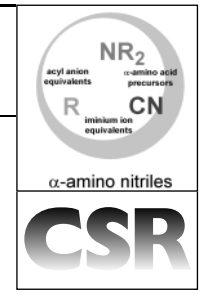
Some recent applications of α-amino nitrile chemistry



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Bifunctional α-amino nitriles are not only versatile intermediates in organic synthesis but also exhibit a valuable dual reactivity, which has been utilized in a broad range of synthetic applications. This review highlights recent developments in the chemistry of α-amino nitriles, including asymmetric synthesis of α-amino acids *via* Strecker reactions using chiral auxiliaries and catalysts, α-amino nitriles as masked iminium ion equivalents in cationic reactions and the synthesis of natural products and heterocycles, and α-metallation to provide nucleophilic acyl anion equivalents and applications to asymmetric *Umpolung* reactions.

1 Introduction

α-Amino nitriles have occupied an important, although often understated, position in organic chemistry ever since Strecker's original report in 1850 on the three component reaction, now bearing his name, between aldehydes, ammonia and hydrogen cyanide.[1] These bifunctional compounds have subsequently been shown to be versatile intermediates in a number of synthetic applications. The various modes of reactivity of α-amino nitriles are summarized in Scheme 1.[2]

One mode of reactivity involves functional group interconversions of the nitrile group in which the original carbon atom connectivity is preserved. In historical terms, the hydrolysis of the nitrile group in order to generate α-amino acids **A**, is perhaps the most important use of α-amino nitriles. Strecker synthesis and subsequent nitrile hydrolysis is indeed a very convenient method for accessing non-proteinogenic α-amino acids. It is also possible to reduce the nitrile group using lithium aluminium hydride as a convenient method of preparing 1,2-diamines **B**.

A second extremely valuable use of α-amino nitriles is as stable precursors to iminium ions, whereby loss of cyanide anion under a variety of conditions (*e.g.* use of silver salts, copper salts, Brønsted or Lewis acids and by thermolysis) generates an intermediate iminium species **C** which in turn may be trapped with nucleophilic reagents. In this way, the cyano group can be substituted by a hydrogen atom using a borohydride reagent or by a carbon chain using an organometallic reagent as in the Bruylants reaction or another carbon nucleophile to provide variously substituted amines **D** and **E** respectively. It is also possible that the intermediate iminium ion can further tautomerize to the corresponding enamine **F** or undergo hydrolysis to reveal the corresponding carbonyl compound **G**.

A third mode of reactivity is complementary to that of the second in that it is formally a reversal in polarity (*Umpolung*) at the α-carbon. When the α-amino nitrile bears an α-hydrogen (R^2 = H) it is possible to deprotonate at this position using strong bases. The carbanion **H** generated is capable of nucleophilic attack on a number of differing classes of electrophiles. This provides a new α-amino nitrile compound **I** which may in turn undergo any of the aforementioned transformations. For instance, hydrolysis of the resulting α-amino nitrile to the corresponding carbonyl compound **J** is overall a nucleophilic acylation, with the metallated α-amino nitrile acting as a masked acyl anion equivalent, (*cf.* metallated dithianes, cyano-ethers, benzotriazole-ethers *etc.*). Alternatively, subsequent replacement of the cyano group by hydrogen or a carbon-based group provides substituted amines.

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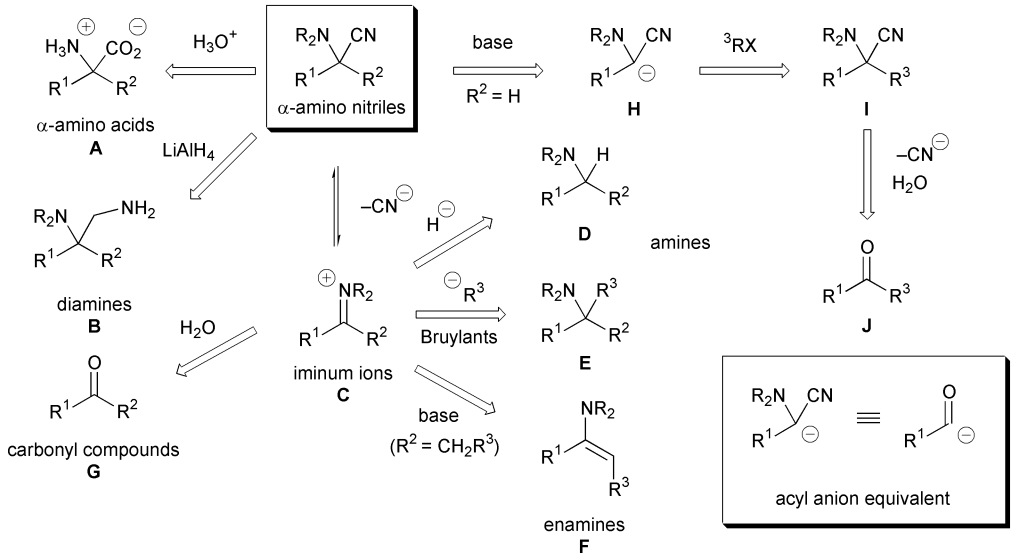
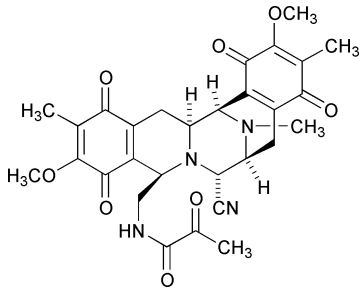


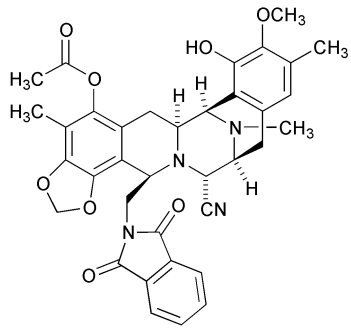
Scheme 1 The various modes of α-amino nitrile reactivity.

Eschenmoser has also proposed and discussed simple α-amino nitriles as being prebiotic precursors to porphyrins, corrins, nicotinic acids and nucleic acids.[3]

Additionally, the α-amino nitrile moiety has been found to occur in saframycin A, a natural product with anti-tumour activity, and phthalascidin, a synthetic analogue, exhibits even greater potency.[4]



Saframycin A

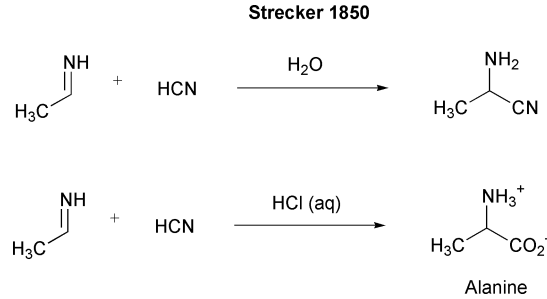


Phthalascidin

It is our aim in this review to highlight some of the recent developments connected with the three modes of reactivity of α-amino nitriles outlined above. In particular, (*i*) examples of the advances in the asymmetric Strecker reaction using chiral auxiliaries and catalysts, (*ii*) the application of α-amino nitriles as iminium ion precursors to the synthesis of natural products and heterocyclic compounds, and (*iii*) chiral metallated α-amino nitriles in asymmetric nucleophilic acylation reactions.

2 Asymmetric Strecker reactions

A report by Strecker[1] in 1850 on his investigations into the chemical synthesis of lactic acid contains the description of an experiment in which he combined acetaldehyde–ammonia imine with hydrogen cyanide to afford the corresponding α-amino nitrile (Scheme 2). In a subsequent experiment, this time



Scheme 2 The classical Strecker reaction.

in the presence of aqueous hydrochloric acid, he described the formation of a different compound by *in situ* hydrolysis of the nitrile—"*Eine ganz andere Verbindung entsteht beim Zusammenbringen von Aldehyd–Ammoniak und Blausäure bei Gegenwart von Säuren*"—"A completely different compound was formed upon the bringing together of the aldehyde–ammonia adduct and hydrocyanic acid in the presence of acids." This compound he named *Alanin* in the German and in addition to his chemical analysis of the new compound, characterized it physically thus—"*Die größeren Krystalle des Alanins sind perlmutterglänzend, hart, und knirschen zwischen den Zähnen*".—"The larger crystals of alanine are mother-of-pearl-shiny, hard and crunch between the teeth." This represented the first and, to this day, the simplest method for the chemical synthesis of α-amino acids.

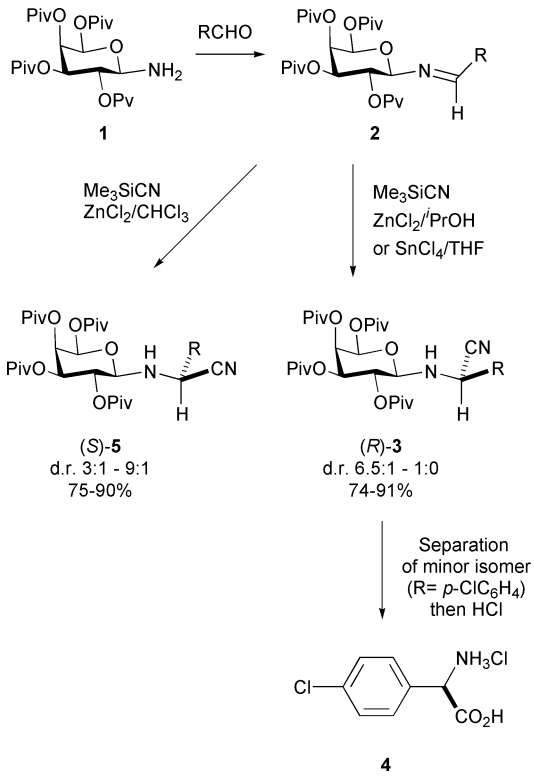
The simplicity of this strategy has obvious advantages for accessing unusual α-amino acids, and in the past few decades, a great deal of effort has been devoted towards developing asymmetric variants of the Strecker reaction, *i.e.* addition of cyanide anion to imines, with the goal of enantioselective synthesis of α-amino acids. We shall now highlight some methods developed for the asymmetric Strecker reaction using chiral auxiliary and chiral catalyst based approaches.

2.1 Chiral auxiliary based methods

Asymmetric Strecker reactions employing chiral amine auxiliaries have been extensively reviewed in the past.[5] We therefore wish to focus on two such methods developed by Kunz and Weinges.

The asymmetric Strecker reaction described by Kunz involves the use of the β-1-amino-tetra-*O*-pivaloyl-D-galactose

auxiliary **1** as a chiral ammonia equivalent (Scheme 3).[6] Addition of the requisite aldehyde affords the imine derivative **2** that has been proposed to adopt an (*E*)-geometry. The cyanide



Scheme 3 Kunz's asymmetric Strecker reaction.

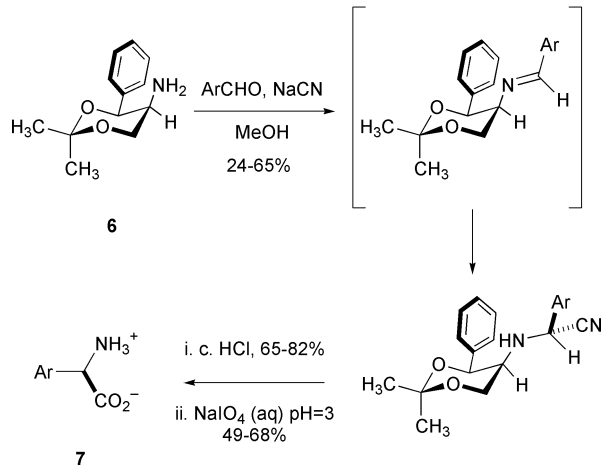
anion addition is carried out by treatment of the imine with trimethylsilyl cyanide and a Lewis acid such as zinc chloride or tin tetrachloride in THF or *i*-PrOH to generate the (*R*)-α-amino nitriles **3** as the major products. The observed diastereoselectivity is therefore a result of attack of cyanide from the face of the (*E*)-imine opposite to the sterically demanding 2-*O*-pivaloyl group. Separation of the minor diastereoisomer and subsequent hydrolysis with hydrochloric acid affords the corresponding enantiomerically pure α-amino acid **4** (R = *p*-ClC_6H_4).

Interestingly, a reversal of diastereoselectivity was observed on performing the reaction in chloroform. This allowed access to the (*S*)-α-amino nitrile products **5** and the corresponding α-amino acids.

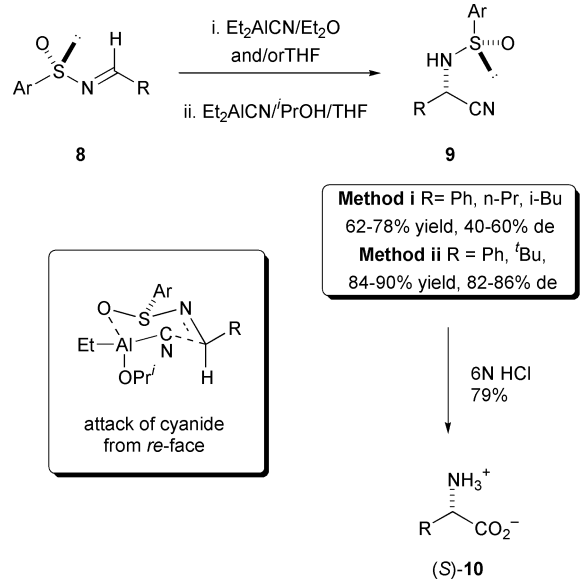
The asymmetric Strecker synthesis has also been studied in some detail by Weinges using (4*S*,5*S*)-5-amino-2,2-dimethyl-4-phenyl-1,3-dioxane **6** as chiral ammonia equivalent, and this version of the reaction has also been employed in the asymmetric synthesis of α,α-disubstituted-α-amino acids. A more recent example of this methodology has involved the improved oxidative cleavage of the auxiliary with periodate to generate arylglycine derivatives **7** (Scheme 4).[7]

Davis has employed enantiomerically pure sulfinimines as chiral ammonia imine equivalents in a wide variety of asymmetric transformations,[8] one of these being an asymmetric version of the Strecker reaction (Scheme 5).[9]

It was found that diethylaluminium cyanide was the only cyanide source reactive enough to undergo addition to the sulfinimine functional group, since complexation by aluminium at the sulfinyl oxygen activates the imine towards subsequent nucleophilic addition. Initially, the diethylaluminium cyanide addition revealed that the reaction with phenyl or aliphatic (S_S)-sulfinimines **8** in THF and/or diethyl ether at −78 °C and warming to between −40 and 0 °C afforded the (S_SS)-α-amino nitrile intermediates **9** in 40–60% de. After purification of the major diastereoisomers, treatment with 6 N hydrochloric acid



Scheme 4 Weinges' asymmetric Strecker reaction.



Scheme 5 Davis' asymmetric Strecker reaction.

effected both the removal of the *N*-sulfinyl auxiliary and the hydrolysis of the nitrile group to afford the corresponding (*S*)-α-amino acids **10** (> 95% ee).

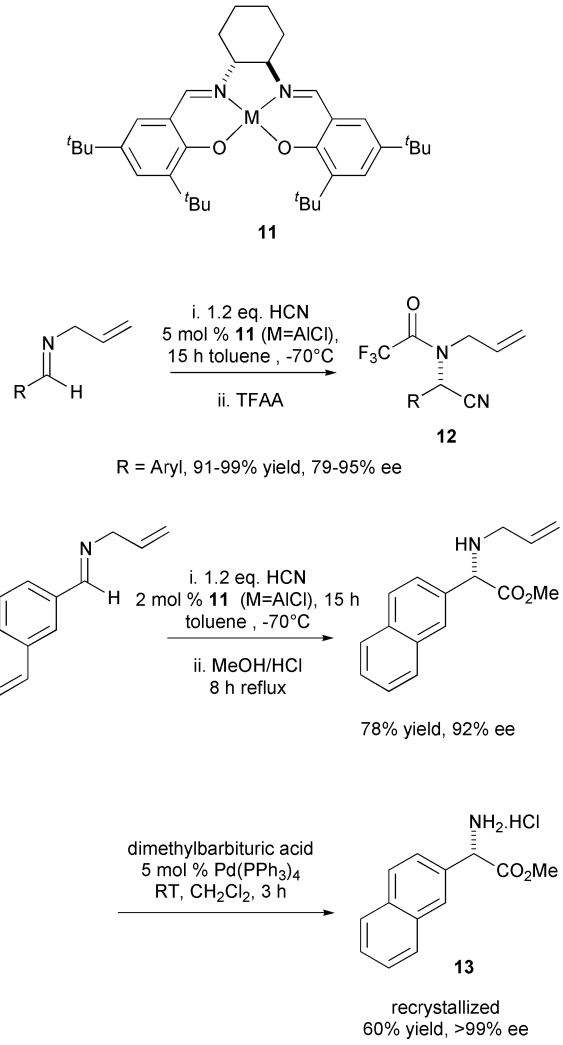
It was subsequently observed that upon the addition of 2-propanol to diethylaluminium cyanide, the diastereoselectivity of the reaction could be markedly improved to 82–86% de. The addition of 2-propanol effects the formation of the corresponding ethylaluminium cyanide alkoxide which has been suggested to have lower Lewis acidity and reactivity, hence rendering it the more selective reagent.

The stereochemical outcome of the addition has been suggested to arise from the co-ordination of the aluminium to the sulfinyl oxygen, and cyanide is delivered to the sulfinimine in a cyclic six-membered transition state with the *S*-aryl group and the imine substituent occupying an equatorial position. From this model, cyanide approaches (S_S)-sulfinimines from the *re*-face. Deterioration in diastereoselectivity may therefore be due to cyanide delivery from an additionally co-ordinated ethylaluminium cyanide species occupying the *si*-face of the sulfinimine.

2.2 Catalytic asymmetric Strecker reactions

2.2.1 Metal complexes. It has been demonstrated that many processes are catalyzed using chiral Schiff-base (salen)–metal complexes with excellent levels of asymmetric induction.

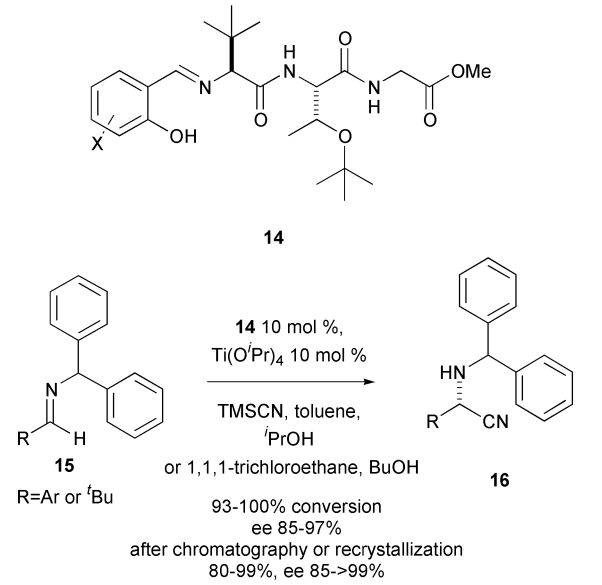
Recently Jacobsen reported an enantioselective catalytic version of the Strecker reaction using such complexes (Scheme 6).[10] Based on complexes of type **11**, a series of metals were



Scheme 6 Jacobsen's catalytic asymmetric Strecker reaction.

screened for their ability to catalyze the asymmetric addition of TMS-cyanide to *N*-allyl benzaldimines in toluene, with subsequent conversion into the corresponding trifluoroacetamide. The best result was observed for the aluminium complex **11** (M = AlCl), which catalyzed the complete conversion, with the α-amido nitrile derivative being obtained in 45% ee at 5 mol% catalyst loading. Upon changing the cyanide source to hydrogen cyanide and performing the reaction at −70 °C, complex **11** (M = AlCl) was found to catalyze the reaction with aromatic aldimines to afford the α-amido nitrile derivatives **12** in high yields (91–99%) and enantiomeric excesses (79–95%). The reaction with alkyl substrates was less successful, with the best result for the *N*-benzyl pivaldimine being 49% ee (97.5% after recrystallization). This provides a route for accessing enantiomerically enriched amino nitriles with low catalyst loadings, as precursors for optically active (*S*)-α-amino acids, and this was demonstrated by the synthesis of naphthyl amino acid **13**.

Another example of a chiral Schiff-base metal complex catalyzed asymmetric Strecker reaction has recently been disclosed by Snapper and Hoveyda, (Scheme 7).[11] They discovered that metal isopropoxide complexes of the tripeptide Schiff-base **14**, promoted TMS-cyanide additions to imines. The optimal reaction conditions were found upon using the titanium complex in toluene containing *iso*-propanol with benzhydryl imines **15** to afford the corresponding amino nitriles **16** in high yields (80–99%) and enantiomeric purities (ee 85–> 99%).



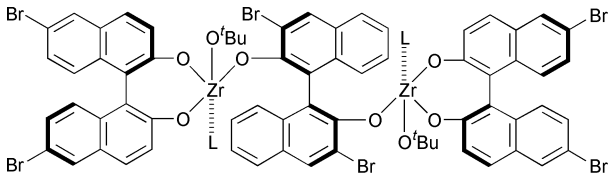
Scheme 7 Hoveyda and Snapper's catalytic asymmetric Strecker reaction.

Kobayashi has shown that several reactions involving imines (Mannich and aza-Diels-Alder reactions) may be carried out asymmetrically in the presence of activating chiral zirconium complex catalysts. It has since been reported that various complexes formed from BINOL derivatives and *N*-methyl imidazole with zirconium tetra-*tert*-butoxide are efficient catalysts for the asymmetric addition of cyanide anion to aldimines using Bu_3SnCN as a cyanide anion source.[12] Investigations indicated that the enantioselectivity of the Strecker reaction was markedly improved by using a mixture of BINOL derivatives as catalyst ligands. The BINOL derivatives used were *(R)*-6-Br-BINOL and *(R)*-3-Br-BINOL, and NMR studies showed the catalyst to have the structure **17** (Scheme 8).

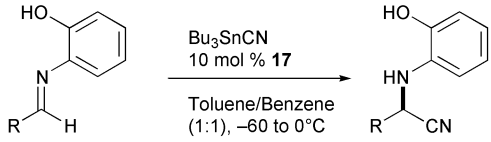
The catalyst consists of two zirconium ions, each complexed by one oxygen of the central *(R)*-3-Br-BINOL unit, with terminal *(R)*-6-Br-BINOL units (*tert*-butoxide and *N*-methyl imidazole (NMI) occupy the other binding sites). This complex was shown to be formed by mixing the components in the ratios [$Zr(O^tBu)_4$, *(R)*-6-Br-BINOL, *(R)*-3-Br-BINOL and NMI; 1 : 1 : (0.5–1):(2–3)]. Asymmetric α-amino nitrile formation was carried out in a (1 : 1) benzene–toluene solvent mixture at −65–0 °C with excellent yields (85–98%) and enantioselectivities (76–92% ee) for aryl aldimines. Lower yields and enantioselectivities were also reported for the alkyl aldimine cases. The conversion of the α-amino nitrile products into (*R*)-α-amino acid derivatives was demonstrated in the synthesis of leucinamide **18**.

2.2.2 Guanidine catalysts. Chiral guanidine derivatives have recently been reported to catalyze the Strecker reaction with very high levels of induction.

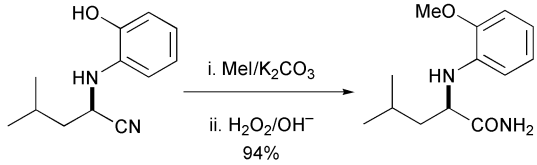
Lipton has described the use of the cyclic dipeptide catalyst **19** in asymmetric Strecker reactions using hydrogen cyanide as cyanide source (Scheme 9).[13] The catalyst **19** is the diketopiperazine of L-phenylalanine and a lower homologue of L-arginine. A strong base such as a guanidine derivative was found to be neccessary in order to accelerate proton transfer under the reaction conditions. During optimization studies, the chiral catalyst was found to catalyse the addition of cyanide anion to *N*-substituted benzaldimines in excellent yields and with very high levels of asymmetric induction possible (up to > 99% ee). The general applicability of the reaction was then examined for a series of *N*-benzhydryl imines **20**, since it was possible to effect simultaneous hydrolysis of the cyano group and removal the nitrogen protection in subsequent conversions of the α-

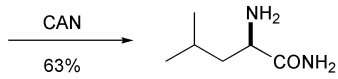


17



R = Aryl, 85-98% yield, 76-92% ee
R = Alkyl, 55-79% yield, 74-83% ee





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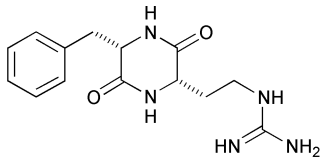
Scheme 8 Kobayashi's catalytic asymmetric Strecker reaction.



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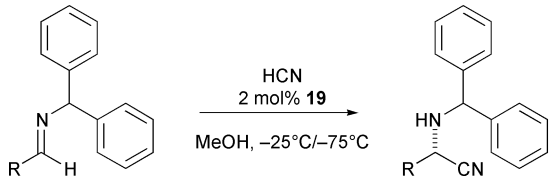


20 21

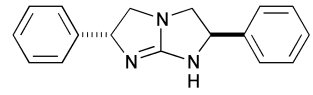
R = Aryl, 71-97% yield, <10 - >99% ee

Scheme 9 Lipton's catalytic asymmetric Strecker reaction.

amino nitriles to the corresponding (*S*)-α-amino acids. For the catalytic asymmetric Strecker reaction using a range of *N*-benzhydryl imines of aromatic aldehydes in methanol at −75 °C, the catalyst generally achieved the conversion to the α-amino nitriles **21** in high yields and enantioselectivities at 2 mol% loading. The reaction with *N*-benzhydryl imines of heteroaromatic and aliphatic aldehydes was however less successful.

Corey has also recently disclosed a catalytic asymmetric Strecker reaction employing C_2-symmetric bicyclic guanidine derivative **22** as catalyst (Scheme 10).[14]

The chiral bicyclic guanidine system based on L-phenylglycine, was shown to catalyze the Strecker reaction between *N*-benzhydryl imines **23** of aromatic aldehydes and hydrogen cyanide in toluene at −40 °C to produce the corresponding (*R*)-α-amino nitriles **24** in excellent yields and high enantiomeric excesses at 10 mol% catalyst loading. Indeed, use of the *N*-



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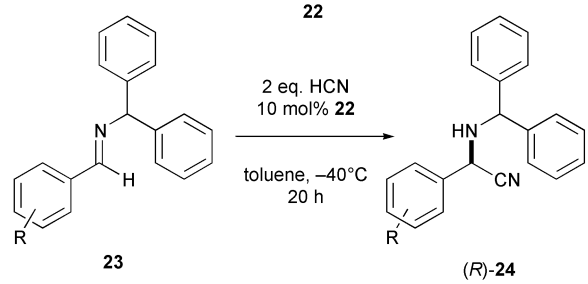
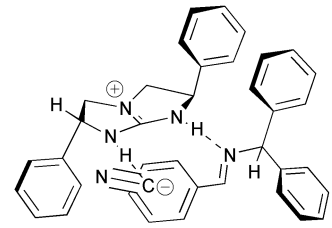


23 (*R*)-24

80-99% yield, 50-88% ee



proprosed pre-transistion-state assembly

Scheme 10 Corey's catalytic asymmetric Strecker reactions.

benzhydryl group was observed to be crucial for obtaining good levels of asymmetric induction. The reaction with *N*-benzhydryl imines of aliphatic aldehydes proceeded with slightly lower enantioselectivities, but interestingly afforded the (*S*)-α-amino nitriles. Corey has suggested that the guanidine base may be responsible for generating a guanidinium cyanide complex that is able to hydrogen bond with the imine in a pre-transition-state assembly. It has been hypothesized that in the pre-transition-state assembly a phenyl ring of the benzhydryl group is able to undergo π-stacking with one of the phenyl rings of the bicyclic catalyst. The conjugated aromatic ring of the imine may then occupy space between the lower face of the guanidinium ion and the other phenyl ring with favourable van der Waals' interactions. The cyanide ion therefore occupies space on the *si* face of the imine, attack from this face affording the observed (*R*)-α-amino nitrile products.

The opposite selectivity for the aliphatic aldimines has been attributed to the possibility that the alkyl group experiences steric repulsion in the phenyl-lower guanidinium face pocket with none of the favourable van der Waals' interactions that might be experienced by an aromatic group. This leads to the imine adopting an alternative orientation in the pre-transition-state assembly.

3 α-Amino nitriles as iminium ion equivalents

The relatively high stability of α-amino nitriles and their ability to undergo cyanide ion loss under very mild conditions to generate iminium ions has led to their application to the synthesis of natural products and important building blocks. This section highlights the synthetic use of α-amino nitriles as stable precursors to iminium ions, often in combination with another of their modes of reactivity.

3.1 Indole alkaloid natural product synthesis

Woodward's remarkable synthesis of the indole alkaloid reserpine **28**, published between 1956 and 1958,[15] involved the formation of the C-ring using a process similar to a Bischler–

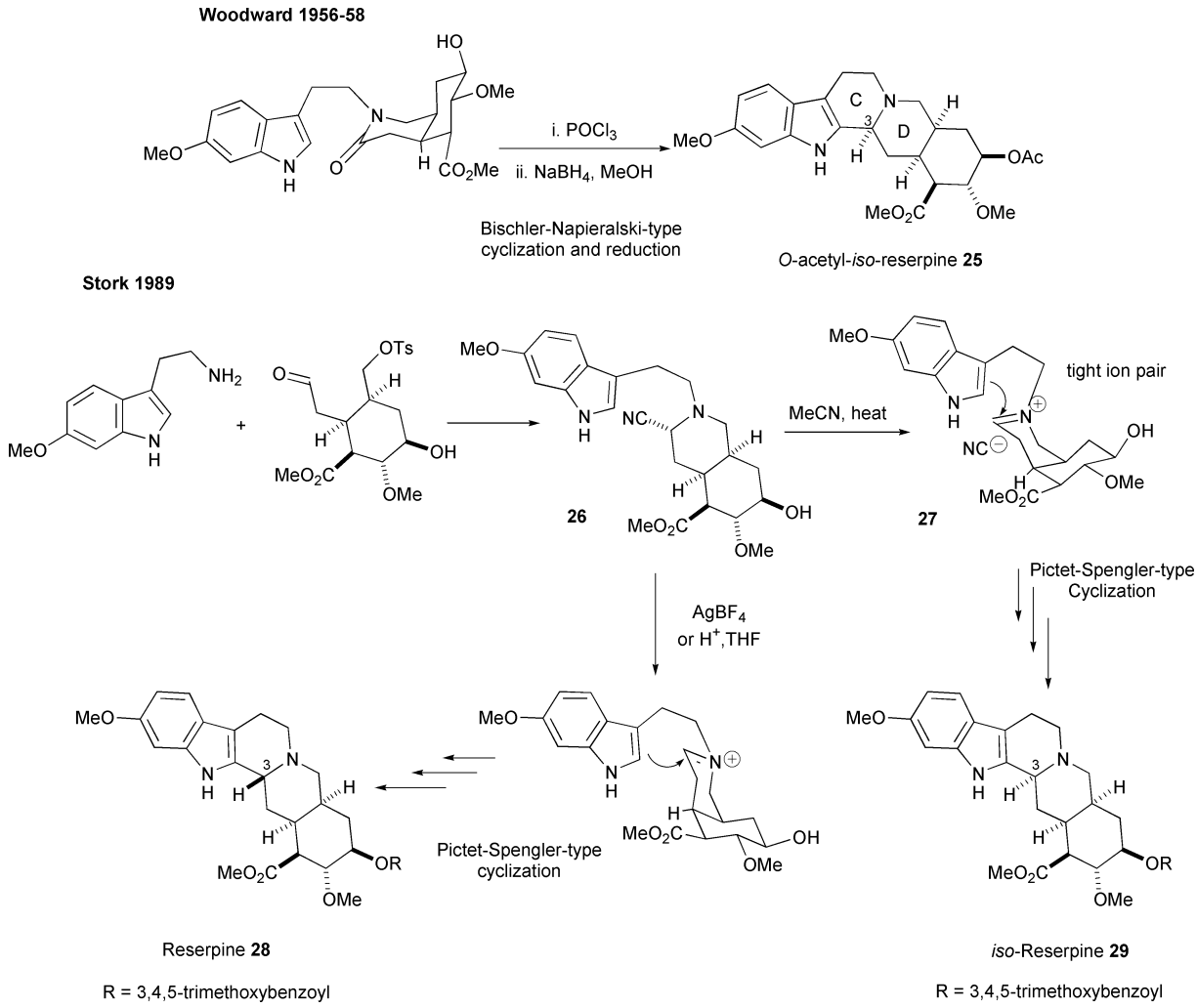
Napieralski isoquinoline synthesis (Scheme 11). The subsequent axial sodium borohydride reduction of the resulting cyclic iminium species led to the formation of a pentacyclic indoloquinolizidine **25** bearing the wrong stereochemisty at C(3). The inversion of this centre was later achieved through locking the molecule in such a conformation that facilitated acid catalyzed epimerization at C(3) *via* a tautomeric form of the indole ring.

More recently, Stork has disclosed a synthesis of reserpine **28** in which the C-ring closure was effected at a lower oxidation state at C(3).[16] This approach aimed to control the C(3) configuration directly in the ring closure step as opposed to the post-ring closure reduction of Woodward. This was achieved by prior formation of the D-ring using a Strecker reaction to give the α-amino nitrile **26** bearing an axial cyano group. The α-amino nitrile **26** here is capable of acting as a masked iminium ion and the C(3) configuration proved to have an important effect in the C-ring closure step. It was observed that C-ring closure occurred by simply heating an acetonitrile solution of **26**, this process however led to the undesired C(3) epimer **29**. This result was rationalized by the suggestion that upon thermolysis, the amino nitrile **26** decomposes to give a tight ion pair. The cyanide anion occupies the axial position of the iminium ion **27** and thus blocks nucleophilic attack from that face, the result being the formation of the equatorially connected indole ring at C(3).

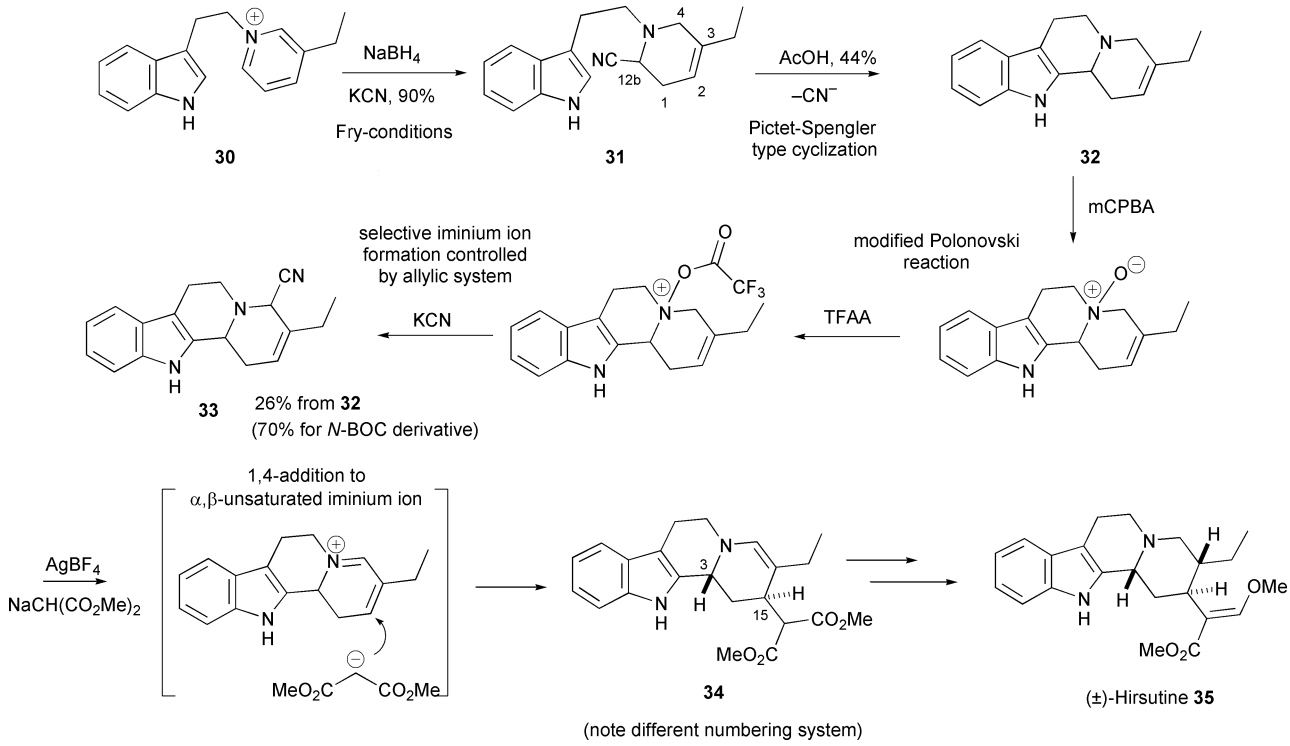
The addition of either silver fluoroborate or dilute hydrochloric acid had the effect of breaking up the tight ion pair to generate the free iminium ion species. C-Ring closure subsequently took place with nucleophilic attack of the indole system from the most stereoelectronically favoured face of the iminium ion to give pentacyclic indoloquinolizidine bearing the configuration C(3) corresponding to reserpine **28**.

A recently reported synthesis of (±)-hirsutine **35** by Lounasmaa involved the very elegant use of α-amino nitriles in the regioselective generation of iminium ions (Scheme 12).[17] Reduction of the pyridinium salt **30** with sodium borohydride in the presence of potassium cyanide led regioselectively to the α-amino nitrile **31** bearing a $\Delta^{2,3}$ double bond. This therefore allowed the subsequent generation of a $\Delta^{N,12b}$ iminium ion by hydrolysis of the α-amino nitrile under acidic conditions. This species then underwent a desired Pictet–Spengler type cyclization in order to generate the tetracyclic indoloquinolozidine system **32**. The next stage of the synthesis required the regioselective generation of a $\Delta^{N,4}$ iminium ion so that C–C bond formation could take place at C(2) *via* 1,4-addition to a 5,6-dihydropyridinium system. Upon investigation into the regioselectivity of iminium ion formation and cyanide trapping under the commonly employed modified Polonovski reaction[18] conditions (Scheme 13), [mCPBA, TFAA, KCN] it was observed that only the desired α-amino nitrile **33** was formed with the cyano group at C(4).

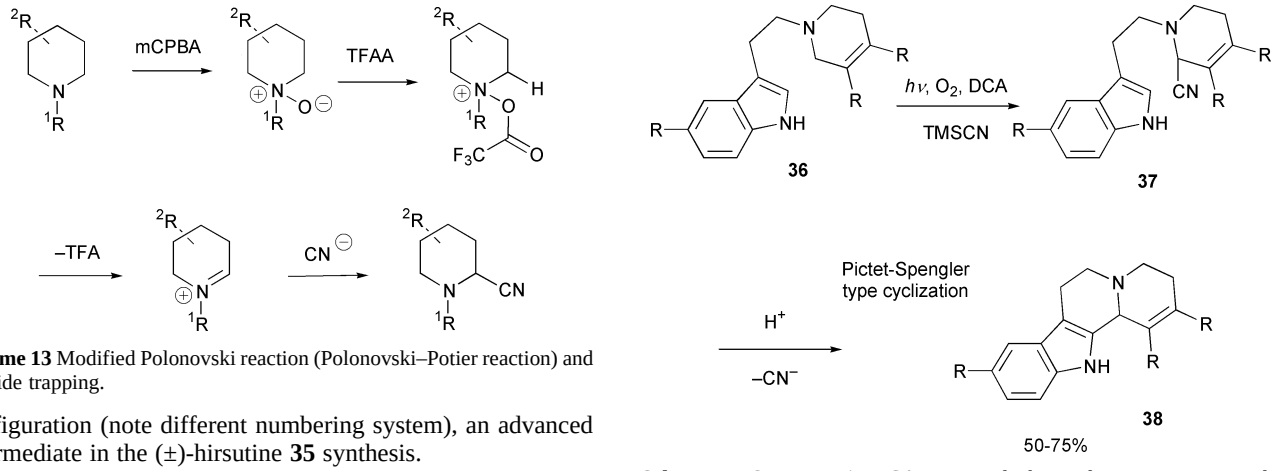
Although this was possible without protection of the indole nitrogen, performing the Polonovski reaction on this of system with the *N*-BOC derivative led to the formation of the tetracyclic system in greater yields. With α-amino nitrile **33** in hand it was then possible to generate the desired 5,6-dihydropyridinium system in the presence of sodium dimethylmalonate by treatment with silver fluoroborate. 1,4-Addition provided the compound **34**, with the correct 3,15-*trans*



Scheme 11 Woodward and Stork's syntheses of reserpine.



Scheme 12 Lounasmaa's synthesis of hirsutine.



Scheme 13 Modified Polonovski reaction (Polonovski–Potier reaction) and cynaide trapping.

Scheme 14 Santamaria's DCA-sensitized photoxidative α-amino nitrile synthesis.

configuration (note different numbering system), an advanced intermediate in the (±)-hirsutine **35** synthesis.

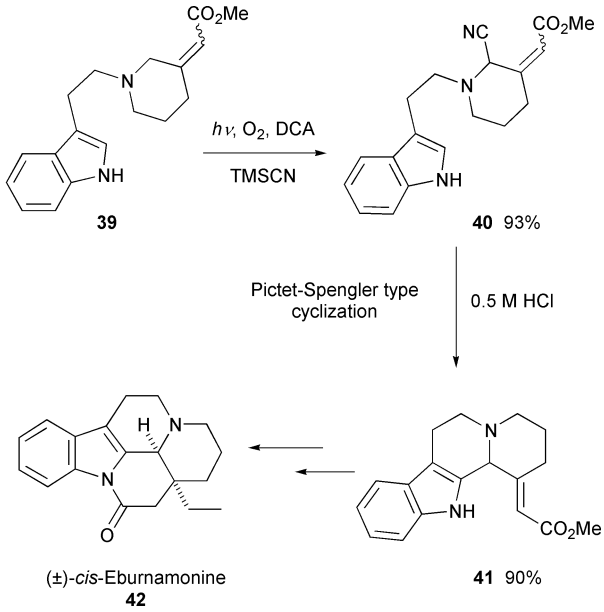
This synthesis demonstrated the excellent application of α-amino nitriles in controlling regioselectivity in generating iminium ions for C–C bond formation by 1,2- and 1,4-addition reactions.

The Polonovski reaction mentioned above, is a powerful and frequently used method for generating iminium ions from 2,3,5,6-tetrahydropyridines. Subsequent cyanide trapping provides an isolable α-amino nitrile as a masked iminium ion equivalent for subsequent synthetic applications. The Polonovski reaction suffers from occasional drawbacks, for instance, the acidic conditions may not be compatible with all functional groups in the molecule and may also preclude the use of *in situ* trapping agents such as carbon nucleophiles and organometallic reagents. Additionally, in many cases use of this procedure in indole alkaloid synthesis has necessitated the prior protection of the indole nitrogen atom as either the *N*-BOC or *N*-phenylsulfonyl derivative.

Santamaria has developed a method for producing 2-cyano-2,3,5,6-tetrahydropyridines of type **37** from 2,3,5,6-tetrahydropyridines **36** as an alternative to a Polonovski-type reaction (Scheme 14).[19] This method involves the 9,10-dicyanoanthracene (DCA)-sensitized photooxgenation of 2,3,5,6-tetrahydropyridines **36** by irradiation in the presence of oxygen and TMS–cyanide as trapping agent. The protocol has been used in systems bearing unprotected indoles with higher overall yields when compared to the Polonovski reaction route and has been applied to the synthesis of indoloquinolizidine alkaloid frameworks of type **38** *via* cyanide loss and Pictet–Spengler cyclization.

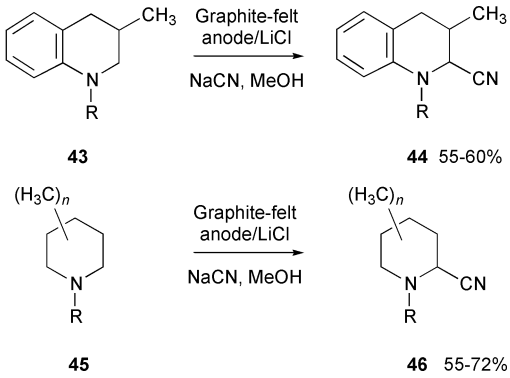
In the synthesis of *cis*-eburnamonine **42**, a mixture of tryptophyl piperidines **39** bearing the *exo*-cyclic enoate were irradiated in the presence of DCA, oxygen and TMSCN to afford the α-amino nitrile **40** in excellent yield (Scheme 15). The regioselectivity of this method of amino nitrile formation is generally directed by unsaturation at the β-position. Treatment of **40** with dilute hydrochloric acid induced loss of cyanide ion to generate an iminium ion which underwent the desired Pictet–Spengler type ring closure *via* nucleophilic attack by the indole ring to provide tetracycle indoloquinolizine **41**. Since the enoate allows the introduction of the desired ethyl group *via* conjugate addition of a cuprate this proved to be a readily available advanced intermediate in the synthesis of *cis*-eburnamonine **42**.

The synthesis of α-amino nitriles using electrochemical methods has also recently been investigated by Hurvois.[20] In one case, methanolic solutions of *N*-substituted tetrahydroquinolines **43** and *N*-phenyl piperidines **45** in the



Scheme 15 Santamaria's synthesis of *cis*-eburnamonine.

presence of sodium cyanide and lithium acetate were found to undergo anodic cyanation at a graphite–felt electrode to provide the corresponding α-amino nitriles **44** and **46** respectively (Scheme 16).



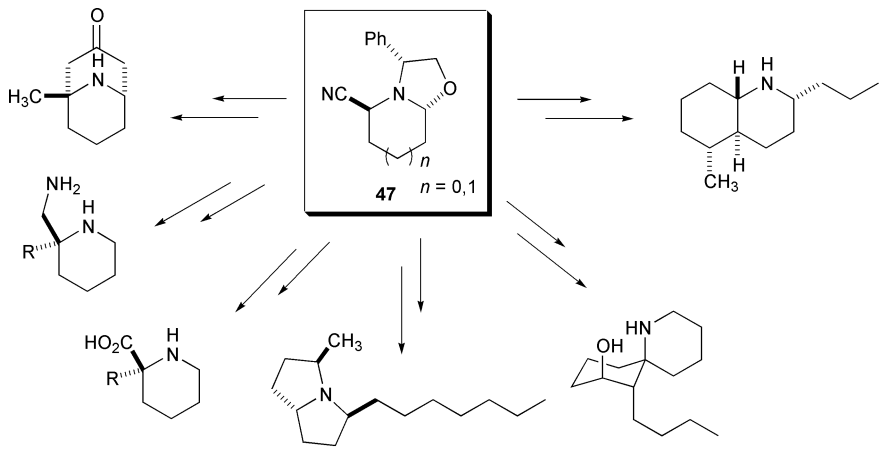
Scheme 16 Hurvois' electrosynthesis of α-amino nitriles.

3.2 Complementary substitution of cyanide using either hydride or carbanions

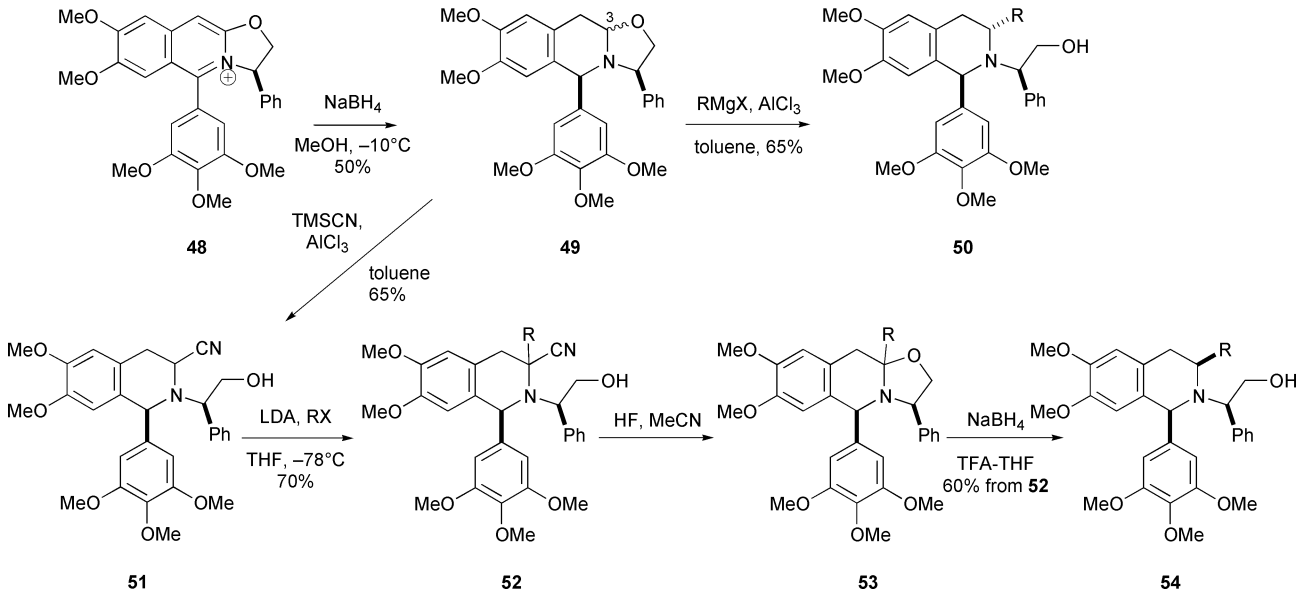
3.2.1 The CN(*R*,*S*) method. In addition to Husson's contribution to alkaloid synthesis employing α-amino nitriles as masked iminium ion equivalents (see citations in ref. 17), his group has also developed a very powerful methodology for the asymmetric synthesis of piperidine and pyrrolidine ring systems based on the incorporation of an enantiomerically pure α-cyanomethyloxazolidine ring, as in compounds of type **47**. The aptly named CN(*R*,*S*) method is based on phenylglycinol as the stereodirecting unit and utilizes the versatile reactivity of α-amino nitriles and oxazolidines to introduce substituents to piperidine and pyrrolidine rings with excellent regio- and stereocontrol. The dual polarity of the α-amino nitrile carbon allows the incorporation of substituents in the following way; (*i*) deprotonation at the α-centre and subsequent trapping by an electrophilic reagent or (*ii*) loss of cyanide to generate an iminium ion and subsequent trapping by a nucleophilic reagent (carbanion or hydride). Further substitution has been achieved at the α′-centre based on the use of *N*,*O*-acetal chemistry. This methodology has been used in the asymmetric synthesis of a large number of natural products bearing piperidine or pyrrolidine rings with broad range of substitution patterns (Scheme 17), and has recently been reviewed in this journal.[21]

We include a representative example focusing on one variation of this methodology, namely in the asymmetric synthesis of 1,3-disubstituted tetrahydroisoquinolines (Scheme 18).[22] The first stereogenic centre is directed by the phenylglycinol moiety upon reduction of the isoquinolinium salt **48** to give the mixture of oxazolidines **49**. Subsequent treatment with an alkyl Grignard reagent in the presence of aluminium trichloride affords the 1,3-*trans*-disubstituted tetrahydroisoquinoline **50**. Here the oxazolidine ring acts as the masked iminium ion and trapping with the organometallic reagent presumably occurs from the least hindered face. In order to achieve the synthesis of the 1,3-*cis*-disubstituted tetrahydroisoquinoline **54** it was found necessary to use α-amino nitrile chemistry so as to allow a polarity reversal at C(3). The cyano group was introduced using TMS–cyanide in the presence of aluminium trichloride to give **51**. Metallation of the α-centre and subsequent alkylation afforded the substituted α-amino nitrile **52**. Stereoselective replacement of the cyano group by a hydrogen atom was achieved in two-step procedure involving loss of cyanide and formation of the oxazolidine **53** under acidic conditions and subsequent sodium borohydride reduction in the presence of TFA. This afforded the 1,3-*cis*-disubstituted tetrahydroisoquinoline **54** *via* reduction of the intermediate iminium ion from the least hindered face, *i.e.* the same face as the Grignard reagent had attacked in the previous case. This demonstrates just how effectively the CN(*R*,*S*) method can allow the controlled formation of either stereocentre simply by choosing the mode of the reactivity at the α-centre.

3.2.2 Related complementary substitution in bicyclic alkaloid synthesis. The dual reactivity of the α-amino nitrile group has regularly been employed in the synthesis of bicyclic

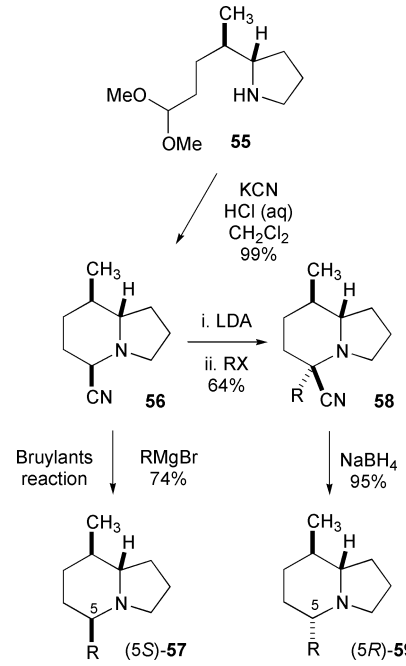


Scheme 17 Compounds available using the CN(*R*,*S*) method.



Scheme 18 Husson's asymmetric synthesis of tetrahydroisoquinolines using the CN(*R*,*S*) method.

alkaloids. In cases where highly facial selective substitution of the cyano group *via* an intermediate iminium ion is possible, by either hydride or a carbanionic species, as in the Bruylants reaction, a choice as to the ultimate configuration of the α-centre may be made. A good example of this can be seen in Polniaszek's synthesis of indolizidine alkaloids (Scheme 19).[23]

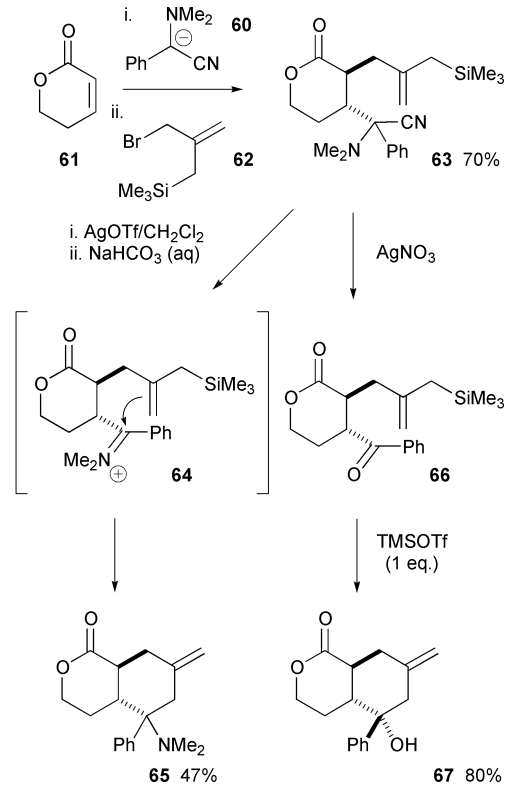


Scheme 19 Polniaszek's complementary use of α-amino nitrile reactivity in bicyclic alkaloid synthesis.

Key intermediate bicyclic α-amino nitrile **56** was available through hydrolysis of amino acetal **55** in the presence of cyanide. By carrying out the Bruylants reaction using an alkyl magnesium bromide, the cyano group was substituted with equatorial attack on the intermediate iminium species to provide the (5*S*)-indolizidine framework **57**. Alternatively, by using the complementary polarity-reversed reactivity of the α-amino nitrile group, it was possible to access the (5*R*)-indolizidine framework **59**. Thus, α-deprotonation using LDA and subsequent alkylation with an alkyl halide affords the substituted α-amino nitrile **58**. Substitution of the cyano group using sodium borohydride again results in equatorial delivery of the nucleophilic species to the intermediate iminium ion to afford the (5*R*)-indolizidine **59**.

3.3 Miscellaneous cationic reactions

3.3.1 [1+2+3]-Annulation. Wartski, Posner and Nierlich have recently decribed a three component [1 + 2 + 3] annulation strategy based on the dual reactivity of α-amino nitriles as both nucleophiles and masked iminium ion equivalents (Scheme 20).[24]

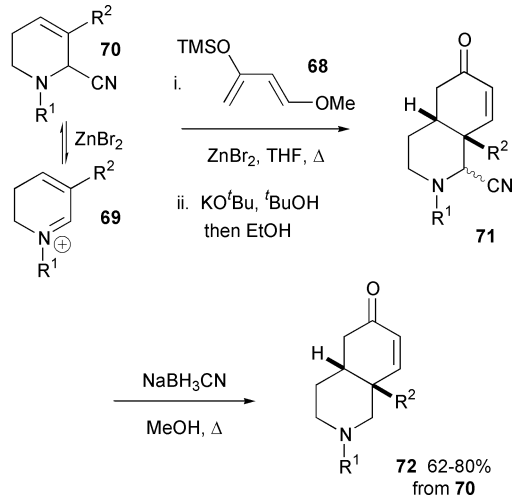


Scheme 20 Wartski, Posner and Nierlich's [1 + 2 + 3] annulation strategy.

It is well known that lithiated α-amino nitriles are excellent donors for conjugate additions to α,β-unsaturated systems (see section 4). This strategy involved the Michael addition of lithio

(*N*,*N*-dimethylamino)phenylacetonitrile **60** as the one-carbon component to dihydropyran-2-one **61** as the two-carbon component. The resulting intermediate enolate was then trapped *in situ* with silyl methyl allyl bromide **62** as the three-carbon component to afford the *trans*-disubstituted tetrahydropyranone **63**. The annulation reaction was subsequently achieved by treatment of **63** with silver triflate to induce loss of cyanide from the α-amino nitrile moiety in order to generate an iminium ion species **64**. Subsequent cationic cyclization by trapping with the nucleophilic allyl silane moiety took place to give the *trans*-bicyclic system **65**, after basic treatment. Treatment of **63** with silver salts and subsequent hydrolysis of the iminium ion intermediate revealed the aroyl ketone **66**,[25] which upon further treatment with one equivalent of TMS–triflate underwent a stereoselective cyclization to give to corresponding bicyclic alcohol **67**.

3.3.2 Iminium ion activated Diels–Alder cycloaddition. As a novel approach to hydroisoquinolines, a core structure occurring in many natural products, Baldwin has recently reported the Lewis acid promoted Diels–Alder reaction of Danishefsky's diene **68** with dihydropyridinium ions **69** (Scheme 21).[26]



Scheme 21 Baldwin's iminium ion activated Diels–Alder reaction.

The dihydropyridinium ions were themselves generated *in situ* by reversible loss of cyanide ion from β,γ-unsaturated-α-amino nitriles **70** in the presence of zinc bromide as Lewis acid promotor. This generation of dihydropyridinium ions was in itself necessary to activate what would otherwise have been an electron rich 3,4-double bond towards cycloaddition. After complete elimination the Diels–Alder adducts were found to be the *exo*-products **71** and were readily converted into the desired hydroisoquinolines **72** by hydride replacement of the cyano group. The Diels–Alder reaction did not proceed in the absence of zinc bromide.

3.3.3 Use in tandem aza-Cope rearrangement–Mannich cyclizations. The extremely elegant tandem aza-Cope rearrangement–Mannich cyclization methodology of Overman has been extensively used as the key element in the stereoselective synthesis of highly functionalized pyrrolidine units within polycyclic alkaloid natural products. The typical reaction scheme for this process is outlined (Scheme 22).

A carbocyclic iminium ion precursor of general type **74** undergoes an aza-Cope [3,3]sigmatropic shift to generate a ring-enlarged species **75** containing an enol and an iminium ion. Subsequent trapping of the iminium ion by the enol in an intramolecular Mannich-type reaction produces a *cis*-fused bicylic keto-pyrrolidine **76** in which the ring size of the original carbocycle has been increased by one.

In several natural product syntheses, Overman has made use of the cyanomethylamino group as in compounds of type **73**. The purpose of this group has been twofold; (*i*) it serves as a convenient protecting group for the amino functionality and (*ii*) it serves as a masked formaldehyde iminium ion, which may be generated by loss of cyanide ion.

This twofold use of the cyanomethylamino group can be well illustrated by the following example from the synthesis of the core structure of the *Amaryllidaceae* alkaloids. As part of the formal synthesis of (±)-6a-epipretazettine **84** (Scheme 23),[27] the vinyl cerium reagent **77** underwent addition to the cyanomethyl-protected amino cyclopentanone **78** to give the key intermediate **79**. Subsequent treatment with copper(II) triflate induced the formation of the formaldehyde iminium ion **80** by irreversible removal of cyanide anion. The iminium ion intermediate **81**, underwent a tandem aza-Cope rearrangement–Mannich cyclization to give the *cis*-fused arylhydroindole system **82**, which after further elaboration gave **83**, an intermediate in Danishefsky's synthesis of 6a-epipretazettine **84**.

Overman has also used an anionic aza-Cope rearrangement in the synthesis of (±)-gelsemine (Scheme 24).[28] In this case the key precursor was secondary α-amino nitrile **85**. Treatment with potassium hydride induced elimination of HCN to generate the formaldehyde imine alkoxide **86**, which underwent an anion accelerated aza-Cope rearrangement to give imine **87** which subsequently gave hexahydroisoquinolinone **88**.

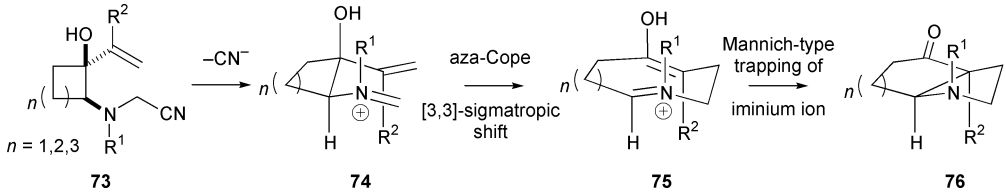
3.3.4 Use in iminium ion–vinylsilane cyclizations. Overman has employed α-amino nitriles as precursors to iminium ions in the preparation of enantioenriched dihydropyridines *via* an iminium ion–vinylsilane cyclization of the general type shown (Scheme 25).[29]

Mechanistic studies point to an equilibrium between the iminium ion–vinylsilane species **89** and the rearranged iminium ion allylsilane **90**, formed by aza-Cope [3,3]sigmatropic shift, with the rearrangement taking place faster than the cyclization. The formation of the piperidine ring **91** then occurs by trapping either of the possible iminium ions by the vinylsilane or the allylsilane, respectively, and subsequent loss of the silicon group. One example of this transformation has been observed upon treatment of the α-amino-nitrile-bearing vinylsilane **92** with silver tetrafluoroborate, generating the corresponding iminium ion which subsequently underwent the cyclization reaction described above to give the corresponding enantioenriched dihydropyridine **93** in moderate yield.

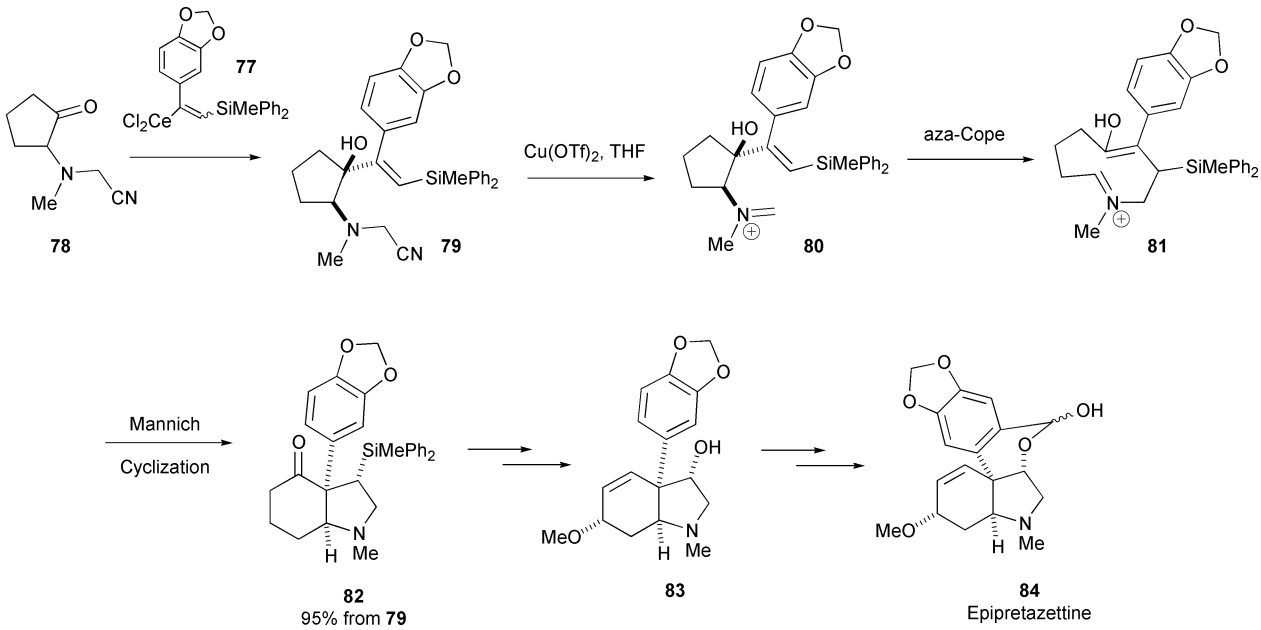
4 Metallated α-amino nitriles

4.1 Reactions of metallated α-amino nitriles

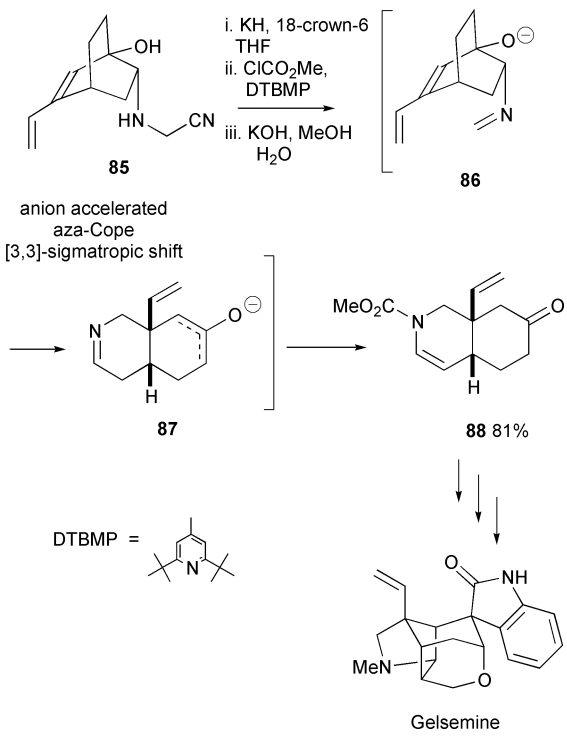
Since the investigations of Hauser,[30] disclosed in 1960, it has been known that under basic conditions α-amino nitriles may be



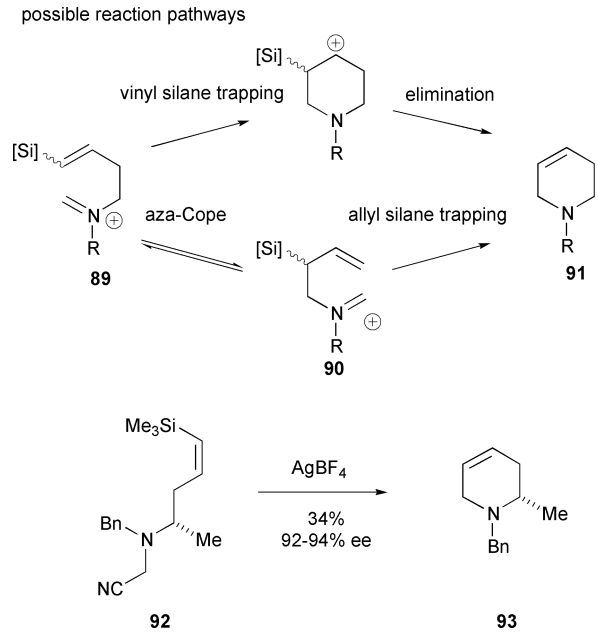
Scheme 22 The tandem aza-Cope rearrangement–Mannich cyclization.



Scheme 23 Overman's synthesis of epipretazettine.



Scheme 24 Anionic aza-Cope from Overman's synthesis of gelsemine.



Scheme 25 Iminium ion–vinylsilane cyclizations.

deprotonated in the α-position and undergo nucleophilic reactions such as alkylation, conjugate additions to α,β-unsaturated carbonyl compounds, 1,2-additions to carbonyl compounds and their analogues, additions to alkynes and epoxide ring opening reactions. (See ref. 2 for leading references.) The resulting adducts, under acidic conditions, undergo cleavage of the α-amino nitrile moiety to generate a carbonyl group. This corresponds to a reversal of polarity (*Umpolung*) of the aldehyde from which the original α-amino nitrile was derived, with the α-amino nitrile anion behaving as an acyl anion equivalent. This d^1 reactivity is akin to that of protected metallated cyanohydrins, dithianes and other α,α-heteroatom stabilized anions.

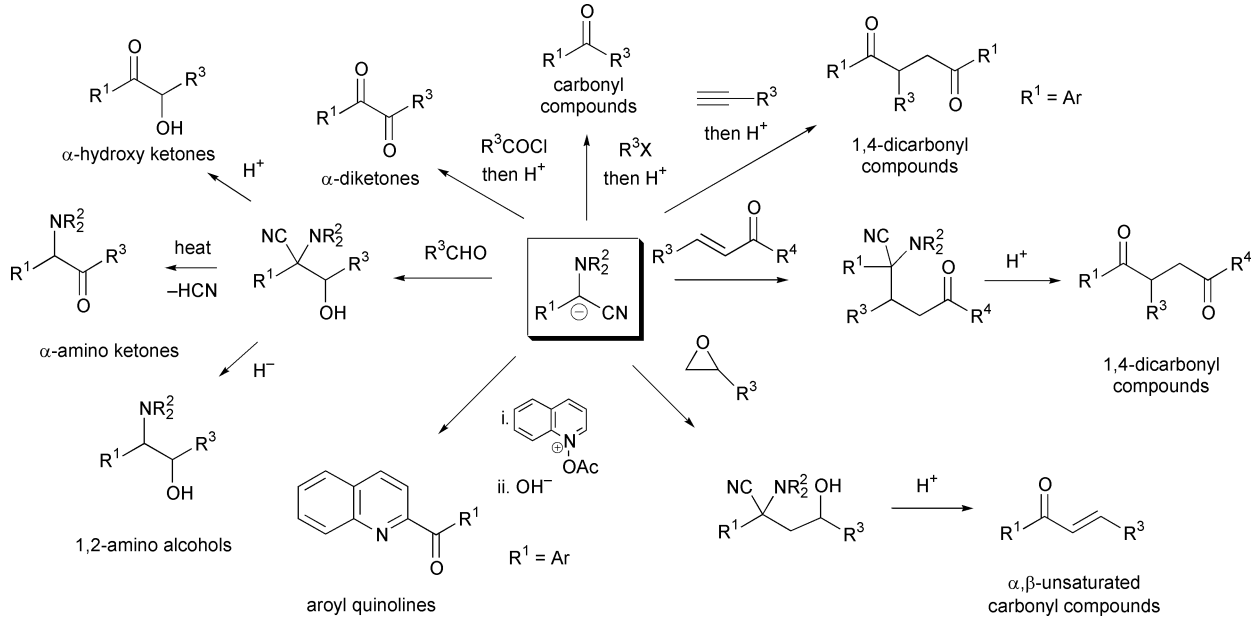
In addition to the cleavage reaction to generate the carbonyl compound, the amino nitrile adduct may be further subjected to the other modes of reactivity as described above (see sections 3.2.1, 3.2.2 and 3.3.1).

The literature concerning the reactions of metallated α-amino nitriles up to the beginning of 1983 has been covered in a review by Albright.[31] In addition to the chemistry detailed above, we wish to summarize just a few examples of the use of these species in synthesis in Scheme 26.

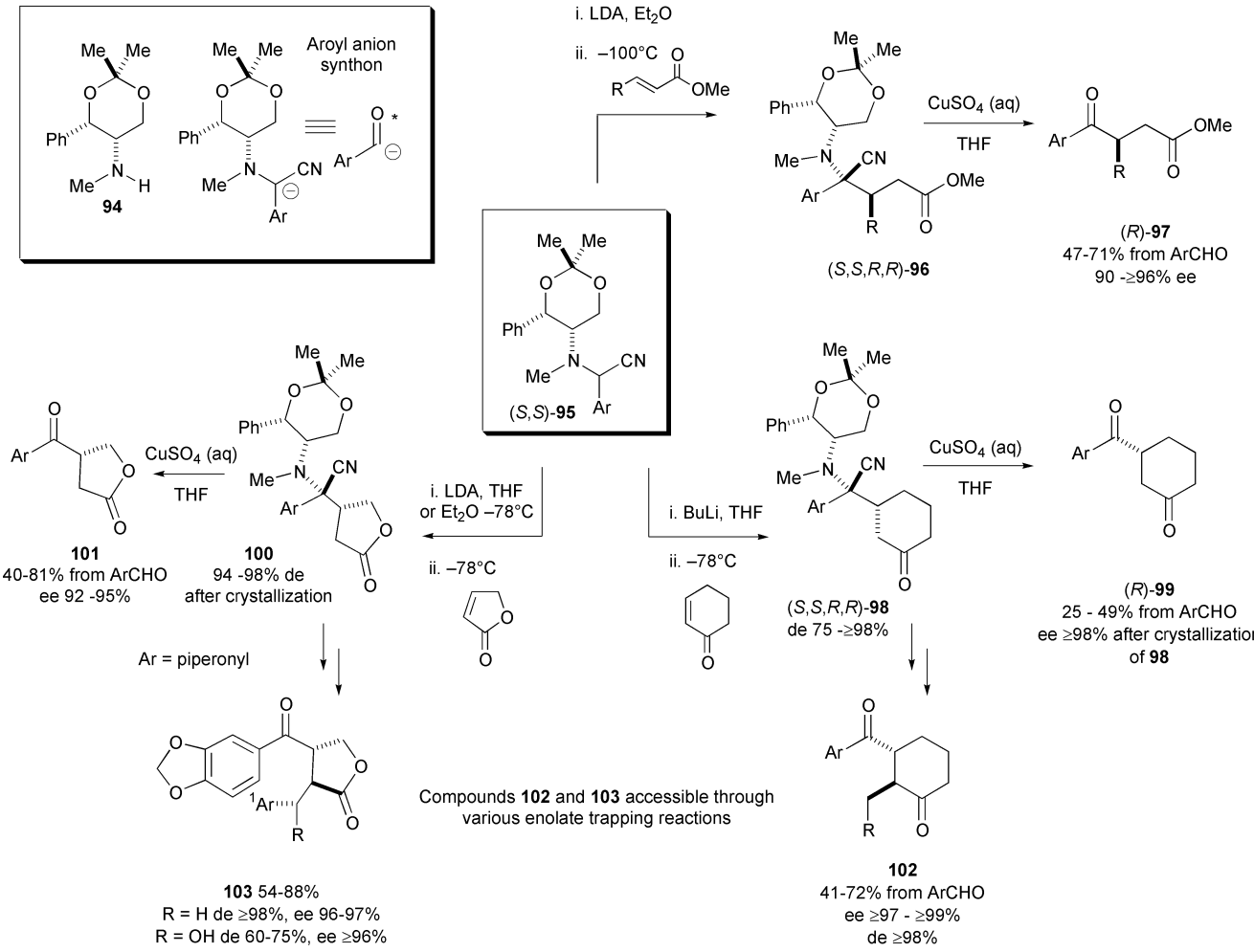
4.2 Asymmetric nucleophilic acylation reactions

The use of metallated α-amino nitriles as acyl anion equivalents opens up the possibility for asymmetric synthesis when an enantiomerically pure chiral amine is employed as the α-amino group. In this way it is possible to carry out asymmetric nucleophilic acylation reactions at prochiral electrophilic centres as in 1,2-additions to aldehydes and 1,4-additions to α,β-unsaturated carbonyl compounds. The study of this kind of asymmetric *Umpolung* process has been carried out within the Enders group over the past few years.

The main focus of these studies has been nucleophilic aroylations using the (*S*,*S*)-2,2-dimethyl-5-*N*-methylamino-4-phenyl-1,3-dioxane **94** as a chiral amine auxiliary, Scheme 27



Scheme 26 Summary of reactions of lithiated α-amino nitriles.

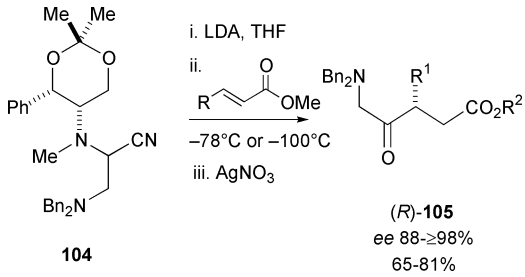


Scheme 27 Enders' asymmetric nucleophilic aroylation reactions.

(this auxiliary is the *N*-methyl derivative of the chiral auxiliary **6** used in Weinges' asymmetric Strecker reactions). After screening a variety of chiral amines it was discovered that the use of this α-amino group resulted in the greatest levels of asymmetric induction in the processes investigated. In particular, Michael additions using metallated α-amino nitriles bearing this auxiliary were used for the asymmetric synthesis of chiral 1,4-dicarbonyl compounds with high enantiomeric purity. Initially,[32] α-amino nitriles of the type **95** were lithiated and treated with open chain (*E*)-methyl enoates to give the Michael adducts, now α,α′-disubstituted amino nitriles **96** in high diastereomeric purity. Treatment with aqueous copper sulfate in THF resulted in hydrolysis of the α-amino nitrile moiety to reveal the ketone functionality within a highly enantiomerically pure (ee 90 –≥96%) 1,4-dicarbonyl compound **97**.

The methodology has been further extended to the asymmetric aroylation of cyclic enones and α,β-unsaturated lactones, *i.e.* acceptors with a fixed (*Z*)-double bond geometry, Scheme 27. For instance, these lithiated α-amino nitriles **95** were found to undergo highly diastereoselective conjugate additions to 2-cyclohexen-1-one[33] and butenolide[34] to give α-amino nitrile adducts **98** and **100**, respectively. Subsequent treatment with aqueous copper sulphate in THF generated the corresponding aroylated materials **99** and **101** in high enantiomeric excesses. Furthermore, the intermediate enolate anions resulting from 1,4-additions to 2-cyclohexen-1-one underwent highly diastereoselective α-alkylation in the presence of an alkyl bromide and HMPA.[35] Upon amino nitrile cleavage with silver nitrate the *trans*-1,4-dicarbonyl compounds **102** were generated in high enantiomeric excess. In the case of addition to butenolide, purification of the intermediate α-amino nitrile adduct **100** and subsequent deprotonation α- to the lactone was used for Ar = piperonyl in order to carry out diastereoselective alkylation and aldol reactions. Subsequent amino nitrile cleavage with silver nitrate produced the aroyl *trans*-2,3-disubstituted γ-butyrolactones **103**, themselves important building blocks for the synthesis of lignan natural products.

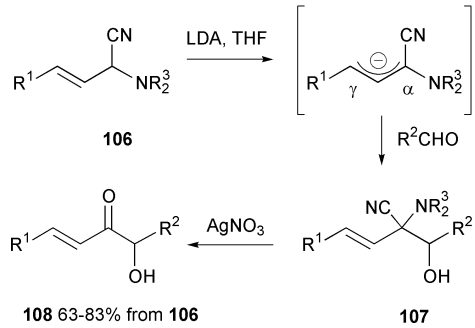
In addition to asymmetric nucleophilic aroylations, this methodology has been extended to asymmetric α-amino acylations[36] using the α,β-diamino nitrile **104**, (Scheme 28).



Scheme 28 Enders' asymmetric nucleophilic α-amino acylation reaction.

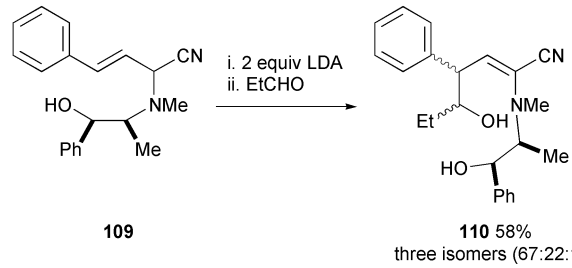
Accordingly, lithiation of **104**, conjugate additions to open-chain enoates and amino nitrile cleavage generated 3-substituted 5-amino-4-oxo-esters **105** in high enantiomeric excess (ee 88–≥98%). The process occurs with no β-elimination upon formation of the lithiated α-amino nitrile.

Aside from this, studies have been carried out[37] into the regiochemistry of the reactions of lithiated β,γ-unsaturated-α-amino nitriles of type **106**, a class of intensively investigated heteroatom stabilized allylic anions (Scheme 29). In these



Scheme 29 Regioselectivity of 1,2-additions with β,γ-unsaturated-α-amino nitriles (Enders).

ambident systems, nucleophilic attack may take place from either the α- or the γ-carbon atom. On taking lithiated achiral β,γ-unsaturated-α-amino nitriles **106** and treating them with range of aldehydes, addition was found to occur only at the α-carbon. Cleavage of the amino nitrile **107** with silver nitrate afforded the α-hydroxyenones **108**. The α-regioselectivity of the more extended conjugated system **106** (R^1 = Ph) is interesting to note when comparing it to earlier work by Fang,[38] in which it was demonstrated that upon lithiation, β,γ-unsaturated-α-amino nitriles **109** reacted with propionaldehyde to give the γ-adducts **110** (Scheme 30). This seems to be a result



Scheme 30 Regioselectivity of 1,2-additions with β,γ-unsaturated-α-amino nitriles (Fang).

of the more sterically demanding amino group in the latter case. Other regioselectivity studies have been detailed elsewhere.[31]

4.3 Structure and reactivity of lithiated α-amino nitriles

The high asymmetric inductions observed for Michael additions using lithiated α-amino nitriles of type **95** has prompted a more detailed investigation of their solid and solution phase structures in an attempt to rationalize the stereochemical outcome of the processes described above.[2]

Initial studies focused on the solid-state structure of lithiated α-amino phenylacetonitriles, such as **95** (Ar = Ph). From the X-ray crystal structure of lithiated **95** (Ar = Ph), crystallized from THF it could be seen that in the solid state such species exist as dimeric, almost linear, *N*-lithiated α-cyano anions containing four membered Li_2N_2 rings, with THF molecules completing the lithium co-ordination sphere (Figure 1). Interestingly, the

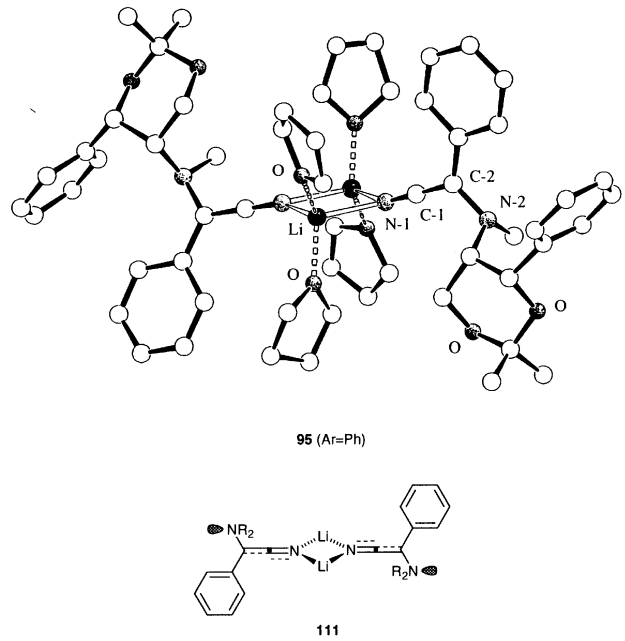


Fig. 1 Solid state representations of lithiated α-amino nitriles of type **95** (Ar = Ph).

conformation of the aromatic group was found to be the same for all cases examined, that being coplanar with the linear *N*-lithiated α-cyano anion in order to achieve maximum mesomeric stabilization. In addition, a common conformation of the amino group was observed, in that the nitrogen lone pair was antiperiplanar to the *N*-lithiated α-cyano anion in order to minimize repulsive interactions. The measured bond lengths and angles point to an almost linear C–C–N unit with partial C–

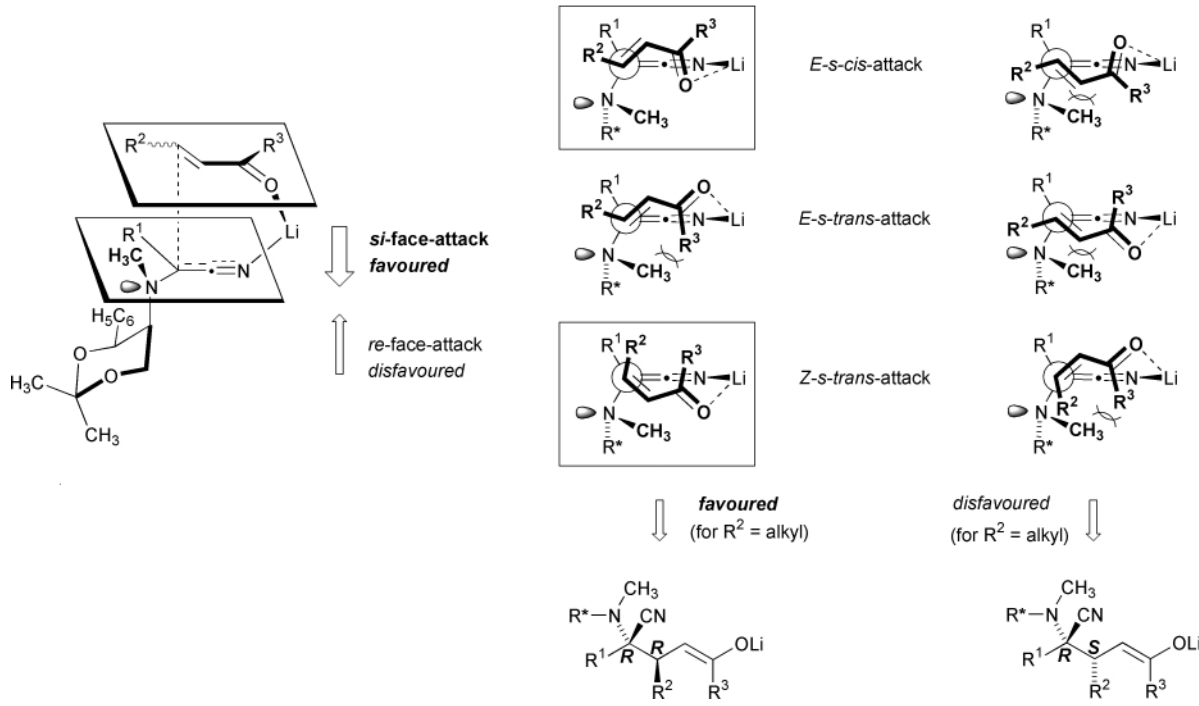
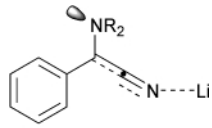


Fig. 2 Proposed transition states for Michael additions with lithated α-amino nitriles of type **95**.

C double character and partial C–N triple bond character. The solid state structure may therefore be formally represented by structure **111**.

The solution state structure of these species was investigated using IR spectroscopy, ^{13}C and ^{1}H-NMR spectroscopy and cryoscopy. Using these techniques it has been concluded that the lithiated α-amino nitriles investigated exist as *N*-lithiated monomeric species with slight ionic character formally represented by a ketene iminate structure **112**..



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Based on this information, a mechanism has been proposed in order to account for the stereochemical outcome of the conjugate addition of such lithiated α-amino nitriles to α,β-unsaturated carbonyl compounds (Fig. 2). The proposed transition state places the nitrogen lone pair antiperiplanar to the linear *N*-lithiated α-cyano anion which forces the *N*-methyl group and the dioxane ring to occupy positions above and below the plane. The whole system is oriented so that *N*-lithiated α-cyano anion points away from the phenyl group on the ring. Assuming fairly static behaviour of the nucleophile, this therefore favours approach of the electrophile from the face opposite to the sterically demanding chiral auxiliary. The *si* face complexation of the α,β-unsaturated carbonyl compound to the nitrogen of the *N*-lithiated α-cyano anion takes place by fast solvent/electrophile exchange and the topicity of the conjugate addition is then governed by minimizing steric interactions of the electrophile with the *N*-methyl group. For those electrophiles investigated the model is consistent with attack of the lithiated α-amino nitrile at the *re*-face of (*E*)-*s*-*cis* and (*Z*)-*s*-*trans* α,β-unsaturated carbonyl compounds to give the observed (*R*,*R*)-configured adduct (R^2 = alkyl).

5 Conclusion

The versatile reactivity of the α-amino nitrile moiety has resulted in their continuing use in many diverse synthetic applications. 150 years after Strecker reported his synthesis of alanine, there is still a great interest in developing asymmetric variants of the Strecker reaction for the enantioselective synthesis of α-amino acids. The use of α-amino nitriles as stable precursors to iminium ions has been of key importance in the synthesis of a wide range of natural products. Finally, α-metallation results in a formal reversal of polarity of α-amino nitriles from being masked carbonyl or imine groups to being masked acyl anion equivalents and therefore further extends the synthetic potential of these remarkable bifunctional compounds.

We believe that the interest in these valuable synthetic intermediates will continue well into the future.

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