D-Phe)	66[b]	93.2[b]	79[c]
14	**10b**-*R*	*i*Pr	$AgNO_3/HNO_3$	**7b**-*R*	(D-Val)	40	96.6	68
15	**10b**-*S*	*i*Pr	$AgNO_3/HNO_3$	**7b**-*S*	(L-Val)	61	96.6	75
16	**10d**-*R*	Bn	$AgNO_3/HNO_3$	**7d**-*R*	(D-Phe)	57	95.4	82

[a] Two steps. [b] Overall yields and *ee*. [c] Recovered after the second step.

amino acids **2a**–**d** with good optical purity (*ee* ≈ 98%) but with poor yields, especially for the -*R* series (entries 1–8 in Table 1), together with important degradation of the cyanodihydrocarvone moiety (Scheme 4).

Under softer acidic conditions, namely saturated hydrochloric acid in aqueous formic acid at room temperature,[16] **10** was converted into a mixture of monohydrated adduct **12**, imidazolidinone **13** and amino amide **11**. Heating this mixture at 100 °C for 12 h after neutralisation, enabled the hydrolysis of both intermediates **12** and **13**, affording the amino amide **11** with better yields than above (41–75% yield depending on R) but with partial racemisation (*ee* averaging 75%, entry 9 in Table 1), while the chiral ketone **8** was recovered in an average yield of 65%. The stability of **12** is mostly due to the weak basicity of the amine group (pK_a around 4), which prevents the elimination of HCN and thus the formation of the α-ketimino amide intermediate **14** (Scheme 5). Intermediate **13** results from the cyclisation of imine **14**.[17] The racemisation occurs during the late steps of the above process and mainly involves the imine **14** intermediate, as already reported by us for other cases.[18] Indeed, while the hydrolysis of L-valinonitrile (**7b**-*S*) with HCl/HCOOH affords L-valinamide (**11b**-*S*) without racemisation, the hydrolysis of enantiopure **13b**-*S* (prepared by condensing **8** with enantiopure **11b**-*S* in ethanol) in hot water (100 °C, 12 h) yields **11b**-*S* with only 81% *ee* (entry 10 in Table 1).



Scheme 5.

Hydrogen peroxide. We finally examined the reaction of **10** with hydrogen peroxide in methanol under moderately alkaline conditions (ammonia). The ability of the hydroperoxide anion HOO^- to convert nitriles into amides much faster than HO^- (discovered by Radziszewski[19]) had been already extended by us to α-aminonitriles.[20] Whereas **10** can be directly converted into amide **11** and chiral ketonic auxiliary **8** after sufficient reaction time (ca. 24 h at room temperature), this method turned out to be somewhat racemising and insufficiently selective. It appeared much more advantageous to limit the reaction to its first step, namely the regioselective hydration of the secondary nitrile group, to yield **12**, then decomposing **12** by another, non-racemising method. The regioselectivity of iminodinitrile **10** hydration is clearly determined by the blocked axial configuration of the tertiary nitrile on the cyclohexyl ring, where 1,3-diaxial steric hindrance limits the access of the nucleophile (either HOO^- or HO^-), as already observed in the hydration of 1-amino-4-*tert*-butylcyclohexane(β)carbonitrile mediated by HOO^-, which is ca. 2000 times slower than that of an acyclic aminonitrile (either secondary or tertiary).[20]

Optimisation. To find out optimal conditions for this reaction, a systematic study was carried out on **10b**-*R*. This showed the efficiency and selectivity of hydration mediated by HOO^- to be dependent on the pH, temperature and the $[H_2O_2]$/[**10b**-*R*] stoichiometric ratio. The reaction rate increases with pH; however, it varies very little above pH 12.5 (Figure 1), roughly following the concentration of HOO^- in the medium (the pK_a of H_2O_2 is 11.6 at 25 °C), thus confirming that HOO^- is the active species. Meanwhile, the selectivity was observed to decrease with increasing pH, so that the optimum was found at pH 12.5, where the rate constant of nitrile hydration with HOO^- is ca. 200 times higher than that involving HO^-.[20] At room temperature, increasing the H_2O_2 stoichiometry (and concentration) resulted in a faster reaction; however, the selectivity of the reaction was not improved with regard to the hydration product **12b**-*R*, whose yield never exceeded 30–35% at the end of the reaction (Figure 2, solid symbols), because of side reactions such as retro-Strecker decomposition and further degradation of the cyanodihydrocarvone moiety (especially above sixfold excess in H_2O_2). At lower temperature, the reaction was much more selective in favour of **12**, and the inverse trend was observed (Figure 2, open symbols): increasing the H_2O_2 stoichiometric ratio resulted in increased yields of **12b**-*R*, up to 90% within 10 h of reaction for a 40-fold stoichiometric excess. This temperature effect can be rationalised by comparing the activation energies of nitrile hydration induced by HOO^- (13 kcal mol^{-1}) with that of cyanide elimination (about 20 kcal mol^{-1}), the former reaction thus being favoured at lower temperature.[20]

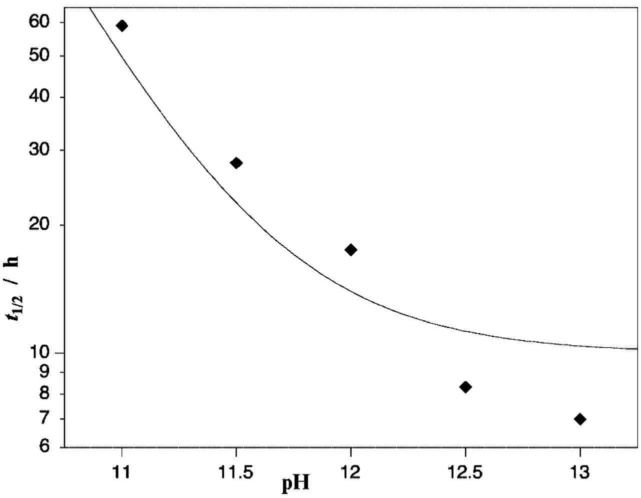


Figure 1. Hydration of **10b** with H_2O_2/NH_3 in methanol: pH dependence of reaction half time $t_{1/2}$ (log scale) at 25 °C (diamonds) for a stoichiometric ratio $[H_2O_2]/[\mathbf{10b}] = 2$ and comparison with the inverse of HOO^- concentration {curve, calculated from the equation $1/[HOO^-] = ([H^+] + K_a)/(K_a \times c)$ with arbitrary c and $pK_a(H_2O_2) = 11.6$ at 25 °C}.

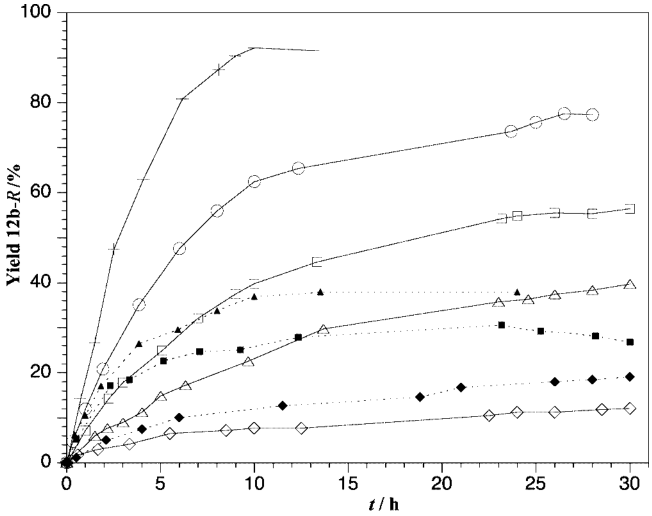
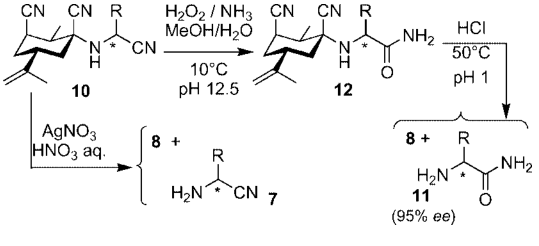


Figure 2. Hydration of **10b** with H_2O_2/NH_3 in methanol: yield of **12b** against time at pH 12.5 at 10 °C (open symbols connected by solid lines) and 25 °C (solid symbols connected by dashed lines) for various stoichiometric ratios $[H_2O_2]/[\mathbf{10b}]$: 2 (diamonds), 6 (triangles), 10 (squares), 20 (circles), 40 (crosses). The data points in the same series are connected for clarity.

In summary, optimised conditions are pH 12.5, 10 °C, $[H_2O_2]/[\mathbf{10b}\text{-}R] = 40$ and a reaction time of ca. 10–15 h. No racemisation occurred at the secondary moiety (only the expected stereoisomer **12b**-*R* was observed by NMR). The above conditions were then successfully applied to compounds **10c–d**-*R*, affording **12c–d**-*R* respectively in *ca.* 90% yield, also without observable epimerisation.

***Cleavage of intermediates* 12b–d.** The subsequent retro-Strecker decomposition of **12** into α-amino amide **11** and ketone **8** was then achieved by classical, straightforward acidic hydrolysis in HCl at pH 1 and 50 °C, without significant racemisation (Scheme 6 and entries 11–13 in Table 1). Iminodinitriles **12b–d**-*R* thus led to comparable overall yields in α-amino amides **11b–d**-*R*, respectively (with *ee* around 95% in the studied cases where R = *i*Pr, *i*Bu, Bn) and cyanodihydrocarvone **8**.



Scheme 6.

Ag$^+$ treatment. Alternately, we showed that the treatment of iminodinitrile **10** with silver nitrate in nitric acid (Scheme 6), leads to the α-aminonitrile **7** through regioselective decomposition of the tertiary moiety with good yield and *ee* (measured after hydrolysis of **7** into amino acid **2**) and with acceptable recovery of the chiral auxiliary **8** (entries 14–16 in Table 1). While acidic conditions prevent the racemisation of the intermediates, the presence of Ag^+ cations (known to catalyse the elimination of HCN) just favours the natural trend of tertiary aminonitriles to decompose faster than secondary ones, thus providing an original asymmetric synthetic route to α-aminonitriles **7**. It is worth mentioning that the asymmetric synthesis of *N*-unsubstituted α-aminonitriles is otherwise quite difficult, usually requiring the dehydration of the *N*-protected α-amino amide, e.g. with the method by Kawashiro starting from *N*-(*o*-nitrophenylsulfoxy)-α-amino amides.[21]

Conclusions

This exploratory work demonstrates the feasibility of the enantioselective synthesis of unprotected α-amino amides and acids from aldehydes through a Strecker reaction, with use of a chiral ketonic auxiliary that is recycled, by improving the selective hydrolysis of the dissymmetric iminodinitrile intermediate **10**. This was achieved through regioselective hydration followed by cleavage of a dissymmetric iminodinitrile under non-racemising conditions. The regioselective hydration of a secondary nitrile is achieved with hydrogen peroxide in aqueous ammonia, while the subsequent cleavage of the resulting *N*-protected α-amino amide is achieved in dilute hydrochloric acid. An alternative, also non-racemising route involving silver nitrate in aqueous nitric acid directly converts the iminodinitrile **10** into an *N*-unprotected α-aminonitrile **7**, thus representing an original, enantioselective synthesis of the latter. In both routes, overall yields and *ee* from iminodinitrile **10** are quite good, as well as the yield of the recovered chiral auxiliary **8**.

Another good asset of the iminodinitrile strategy outlined in this paper is its ability to use alkyl aldehydes as substrates, thus involving alkylimines as intermediates; the latter were otherwise known to give rise to serious problems when used in classical Strecker reactions. Our next goal is now the investigation of more efficient chiral ketonic auxiliaries in order to improve the diastereoselectivity of dissymmetric iminodinitrile **10** formation through the Strecker reaction. This new perspective in asymmetric Strecker synthesis that uses small auxiliaries bearing only few stereogenic centres opens new potential routes for the asymmetric synthesis of aminophosphinic acids and for the Ugi reaction.

Experimental Section

^{1}H NMR spectra were recorded with a Bruker AC250 (250 MHz) or a Varian EM360 (60 MHz) spectrometer. Chemical shifts are expressed in parts per million downfield from TMS, which is used as an internal standard. ^{13}C NMR spectra were recorded with a Bruker AM300 spectrometer (75 MHz) using broadband decoupling. Chemical shifts are expressed in parts per million downfield from TMS, using the middle resonance of $CDCl_3$ (δ =77 ppm) as an internal standard. Infrared spectra were recorded with a Perkin–Elmer 1420 spectrophotometer. Mass spectra were obtained with a Jeol JMS D100 spectrometer. Elemental analyses were performed with a Perkin–Elmer 2400 CHN recorder. Optical rotations were measured at 589 nm (Na) with a Perkin–Elmer 241 polarimeter. Melting points (uncorrected) were measured with a Totoli instrument. HPLC separations were performed with a Varian system equipped with a UV detector (Varian 2550), a pump (Varian 2510), a Shimadzu C-R6A Chromatopac integrator and a Kromasil C18 column (25 cm, 5 μm). GC analyses were recorded with a Dani 3900 system equipped with a silica capillary column OV1701 (30 m, 0.25-mm i.d., 0.25-μm stationary phase) and a Shimadzu C-R6A Chromatopac integrator. TLC was performed with silica 60 F254 (Merck) plates and revealed with iodine and/or ninhydrin. pH measurements were performed with a Metrohm Titrino SM 702 pH-meter/pH-stat.

(–)-(1*R*,2*R*,5*R*)-2-Methyl-5-(1-methylethenyl)-3-oxocyclohexane carbonitrile (**8**) and iminodinitriles **10a–d** (both -*R* and -*S*) were prepared according to our previously described procedures.[11a]

Hydrolysis of Iminodinitriles 10a–d into Amino Acids 2a–d with Hot HCl (Entries 1–8 in Table 1)

A solution of iminodinitrile **10a**, **10b**, **10c** or **10d** (-*R* or -*S*) (10 mg) in hydrochloric acid (1 mL, 6 N) was heated in a sealed tube at 110 °C for 12 h. After being cooled to room temperature, the tube was opened, and the reaction mixture was washed with chloroform (3 × 2 mL). After removal of the solvent in vacuo, the residue was dissolved in HCl (1 mL, 0.1 N).

Determination of *ee*:[22] An aliquot of the above solution (50 μL) was mixed in a vial tube with a pyridine/methanol mixture (40 μL, 20:80 v/v) and (–)-menthyl chloroformate (10 μL), stirred for 20 min, and then extracted with chloroform (100 μL). Aliquots of the lower (chloroform) layer (2 μL) were then analysed by gas chromatography.

Hydration of Iminodinitrile 10d-*R* into Amino Amide 11d-*R* with HCl/HCO_2H: Gaseous HCl was bubbled through a stirred solution of iminodinitrile **10d**-*R* (1 g, 3 mmol) in formic acid (15 mL) for 18 h. Water (100 mL) was then added to the mixture, which was further stirred for 24 h at room temperature. After removal of both formic and hydrochloric acids in vacuo, chloroform was added, and the resulting solution was bubbled with ammonia. Precipitated salts were filtered off, and chloroform was removed in vacuo. The residue was dissolved in water, and the pH was adjusted to 7 with KOH. The solution was then heated under reflux for 12 h to complete the hydrolysis of the intermediates. After acidification, the resulting solution was washed with dichloromethane to recover ketone **8**. The pH of the aqueous layer was adjusted to 11, the solution was saturated with sodium chloride and extracted with dichloromethane. Bubbling gaseous HCl through the organic layer caused the α-amino amide **11d**-*R* (D-phenylalanylamide) to precipitate as the hydrochloride salt. Yield: 78%. Enantiomeric excess: 77.3% (based on $[\alpha]_D$ = –34.8, *c* 0.5, MeOH).

Hydration of L-2-Amino-3-methylbutanenitrile (7b-*S*) with HCl/HCO_2H: Gaseous HCl was bubbled through a stirred solution of L-valinonitrile (**7b**-*S*) (0.5 g, 3.27 mmol) in formic acid (15 mL) for 4 h. The reaction medium was treated with water (100 mL) to remove residual HCl by steam stripping in vacuo. After drying, L-valinamide hydrochloride (**11b**-*S*·HCl) was obtained with an optical purity of 100% ($[\alpha]_D$ = –34.8, *c* 0.5, MeOH).

Synthesis of Compound 13b-*S*: L-Valinamide (**11b**-*S*) (1.5 g, 12.4 mmol) and **8** (2.2 g, 13 mmol) were dissolved in absolute ethanol (40 mL) and heated under reflux for 5 d. The solvent was then evaporated in vacuo, and the residue was dissolved in hydrochloric acid (10 mL, 1 N). The aqueous phase was extracted with dichloromethane. Organic layers were joined, dried with Na_2SO_4, and the solvent was removed in vacuo to give the crude product, which was purified by column chromatography (Silica, ethyl acetate) to afford **13b**-*S*. Yield: 0.4 g, 11%. IR ($CHCl_3$): 3410 (NH), 3080 (CH_2=CH), 2240 (CN), 1700 (C=O) cm^{-1}. ^{1}H NMR (60 MHz, $CDCl_3$, 25 °C, TMS): δ = 4.8 (s, 2 H, CH_2), 3.6 (d, 1 H, *HC*-*i*Pr), 1.8 (s, 3 H, CH_3), 1.4 (t, 6 H, *i*Pr), 1.1 (d, 3 H, CH_3) ppm.

Hydrolysis of Imidazolidin-4-one 13b-*S* in Neutral Aqueous Medium: A solution of **13b**-*S* (0.4 g, 1.45 mmol) in water (30 mL) was heated under reflux for 36 h. Ketone **8** was recovered after extraction with diethyl ether. After removal of the solvent in vacuo, CH_2Cl_2 (30 mL) was added to the crude product and HCl was bubbled through it. L-Valinamide hydrochloride (**11b**-*S*·HCl) was obtained with an optical purity of 81% based on $[\alpha]_D$ = 34.8, (*c* 0.5, MeOH).

Hydration of Iminodinitriles 10b–d-*R* into 12b–d-*R* with Hydrogen Peroxide

Compound **10b**-*R* (227 mg, 0.8 mmol) was suspended in MeOH (30 mL) in a magnetically stirred, thermostatted (10 or 25 °C) reactor. After complete dissolution of **10b**-*R*, the pH was adjusted to the desired value by addition of aqueous NH_3 (32% w/w); the pH was then maintained at the same value along the reaction, by further NH_3 addition controlled by means of a pH-stat. Aqueous hydrogen peroxide (33% w/w and 2, 6, 10, 20 or 40 equiv. with respect to **10b**-*R*) was then added to the medium (time $t = 0$). The reaction kinetics was monitored by HPLC analysis of 0.1-mL aliquots diluted in HPLC eluent (1 mL): MeOH/KH_2PO_4 buffer (0.05 M, pH 6) 55:45.

Optimised Conditions: Iminodinitrile **10** in methanol (0.8 mmol, 16 mL, 0.05 mol L^{-1}), reaction temperature 10 °C, pH 12.5 (pH-stat controlled by addition of aqueous NH_3 32% w/w), aqueous hydrogen peroxide (1.5 mL, 33% w/w, 40 equiv.). After completion of the reaction (consumption of compound **10** monitored by TLC, eluent $CHCl_3$/acetone, 97:3), the solvent was removed in vacuo to afford **12** as white crystals in 90% yield.

Compound 12b-*R*: M.p. = 179 °C. IR ($CHCCl_3$): 3305–3380 (NH), 3080 (CH_2=CH), 2240 (CN), 1680 (C=O), 1645 (C=C) cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 1.04 (dd, $^3J_{HH}$ = 6.9 Hz, $^4J_{HH}$ = 2.7 Hz, 6 H, *i*Pr), 1.35 (t, $^3J_{HH}$ = 12.9 Hz, 1 H, 6-H$_{ax}$), 1.48 [d, $^3J_{HH}$ = 6.8 Hz, 3 H, $(CH_3)_a$], 1.55 (m, 1 H, 4-H$_{ax}$), 1.74 (s, 3 H, CH_3), 1.82 (m, 1 H, 2-H$_{ax}$), 2.13 (m, 1 H, β-H), 2.22 (m, 1 H, 6-H$_{eq}$), 2.54 (m, 1 H, 5-H$_{ax}$), 3.12 (m, 1 H, 3-H$_{eq}$), 3.24 (t, $^3J_{HH}$ = 4.6 Hz, 1 H, α-H), 4.77 (d, $^2J_{HH}$ = 24 Hz, 2 H, CH_2), 6.1 (s, 1 H, CONH-H), 6.35 (s, 1 H, CONH-H) ppm. $[a]_D$ = +12.4 (*c* 0.5, MeOH). $C_{17}H_{26}N_4O$ (302): calcd. C 67.55, H 8.61, N 18.54; found C 67.45, H 8.80, N 18.23.

Compound 12c-*R*: M.p. = 144 °C. IR ($CHCCl_3$): 3305–3380 (NH), 3080 (CH_2=CH), 2240 (CN), 1680 (C=O), 1645 (C=C) cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 1.0 (dd, $^3J_{HH}$ = 6.8 Hz, $^4J_{HH}$ = 2.5 Hz, 6 H, *i*Pr), 1.4 [d, $^3J_{HH}$ = 13.1 Hz, 3 H, $(CH_3)_a$], 1.7 [s, 3 H, $(CH_3)_b$], 2.20–2.57 (m, 9 H, H$_{cyclic}$, β-γ-H), 3.1 (m, 1 H, 3-H$_{eq}$), 3.45 (m, 1 H, α-H), 4.75 [d, 2 H, $(CH_2)_c$], 5.8 (s, 1 H, CONH-H), 6.5 (s, 1 H, CONH-H) ppm. $[a]_D$ = +11.7 (*c* 0.5, MeOH).

Compound 12d-*R*: M.p. = 145 °C. IR ($CHCCl_3$): 3305–3380 (NH), 3080 (CH_2=CH), 2240 (CN), 1680 (C=O), 1645 (C=C) cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 1.07 [d, 3 H, $(CH_3)_a$], 1.31 (t, $^3J_{HH}$ = 12.9 Hz, 1 H, 6-H$_{ax}$), 1.45 (m, 1 H, 4-H$_{ax}$), 1.72 [s, 4 H, $(CH_3)_a$, H$_{ax}$], 2.17 (m, 3 H, NH, 4-H$_{eq}$, 6-H$_{eq}$), 2.95 (q, 1 H, CH-H), 3.05 (m, 1 H, 3-H$_{eq}$), 3.30 (m, 1 H, CH-H), 3.70 (t, 1 H, α-H), 4.75 [d, 2 H, $^3J_{HH}$ = 26.5 Hz $(CH_2)_c$], 6.01 (s, 1 H, CONH-H), 6.65 (s, 1 H, CONH-H), 7.30 (m, 5 H, C_6H_5) ppm. $[a]_D$ = –17.7 (*c* 0.5, $CHCl_3$).

Hydrolysis of Compounds 12b–d-*R* (Entries 11–13 in Table 1)

Compound **12** (1 mmol) was dissolved in a mixture of methanol (25 mL) and water (25 mL). The pH was adjusted to 1 by addition of HCl (6 N), and then the solution was heated to 50 °C for 4 h. After completion of the reaction (monitored by TLC with chloroform/acetone 97:3), the solvent was removed in vacuo. The resulting aqueous phase was washed with diethyl ether (3 × 10 mL) to recover the chiral ketonic auxiliary **8**. Evaporation of the aqueous layer in vacuo afforded α-amino amide **11**-*R* as the hydrochloride salt (*ee* measured by polarimetry).

D-Valinamide (11b-*R*): $[a]_D$ = –33.3 (*c* 0.5, MeOH). ^{1}H NMR (60 MHz, CD_3OD, 25 °C): δ = 1.1 (d, 6 H, *i*Pr), 2.2 (m, 1 H, β-H), 3.8 (d, 1 H, α-H), 2.2 (m, 1 H, β-H), 3.8 (d, 1 H, α-H), 7.5–8.0 (s, 2 H, $CONH_2$) ppm (identical to literature data).

D-Leucinamide (11c-*R*): $[a]_D$ = –11.0 (*c* 0.5, MeOH). ^{1}H NMR (60 MHz, CD_3OD, 25 °C): δ = 1.15 (d, 6 H, δ-H), 1.8 (m, 3 H, β-γ-H), 4.0 (t, 1 H, α-H), 7.5–8 (s, 2 H, $CONH_2$) ppm (identical to literature data).

D-Phenylalaninamide (11d-*R*): $[a]_D$ = –20.7 (*c* 0.5, MeOH). ^{1}H NMR (60 MHz, CD_3OD, 25 °C): δ = 3.2 (m, 2 H, β-H), 4.2 (m, 1 H, α-H), 7.4 (br., 5 H, C_6H_5), 7.5–8.0 (s, 2 H, $CONH_2$) ppm (identical to literature data).

Decomposition of Iminodinitriles 10 (10b-*R*, 10b-*S*, 10d-*R*) with $AgNO_3/HNO_3$ (Entries 14–16 in Table 1)

A solution of iminodinitrile **10** (1 mmol) in methanol was added to aqueous $AgNO_3$ (2 mmol, 20 mL, 0.1 N) adjusted to pH 1 by addition of HNO_3 (63% w/w). This solution was heated at 50 °C for 8 h (completion monitored by TLC, eluent chloroform/acetone 97:3). Insoluble silver cyanide salts were filtered off, and then methanol was removed in vacuo. The resulting aqueous solution was washed with diethyl ether (2 × 20 mL) to recover the chiral ketone **8**. The aqueous layer was then neutralised to pH 7 by addition of NaOH (4 N) and extracted with dichloromethane (4 × 10 mL). The combined organic layers were dried with Na_2SO_4, and the solvent was removed in vacuo to obtain the α-aminonitrile **7**. The *ee* was measured as described above by GC analysis of (–)-menthyloxycarbonyl derivatives after hydrolysis of **7** with HCl (6 N) at 110 °C.

2-Amino-3-methylbutanenitrile (D/L-Valinonitrile) (7b-*R* and 7b-*S*): ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 1.04 (d, $^3J_{HH}$ = 6.7 Hz, 6 H, *i*Pr), 1.56 (s, 2 H, NH_2), 1.90 (m, 1 H, β-H), 3.49 (d, $^3J_{HH}$ = 5.7 Hz, 1 H, α-H) ppm. ^{1}H NMR (250 MHz, CD_3OD, 25 °C): δ = 1.15 [d, $^3J_{HH}$ = 8 Hz, 6 H, (γ-Me)$_2$], 2.28 (m, 1 H, β-H), 4.45 (d, $^3J_{HH}$ = 5.7 Hz, 1 H, α-H) ppm.

2-Amino-3-phenylpropanenitrile (D-Phenylalaninonitrile) (7d-*R*): ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.60 (s, 2 H, NH_2), 3.00 (d, $^3J_{HH}$ = 13.8 Hz, 2 H, CH_2), 3.90 (t, $^3J_{HH}$ = 7.1 Hz, 1 H, α-H), 7.30 (m, 5 H, C_6H_5) ppm. ^{1}H NMR 250 MHz (CD_3OD): δ = 3.20 (d, $^3J_{HH}$ = 13.8 Hz, 2 H, CH_2), 4.70 (t, $^3J_{HH}$ = 7.1 Hz 1 H, α-H), 7.40 (m, 5 H, C_6H_5).

Acknowledgments

We are grateful to the French Ministry of Education and Research for a grant to one of us (M. M.).

[1] K. Harada, *Nature* **1963**, *200*, 1201.
[2] A. Strecker, *Justus Liebigs Ann. Chem.* **1850**, *75*, 27–45.
[3] a) H. Kunz, W. Sager, *Angew. Chem. Int. Engl.* **1987**, *26*, 557–559; b) H. Kunz, W. Sager, W. Pfrengle, D. Schanzenbach, *Tetrahedron Lett.* **1988**, *29*, 4397–4400; c) H. Kunz, W. Sager, D. Schanzenbach, M. Decker, *Liebigs Ann. Chem.* **1991**, 649–654.
[4] F. A. Davis, P. S. Portonovo, R. E. Reddy, Y. Chiu, *J. Org. Chem.* **1996**, *61*, 440–441.
[5] T. Shiori, S. Harusawa, Y. Hamada, *Tetrahedron Lett.* **1979**, *20*, 4663–4666.
[6] H. Acherki, C. Alvarez-Ibarra, A. De-Dios, M. Quiroga, *Tetrahedron* **2002**, *58*, 3217–3327.
[7] R. O. Duthaler, *Tetrahedron* **1994**, *50*, 1539–1650.
[8] H. Gröger, *Chem. Rev.* **2003**, *103*, 2795–2827.
[9] M. Béjaud, L. Mion, A. Commeyras, *Tetrahedron Lett.* **1975**, *16*, 2985–2986.
[10] R. Pascal, J. Taillades, A. Commeyras, *Tetrahedron* **1978**, *34*, 2275–2280.
[11] a) C. Bousquet, Z. Tadros, J. Tonnel, L. Mion, J. Taillades, *Bull. Soc. Chim. Fr.* **1993**, *130*, 513–520; b) J. Taillades, M. Marull, J. C. Rossi, unpublished results.
[12] A. Commeyras, J. Taillades, J. Brugidou, R. Sola, A. Previero, R. Pascal, M. Laspéras, A. Rousset, U. S. patent 4.851576, **1983**.
[13] V. P. Kukhar, H. R. Hudson, *Aminophosphonic and Aminophosphinic Acids*, Wiley, **2000**.
[14] A. Commeyras, J. Taillades, L. Mion, R. Pascal, M. Lasperas, A. Rousset A *U. S. patent*, 4.2423814, **1981**.
[15] R. Sudo, S. Ichihara, *Bull. Chem. Soc. Jpn.* **1963**, *36*, 34–37.

[16] F. Becke, H. Fleig, P. Pässler, *Justus Liebigs Ann. Chem.* **1971**, *749*, 198–201.

[17] a) Y. Ariyoshi, N. Sato, *Bull. Chem. Soc. Jpn.* **1972**, *45*, 2015–2018; b) A. Tsujita, T. Yamana, *Chem. Pharm. Bull.* **1974**, *22*, 2434–2443; c) U. Zehavi, D. Ben-Ishai, *J. Org. Chem.* **1961**, *26*, 1097–1101.

[18] a) P. M. Hardy, D. J. Samworth, *J. Chem. Soc., Perkin Trans. 1* **1977**, 1954–1960; b) R. Polt, D. Seebach, *Helv. Chim. Acta* **1987**, *70*, 1930–1936.

[19] B. Radziszewski, *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 1289.

[20] a) J. C. Rossi, L. Garrel, J. Taillades, A. Commeyras, *C. R. Acad. Sci., Ser. II* **1996**, *322(IIb)*, 767–773; b) J. Taillades, J. C. Rossi, L. Garrel, M. Marull, A. Commeyras, *Bull. Soc. Chim. Fr.* **1996**, *133*, 89–100.

[21] K. Kawashiro, H. Yoshida, S. Moritomo, *Chem. Lett.* **1976**, *5*, 417–418.

[22] N. Domergue, M. Pugnière, A. Previero, *Anal. Biochem.* **1993**, *214*, 420–425.

Received: April 4, 2006