The Chemistry of Deprotonated α-Aminonitriles

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Abstract: This review highlights various aspects of the chemistry of the anions of α-aminonitriles. Their structural features and their characteristic reactivity are discussed, along with various methods for their preparation. Special emphasis is given to synthetic applications of deprotonated α-aminonitriles which have been used as valuable and readily accessible synthetic equivalents of acyl anions and α-aminocarbanions.

1 Introduction

The chemistry of α-aminonitriles was first described by Adolph Strecker in 1850. Although more than 150 years old, his famous three-component condensation of amines, carbonyl compounds and hydrocyanic acid is still the fastest and most widely used access to this highly versatile compound class. The combination of an amino and a nitrile group, and thus of a latent imine or carbonyl function, accounts for the usefulness of α-aminonitriles as starting materials for the preparation of a multitude of mono- or difunctional compounds. Acid hydrolysis of α-aminonitriles furnishes α-amino acids, and numerous methods for the preparation of enantiomerically pure α-aminonitriles have been described. Nucleophilic displacement of the nitrile group by hydride or a carbanion (Bruylants reaction) furnishes amines, full reduction of the nitrile group yields 1,2-diamines and the preparation of α-aminoaldehydes via partial hydrogenation and hydrolysis has been described. The action of organometallics on α-aminonitriles may also lead to nucleophilic attack on the nitrile carbon. Enamines are accessible by dehydrocyanation and various methods for the reversal of the Strecker reaction have been described, normally converting α-aminonitriles back into their parent carbonyl compounds (Scheme 1). Aminonitriles can also serve as starting materials for the preparation of nitrogen heterocycles. Although the anion-stabilizing effect of the nitrile group in Strecker products derived from aldehydes was first employed by von Miller and Plöchl as early as 1898 (see section 10), it took more than 60 years before the metallation of α-aminonitriles found wider application. The groups of Boekelheide and Popp recognized the synthetic potential of deprotonated Reissert compounds in the 1950s and reported on their alkylations and on direct and vinylogous additions. In 1960, Hauser, Taylor, and Ledford described the α-alkylation of the potassium salts of N,N-disubstituted α-aminonitriles and the subsequent base-induced elimination of HCN from the substitution products to form enamines as well as their acidic hydrolysis to form ketones. In the following two decades, deprotonated aminonitriles experienced a boom and were extensively employed as reactive, readily available and inexpensive acyl anion equivalents. They turned out to be more versatile than O-protected cyanohydrins or the widely used 1,3-dithianes and even sterically hindered groups could be introduced in high yield. While nucleophilic acylations using deprotonated N,N-dialkylaminonitriles as well as various aspects of α-aminonitrile chemistry have already been reviewed by Albright in 1983, by Shafran, Bakulev, and Mokrushin in 1989, and by Enders and Shilvock in 2000, the present review focuses on

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the general chemistry of metallated \( \alpha \)-aminonitriles and their synthetic applications.

2 Structure and Reactivity of Deprotonated \( \alpha \)-Aminonitriles

The structures of the lithium salts of the \( \alpha \)-aryl-substituted \( \alpha \)-aminonitriles \( 13, 15, \) and \( 16 \) have been determined by X-ray crystallography.\(^ {69} \) All three salts form dimers of \( \alpha \)-lithiated cyanocarbanions containing a central \( \text{Li}_2\text{N}_2 \) ring with exact or approximate \( \text{C}_2 \) symmetry. The bond lengths of the \( \text{C}1–\text{C}2 \) and the \( \text{C}1–\text{N} \) bond (136–138 \( \text{pm} \) and 117–120 \( \text{pm} \)) are almost exactly intermediate between the values expected for single/double and double/triple bonds, respectively. Similar values have been obtained for aggregates of lithiated phenylacetonitrile.\(^ {70,71} \)

As would be expected, the aryl rings in \( 13–16 \) are aligned parallel to the \( \text{C}2–\text{C}1–\text{N} \) axis to maximize charge delocalization and the nitrogen lone pairs are oriented in an anti-periplanar fashion to reduce the repulsive interaction with the negatively charged conjugated system (Figure 1). IR spectroscopic studies of tetrahydrofuran solutions of \( 12, 14, \) and \( 16 \) at 25 °C revealed the presence of dimers and monomers in equilibrium while the freezing point depression of tetrahydrofuran solutions of \( 16 \) indicated a monomeric structure at \( -108.5 \°C \).\(^ {72} \) The ambident character of lithiated \( \alpha \)-aminonitriles allows reactions with electrophiles to take place at either carbon or nitrogen.

Soft electrophiles like methyl iodide, acetaldehyde or cyclohexenone react exclusively at carbon, while hard electrophiles like acetyl chloride, trimethylsilyl chloride or trimethylsilyl triflate furnish predominantly the \( \alpha \)-substituted ketene imines which may slowly rearrange to the \( \alpha \)-substituted enamines like acetyl chloride, trimethylsilyl chloride or trimethylsilyl triflate furnish predominantly the \( \alpha \)-substituted ketene imines which may slowly rearrange to the \( \alpha \)-substituted enamines. This parallels findings obtained with metallated silyl cyanohydrins.\(^ {73} \)

3 Alkylations

The first reported alkylation of a metallated acyclic \( \alpha \)-aminonitriles \( 27 \) obtained by \( \alpha \)-alkylation of \( \alpha \)-(dimethylamino)phenylacetonitrile to convert them into \( \alpha \)-(dimethylamino)phenylacetonitrile (19).\(^ {29,74} \) They found that \( \alpha \)-(dimethylamino)phenylacetonitrile (22) gave essentially the same results, including the base-induced \( \beta \)-elimination of HCN, in similar yield. The only significant difference was the heat sensitivity of aminoalkylacetonitrile 23, from which enamine 24 was obtained upon distillation or attempted recrystallization as a mixture of geometrical isomers. This behavior can be attributed to the electron-donating properties of the dimethylamino group which promotes the elimination of cyanide under formation of an iminium ion. Enamine 24 was converted into desoxybenzoin (26) upon acid hydrolysis, while its reduction with sodium in liquid ammonia furnished amine 25, demonstrating the use of the anion of 22 as both an acyl anion and an \( \alpha \)-aminocarbanion equivalent (Scheme 2).\(^ {75} \) These reactions were later extended to aminoalkylacetonitriles derived from aliphatic aldehydes.\(^ {30} \)

The same authors subsequently reported on the exploitation of the latent iminium ion reactivity of aminonitriles in a Bruylants reaction with organomagnesium ha-

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**Biographical Sketch**

**Till Opatz** was born in Bad Homburg, Germany, in 1973. He obtained his diploma degree in 1997 with Professor Johann Mulzer at the University of Frankfurt and his doctorate in 2001 with Professor Horst Kunz at the University of Mainz. After a postdoctoral stay with Professor Rob Liskamp, University of Utrecht (The Netherlands), he completed his Habilitation at the University of Mainz in 2006. Since 2007, he is professor of organic chemistry at the University of Hamburg. His research interests are new synthetic methods, the synthesis of biologically active compounds and the chemistry of natural products.
The anions of (dialkylamino)acetonitriles (formyl anion equivalents) are prone to self-condensation unless the metal organyl to the resulting iminium ion. While primary Grignard reagents gave the desired substitution products, the application of secondary or tertiary organomagnesium halides resulted in Grignard reduction under formation of the benzylic amines instead. Moreover, the acid-induced retro-Strecker reaction of the alkylation products was used to prepare phenyl ketones in appreciable yield (Scheme 3).

While Strecker products derived from aromatic aldehydes furnish anions stabilized by additional delocalization, α-alkyl- and especially α-unsubstituted dialkylaminonitriles have been reported to undergo undesired side reactions and with most electrophiles, cleaner reactions are observed with α-aryl or α-hetaryl substituted nucleophiles. The anions of (dialkylamino)acetonitriles (formyl anion equivalents) are prone to self-condensation unless the steric hindrance of the N-substituents becomes prohibitive. Remarkably, the lithium salt of (dimethylamino)acetonitrile has been reported to be unstable, while its diethyl analogue did not cause such problems: Two consecutive alkylations of (diethylamino)acetonitrile without isolation of the monoalkylated intermediate have been employed by Stork et al. to prepare cyclopentenone, an intermediate in the synthesis of cis-jasmone and methyl jasmonate. The dialkylated product was hydrolyzed to ketone under mild conditions using copper sulfate pentahydrate in ethanol. Cleavage of the cyclic acetal with oxalic acid and intramolecular aldol condensation under basic conditions furnished in 76% overall yield (Scheme 4).

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benzylolation and reaction with formaldehyde. Ring opening with citric acid and potassium cyanide furnished aminonitriles \( \text{41} \) which were converted into the corresponding chlorides using thionyl chloride. In case of the phenylglycinol derivative, quantitative rearrangement took place. Deprotonation with lithium hexamethyldisilazide furnished the azetidine carbonitriles in high yield but low diastereoselectivity (Scheme 6)\(^{83} \).

A combination of an \( \alpha \)-alkylation with the trapping of an iminium ion generated by elimination of cyanide from the substitution product with an allylsilane was chosen by the Martin group to prepare the tricyclic compound \( \text{53} \).\(^{84} \) Cyclization of the imine obtained from the amino-functionalized allylsilane \( \text{47} \) and glutaric aldehyde dimethyl acetal in the presence of trifluoroacetic acid and subsequent addition of sodium cyanide gave the bicyclic aminonitrile \( \text{50} \) in 89% yield as an 88:12 epimeric mixture. Lithiation and alkylation with the functionalized tosylate \( \text{51} \) gave \( \text{52} \) (62%), the treatment of which with silver triflate led to the intermediate formation of the iminium ion,\(^{85} \) which cyclized diastereoselectively to the spirocyclic product \( \text{53} \) in 81% yield. Thus, the short reaction sequence allows the efficient construction of a product of considerable complexity (Scheme 7).

![Scheme 6](image)

**Scheme 6** Intramolecular alkylations to azetidines by Couty and co-workers

4 Opening of Epoxides

An early example of epoxide opening with deprotonated aminonitriles was reported by Stork and co-workers who reacted lithiated (diethylamino)acetonitrile with styrene oxide or heptene oxide. The intermediate \( \gamma \)-amino alcohols were not isolated but rather hydrolyzed under elimination with aqueous oxalic acid to furnish cinnamaldehyde and trans-oct-2-enal (Scheme 8, top).\(^{35} \)

Katagiri et al. used an intriguing combination of an epoxide opening and a consecutive intramolecular alkylation in their synthesis of a trifluoromethylated 1-aminocyclopropane-1-carboxylic acid.\(^{86} \) Starting from the protected glycine nitrile \( \text{54} \), alcohol \( \text{55} \) was converted into the tosylate, the deprotonation of which furnished cyclopropane \( \text{56} \). The latter, after recrystallization in order to increase the enantiomeric excess, was converted into the target compound \( \text{57} \) by oxidative degradation of the pyrrole ring to the \( N \)-acyl compound and double hydrolysis. Remarkably, the cyclization proved to be completely diastereoselective (Scheme 8, middle).

Laurent et al. utilized an intramolecular epoxide opening for a quick access to the eastern half of the potent \( \beta \)-lactam antibiotic thienamycin. The homochiral epoxy amide \( \text{60} \) was deprotonated with lithium hexamethyldisilazide and furnished an almost equimolar mixture of the diastereomeric products \( \text{61} \) (Scheme 8, bottom).\(^{37} \)

5 1,2-Additions

The synthesis of \( \beta \)-amino alcohols by 1,2-addition of deprotonated dialkylaminonitriles to aldehydes was described by Stork et al. in 1979. While the reaction of the lithium salt of 2-(dimethylamino)propionitrile \( \text{62} \) with benzaldehyde and subsequent reduction of the primary addition product with sodium borohydride furnished predominantly the syn-configured product \( N \)-methylpseudoephedrine \( \text{63} \) in 93% yield, a similar reaction of \( N \)-benzoyl-L-piperidine-2-carbonitrile with aromatic or aliphatic aldehydes gave the anti-diastereomers.\(^{88} \) The authors explain this difference with the dipole repulsion in the iminium salt resulting from elimination of cyanide from the \( N,N \)-dialkylated addition product. A special feature of the reaction with \( N \)-acylated aminonitriles to aldehydes is the \( N \)-to-O migration of the acyl residue in the alcoholate \( \text{67} \). Nucleophilic attack leads to formation of the tetrahe-
elimination of cyanide. Reduction of 69 furnishes ester 70, which is finally solvolyzed by the methanolic sodium borohydride solution to amino alcohol 71 (Scheme 9).

The same principle had already been employed earlier by the groups of McEwen and Popp for the synthesis of hydroxyalkylated isoquinolines from Reissert compounds.46,47,89–91 In the case of the N-acylated starting materials 72, the primary addition products undergo acyl migration under formation of the aromatic esters 73 (Scheme 10, top). If, however, the migration under formation of the aromatic esters results in formation of tricyclic oxazolidinones 76, from which HCN can be eliminated to form oxazolinones of type 75 (Scheme 10, bottom).92 The analogous 1,2-addition to benzalanilines has also been described. This is one of the rare instances where aldimes were chosen as the reaction partners for deprotonated \( \alpha \)-aminonitriles (see also section 10).93

Lithiated (dialkylamino)acetonitriles have been utilized as acyl anion equivalents to prepare \( \alpha \)-hydroxy ketones 81 and 82 from aliphatic aldehydes and cyclic ketones in moderate to high yield (Scheme 11, top).84 Enders and Lotter combined the same reaction with the thermal dehydrocyanation of the addition products 84 for the preparation of \( \alpha \)-(dimethylamino) ketones 86.31 After elimination of cyanide from 84, the iminium ion loses a proton to form the enamine, which tautomerizes to the thermodynamically more stable product 86 (Scheme 11, bottom).

In contrast to the considerable number of reports on the diastereoselective aldolizations of metallated allylacetonitriles,95–98 the respective chemistry of aminonitriles has not been investigated in great detail.85,90 The 1,2-addition of lithiated (dialkylamino)acetonitriles to aliphatic aldehydes shows a strong dependence on the substituents at nitrogen with regard to the diastereoselectivity.100 While (dibenzylamino)acetonitrile (87) gave good \( \text{anti/syn} \) ratios only in combination with pivalaldehyde, the more bulky tert-buty1 benzyl derivative 89 produced high selectivities with both unhindered and hindered aliphatic as well as aromatic aldehydes (Scheme 12). Unfortunately, the addition to \( \alpha \)-chiral aldehydes was not accompanied by a pronounced facial selectivity.

Depending on the reaction conditions, aminoacetonitriles can also be condensed with carbonyl compounds to form \( \alpha,\beta \)-unsaturated \( \alpha \)-aminonitriles 92 which can be hydrolyzed with aqueous acid to yield carboxylic acids.93 This sequence can be employed for the homologation of aro-
matic aldehydes but its application to aliphatic aldehydes failed.\textsuperscript{101} The latter substrates were, however, brought to reaction in a one-pot sequence involving the trimethylsilylated aminonitrile generated in situ (Scheme 13), which also permitted the homologation of benzophenone.\textsuperscript{102}

Scheme 13 Takahashi’s carbonyl homologations

6 Acylations

As already mentioned, acylation of deprotonated aminonitriles can occur at the \(\alpha\)-carbon as well as at the terminal nitrogen atom. According to an early observation by Boekelheide, deprotonated Reissert compounds may undergo 1,2-acyl migration to furnish the 1-substituted isoquinolines after concomitant elimination of cyanide.\textsuperscript{44} It is unclear whether this reaction proceeds strictly in an intramolecular fashion.

A Dieckmann-type cyclization of aminonitrile ester 98 has been described by Uchibayashi\textsuperscript{103} as well as by Blake et al.\textsuperscript{104} (Scheme 14). Remarkably, attack of the ester enolate at the nitrile carbon has been observed for 98, if the deprotonation was carried out under equilibrating conditions with ethanolic sodium ethanolate as the base. Therefore, 99 is not the thermodynamic reaction product in spite of its CH-acidity.

Scheme 14 Acyl migration and Dieckmann condensation

The first intermolecular C-acylation of a deprotonated aminonitrile was reported by Hauser and co-workers who treated the sodium salt of (dimethylamino)acetonitrile (100) with methyl benzoates to obtain the aroyl-substituted products 101 in 45–65% yield (Scheme 15, top).\textsuperscript{105} The same reaction can be adopted for the preparation of \(\alpha\)-ke-

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Deprotonated \(a\)-Aminonitriles

**Scheme 15** Intermolecular C-acylations of deprotonated \(a\)-aminonitriles

Toamides 106 if the anions of the primary acylation products are oxidized with sodium hypochlorite (Scheme 15, middle).\(^{106}\) This process presumably involves the elimination of HCN from the \(a\)-hydroxylated acylaminonitrile, a cyanohydrin.

Recent work by Mangeney, Vrancken and co-workers demonstrates that the reduction of acylaminonitriles with sodium borohydride in the presence of magnesium bromide proceeds with high diastereoselectivity to afford syn-\(\beta\)-hydroxy-\(a\)-aminonitriles 107 in moderate to high overall yield (Scheme 15, bottom).\(^{107}\)

**7 1,4-Additions**

Probably the earliest report on the \(\alpha\)-substitution of a deprotonated N,N-disubstituted \(a\)-aminonitrile involving a vinylogous addition is the synthesis of 1-skatylisoquinoline (110) by Boekelheide and Ainsworth.\(^{45}\) The Reissert compound 96 and gramine (108) reacted in boiling xylene in the presence of a small piece of metallic sodium. Under evolution of dimethylamine, the substitution product 109 was formed in 46\% yield. This reaction presumably proceeds via the intermediate formation of the electrophilic 3-methyleneindolenine (111), which then reacts with the anion of 96. Hydrolytic removal of the benzyl group under basic conditions and concomitant elimination of cyanide furnished 110 in quantitative yield (Scheme 16, top). 1,4-Additons of deprotonated Reissert compounds to acrylonitrile are followed by ring closure to pyrroloisoquinolines due to nucleophile attack of the resulting carbon on the amide carbon.\(^{108}\) Surprisingly, it is not the nitrile but instead the corresponding amide that is obtained as the the final product (Scheme 16, bottom).\(^{109}\)

The addition of deprotonated \(N\)-acyl-\(a\)-aminonitriles (open-chain Reissert compounds) of type 114 to vinyltriphenylphosphonium bromide provides a direct and efficient access to 1,2,5-trisubstituted pyrroles as demonstrated by Cooney and McEwen. The phosphonium ylide formed upon vinylogous addition undergoes an intramolecular Wittig reaction with the amide carbonyl under closure of the five-membered ring (Scheme 17).\(^{110,111}\)

**Scheme 16** Vinylogous additions of metallated Reissert compounds

Whereas the former reactions do not suffer from the risk of a competing 1,2-addition, the regioselectivity may be an issue for reactions of aminoketeneimines with enones, \(\alpha,\beta\)-unsaturated aldehydes or even unsaturated esters. The substituents on the aminonitrile are often crucial for determining the regioselectivity, but solvents and counterions are also known to play an important role. Aromatic substituents bound to nitrogen or the \(\alpha\)-center of a deprotonated aminonitrile lead to a more stabilized...
carbanion and increase its tendency towards vinylogous addition.\textsuperscript{112,113} For instance, Ahlbrecht and Kompter observed that the lithium salts of Strecker products derived from N-methylaniline and aliphatic aldehydes underwent clean 1,4-additions to cyclic enones and vinyl ketone when hexamethylphosphoramide was added to the reaction medium and the electrophiles were activated by complexation with lithium bromide.\textsuperscript{114} If no further precautions were taken, the same combination of reactants resulted in 50–60% deprotonation of the electrophile by the lithium keteneiminate. Acid hydrolysis of the addition products furnished 1,4-dicarbonyl compounds 121 in moderate to high yield.\textsuperscript{115} As an alternative to the classical generation of the nucleophiles by deprotonation, the authors used the Michael addition of lithium organyls to the α,β-unsaturated aminonitrile 118 (Scheme 18).\textsuperscript{116}

\[ \text{RCN} + \text{R}^2\text{Li} \rightarrow \text{RCN} \cdot \text{R}^2\text{Li} \]

\[ \text{RCN} \cdot \text{R}^2\text{Li} + \text{RX} \rightarrow \text{RCN} \cdot \text{R}^2\text{X} \]

\[ \text{RCN} \cdot \text{R}^2\text{X} \rightarrow \text{RCN} \cdot \text{R}^2\text{H} + \text{X} \]

\[ \text{RCN} \cdot \text{R}^2\text{H} + \text{H}^+ \rightarrow \text{RCN} + \text{R}^2\text{H}^+ \]

\[ \text{RCN} + \text{H}^+ \rightarrow \text{RC} = \text{C} + \text{N}_2 \]

\[ \text{RC} = \text{C} + \text{N}_2 + \text{R}^2\text{H} \]

\[ \text{RC} = \text{C} + \text{N}_2 + \text{R}^2\text{H} + \text{X} \]

\[ \text{RC} = \text{C} + \text{N}_2 + \text{R}^2\text{H} + \text{X} + \text{H}^+ \]

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\[ \text{RC} = \text{C} + \text{N}_2 + \text{R}^2\text{H} + \text{X} + \text{H}^+ + \text{H}_2 \]

\[ \text{RC} = \text{C} + \text{N}_2 + \text{R}^2\text{H} + \text{X} + \text{H}^+ + \text{H}_2 \]

**Scheme 18** Synthesis of 1,4-dicarbonyl compounds

Wakamatsu et al. studied the influence of the reaction temperature on the regioselectivity of the addition of the lithiated (2,6-dimethylpiperidin-1-yl)acetonitrile (122) to cyclohexenone.\textsuperscript{117} While at −78 °C the 1,2-adduct was predominantly formed, warming to ambient temperature resulted in a preponderant formation of the 1,4-adduct due to the reversibility of the 1,2-addition. The best 1,4-selectivity (97:3) was observed when a higher reaction temperature on the regioselectivity of the addition of the lithiated (2,6-dimethylpiperidin-1-yl)acetonitrile (117) to cyclohexenone.

\[ \text{R}^1\text{Me} \text{C} = \text{N} + \text{LiHMPA} \rightarrow \text{R}^1\text{Me} \text{C} = \text{N} \cdot \text{LiHMPA} \]

\[ \text{R}^1\text{Me} \text{C} = \text{N} \cdot \text{LiHMPA} + \text{RX} \rightarrow \text{R}^1\text{Me} \text{C} = \text{N} \cdot \text{R}^2\text{X} \]

\[ \text{R}^1\text{Me} \text{C} = \text{N} \cdot \text{R}^2\text{X} \rightarrow \text{R}^1\text{Me} \text{C} = \text{N} \cdot \text{R}^2\text{H} + \text{X} \]

\[ \text{R}^1\text{Me} \text{C} = \text{N} \cdot \text{R}^2\text{H} + \text{H}^+ \rightarrow \text{R}^1\text{Me} \text{C} = \text{N} + \text{R}^2\text{H}^+ \]

\[ \text{R}^1\text{Me} \text{C} = \text{N} + \text{H}^+ \rightarrow \text{R}^1\text{Me} \text{C} = \text{N} + \text{H}_2 \]

\[ \text{R}^1\text{Me} \text{C} = \text{N} + \text{H}_2 \]

**Scheme 19** Regioselectivity of the addition to cyclohexenone

Trapping of the enolates generated in 1,4-additions of deprotonated aminonitriles to various electrophiles has been described.\textsuperscript{122} Wartski, Posner, and Nierlich have combined this reaction with an iminium ion allylsilane cyclization to a [1+2+3]-annulation sequence.\textsuperscript{123} [2-(Iodomethyl)-2-propenyl]trimethylsilane served as the bifunctional electrophile and silver-induced decyanation of the intermediate 130 gave the bicyclic product 131 in 33% overall yield as a single diastereomer of unknown relative configuration at the newly formed benzyl quaternary stereocenter (Scheme 21). The allylsilane moiety turned out to be crucial for the cyclization since the unsubstituted methallyl residue was not attacked.\textsuperscript{124}

8 Reactions of Unsaturated α-Aminonitriles

β,γ-Unsaturated α-dialkylaminonitriles form ambident anions which can react with electrophiles in either the α- or the γ-position. As for the addition of simple deprotonated α-aminonitriles to α,β-unsaturated carbonyl compounds, the regioselectivity depends on the electrophile, on the substitution of the nitrile, and on the reaction conditions. While the morpholino derivative 132 is predominantly alkylated in the α-position, the lithium salt of the sterically

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more demanding cyclohexyl derivative 134 reacts exclusively in the less hindered γ-position (Scheme 22, top). For the reaction of the aminonitriles 136 with cyclic ketones, the α-addition to form 137 is kinetically controlled, while the γ-addition product 138 is obtained under thermodynamic reaction conditions. Congruously, the former can be converted into the latter upon treatment with lithium diisopropylamide (Scheme 22, bottom). Thus, substrates 136 permit an easy switch between acyl anion and homoenolate reactivity. The addition of zinc chloride inhibits the undesired aldolization of the ketone and increases the overall yield. Acid hydrolysis of the γ-addition products leads to spirolactones 139 in moderate to good yield. These compounds can in turn be converted into the annulated cyclopentenones 140 upon treatment with polyphosphoric acid or phosphorus pentoxide and methanesulfonic acid.

Pierre and Enders described the α-selective 1,2-addition of the lithium salts of aminonitriles 141 to various aldehydes. The resulting aminonitriles 142 were transformed into α-hydroxyenones 143 upon treatment with aqueous silver nitrate (Scheme 23, top). An earlier report by Fang on both 1,2-additions and alkylations of the di-lithium salt of aminonitrile 144 derived from ephedrine indicated exclusive reaction in the γ-position (Scheme 23, bottom). The stereochemical control over the γ-center is moderate and little influence can be imposed on the configuration of the carbinol center.

Grierson, Husson and co-workers utilized 1,2,5,6-tetrahydropyridine-2-carbonitriles of type 149 for the preparation of several mono- or polycyclic alkaloids containing the piperidine ring. The starting materials were readily prepared from pyridinium salts like 146 by means of partial reduction to the corresponding 1,2,5,6-tetrahydropyridine, N-oxidation, regioselective Potier-Polonovski rearrangement to the 1-substituted 5,6-di-hydropyridinium ion, and, finally, addition of cyanide. In the case of compound 149, the overall yield amounted to 35%. Deprotonation with lithium diisopropylamide and α-alkylation furnished 150 (97%), which was then subjected to a Bruylants reaction with phenyl magnesium chloride, followed by Grewe cyclization to the benzomorphant derivative 152 (Scheme 24). In contrast to the classical addition of a benzylic Grignard reagent to the pyridinium salt, this technique permits the facile introduction of an angular substituent.
9 Other Reactions

Arnott et al. studied the spirocyclization of deprotonated aminonitriles onto N-alkoxy carbonylpyridinium ions to furnish diazaspiron[5.3]nonanes of type 154.140 Isonicotinamides 153 were lithiated with lithium disopropylamide and then N-acylated with methyl chloroformate to deliver the products in moderate yield (Scheme 25, top). An NMR study on a closely related glycine derivative proved that even with this order of addition of the reagents, spirocyclization does not take place unless the pyridine has been N-acylated. While high stereoselectivities have been observed with N-linked benzylic auxiliaries in the glycine ester series, the extension of the asymmetric variant to glycine nitriles has not been reported. Under identical conditions, the isomeric nicotinamides 155 gave the aza-isoindolinones 156 in moderate yield (Scheme 25, bottom).

Couty et al. have developed a cyclopropanation reaction of Michael acceptors based on cyanide-stabilized azetidinium ylides like 160.141 The N-substituted azetidine-2-carbonitrile 158 was prepared by the intramolecular alkylation methodology described in section 3. Quaternization with methyl triflate yielded the azetidinium triflate 159, which reacted with Michael acceptors in the presence of lithium hexamethyldisilazide to give cyclopropane carbonitriles 162 in moderate to high yield. After α-deprotonation, vinylogous addition to the α,β-unsaturated carbonyl compound produced the enolate, which opened the azetidinium ring under formation of the aminothethyl cyclopropanes 162 (Scheme 26). Since free rotation about the α,β-bond in the enolate can occur, it is not surprising that diethyl maleate furnished the same product, albeit in significantly lower yield. As expected for ammonium ylides, compound 160 reacts with aldehydes under formation of epoxides.142

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Aryl and hetaryl halides susceptible to nucleophilic aromatic substitution by means of an addition–elimination sequence may be subjected to nucleophilic acylations with deprotonated Strecker products. Albright and Moran used their rugged lithiated (morpholin-4-yl)arylacetonitriles, which often give superior results compared to dialkylamino substituted nucleophiles, to effect halide substitution on 1-benzyl-5-bromo-2-methyl-4-nitroimidazole. The primary products were subsequently converted into the corresponding aryl ketones by treatment with copper sulfate pentahydrate (Scheme 28, top). The same type of nucleophile permitted the conversion of 4-fluoronitrobenzene into 3-methoxy-4-nitrobenzophenone (Scheme 28, bottom).

Although heterocumulenes are highly reactive electrophiles, only a few publications have addressed their reactions with deprotonated aminonitriles. Notable exceptions are reactions involving isocyanates and isothiocyanates. While chloroformate-derived Reissert compounds of isoquinolines furnish addition products that cyclize to imidazo[5,1-a]isoquinolines of type, their cyclization to imidazo[5,1-a]phthalazines can be effected by heating, albeit in low yield (Scheme 29).

Among the further reactions involving deprotonated aminonitriles are [2,3]-sigmatropic rearrangements of nitrene-stabilized ammonium ylides, Thorpe–Ziegler cyclizations, additions to arynes, and trichloromethylations. A more exotic example is the preparation of azines by reaction of lithiated aminonitriles with sulfonfonylhydrazones reported by Takahashi and co-workers.

10 Deprotonation of N-Monosubstituted and N-Unsubstituted α-Aminonitriles

Despite the fact that N-monosubstituted and N-unsubstituted α-aminonitriles are susceptible to the base-induced elimination of HCN, that is, the retro-Strecker reaction, the first reported reaction involving deprotonated aminonitriles is the von Miller–Plöchl reaction published as early as 1898. In the presence of ethanolic potassium hydroxide, a-phenyl toluidinoacetonitrile reacts with cinnamaldehyde to form a trisubstituted pyrrole. Although the authors mistakenly identified the product as the 1,2,5-trisubstituted isomer, their error was corrected by Bodforss, who recognized the 1,2,3-trisubstitution of the resulting pyrrole.

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the impending retro-Strecker reaction under thermodynamic deprotonation conditions.

For a long time, the von Miller–Plöchl reaction and the closely related vinylogous addition to \(\alpha,\beta\)-unsaturated esters remained the only transformations involving deprotonated \(\alpha\)-monosubstituted \(\alpha\)-aminonitriles. Recent investigations on this topic have been carried out by the Opatz group. Using potassium hexamethyldisilazide in tetrahydrofuran at low temperatures, Strecker products derived from aromatic aldehydes and primary amines or ammonia could be deprotonated and the resulting potassium keteniminates were subjected to alkylations, 1,2-additions, and 1,4-additions. Upon reaction with \(\alpha,\beta\)-unsaturated ketones and aldehydes, 2-cyano-5-hydroxy-pyrrolidines result from cyclization of the primary addition products. These compounds are thermally unstable and decompose under formation of pyrroles according to the mechanism proposed by Treibs and Derra for the von Miller–Plöchl synthesis. Twofold reduction of these double iminium ion equivalents with sodium cyanoborohydride furnishes pyrrolidines (Scheme 31).

If \(\alpha,\beta\)-unsaturated esters are used as the electrophiles, \(\gamma\)-amino acid esters can be obtained after reductive decyanation of the primary addition products. An intramolecular 1,4-addition can be employed for the preparation of indoles from 2-aminocinnamic acid esters and amides. Their Strecker reaction with aromatic or \(\alpha,\beta\)-unsaturated aldehydes produces aminonitriles of type, which cyclize in up to quantitative yield even under thermodynamic deprotonation conditions to furnish indole-3-acetic acid derivatives like (Scheme 32).

Aminonitrile, available in three steps from homoveratrylamine, can be deprotonated and \(\alpha\)-alkylated with 3,4-dimethoxybenzyl bromide. The substitution product spontaneously eliminates HCN, yielding the 3,4-dihydroisoquinoline, which can be subjected to an asymmetric transfer hydrogenation with Noyori’s catalyst to furnish \((R,R)\)-norlaudanosine in 93% ee and 78% yield over three steps (Scheme 33). Various isoquinoline alkaloids, as well as the pyrroloisoquinoline lamellarin U, have been prepared accordingly.

1,2-Addition of the potassium keteniminates to aldehydes and imines and subsequent reduction in a one-pot reaction sequence furnishes trisubstituted amino alcohols and tetrasubstituted 1,2-diamines, respectively. Ad-

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**Scheme 30** The von Miller–Plöchl pyrrole synthesis

**Scheme 31** Pyrroles and pyrrolidines from \(\alpha\)-monosubstituted aminonitriles

**Scheme 32** Cyclization to indoles

**Scheme 33** Catalytic asymmetric synthesis of tetrahydroisoquinolines
dation to imines followed by aerobic oxidation of the intermediate enediamines yields 1,2-diimines 197, which can be cyclized to tetrasubstituted imidazolium salts 198. The latter are suitable as carbene precursors or can be reduced to 1,2-diamines with high diastereoselectivity.180,181 If the more reactive N-acylimines 200 are used as the electrophiles, the addition proceeds rapidly, even at −78 °C. Elimination of HCN from the reaction products with 1,8-diazabicyclo[5.4.0]undec-7-ene in hot toluene furnishes the α-amidoiminoes 202, which can be cyclized to tetrasubstituted imidazoles 203 with phosphorus pentachloride. Acid hydrolysis of imines 202 yields the corresponding α-amido ketones 204, the cyclization of which results in trisubstituted oxazoles 205 (Scheme 34).182

11 Deprotonated α-Aminonitriles in Asymmetric Synthesis

Considering their versatility in carbon–carbon-bond formations, the development of asymmetric reactions involving deprotonated α-aminonitriles is almost imperative.183,184 Husson and Royer have applied the homochiral bicyclic aminonitriles 206 and 207 for the stereoselective preparation of a variety of substituted piperidines, pyrrolidines and their bi- and tricyclic derivatives (Scheme 35).185–206 The starting materials are readily available from phenylglycinol and the corresponding α,α-dialdehyde. High diastereoselectivity was achieved in α-alkylations, reductions and Bruylants reactions. Moreover, the aminal moiety could be used as an iminium ion equivalent. The benzylc stereodirecting substituent at nitrogen can ultimately be removed by hydrogenolysis. As an example of this powerful methodology, the synthesis of two tetraponersins, members of a series of ant venoms, is discussed here. Starting with the diastereoselective α-alkylation of the aminonitrile moiety, the oxazolidine ring is reductively opened and the auxiliary is removed by catalytic hydrogenation. The single stereogenic center in 209 then controls the formation of both the N,N-acetal and the α-aminonitrile. Another deprotonation–alkylation sequence in combination with the reductive removal of the nitrile function by sodium in liquid ammonia gave T-8, while its diastereomer T-7 was obtained by Bruylants reaction of 210 with α-pentylmagnesium bromide (Scheme 36).207

The synthesis of the tropane alkaloid ferruginine (215), an agonist of the nicotinic acetylcholine receptor that was isolated from the bark of the arboreal species Darlingiana ferruginea, was achieved starting from 207.208 In contrast to 206, its higher homologue, this material is conveniently prepared and used as an inconsequential epimetric mixture. Deprotonation, alkylation with bromoacetaldehyde

Scheme 34 1,2-Additions of N-monosubstituted aminonitriles by Opatz and co-workers

Scheme 35 Asymmetric synthesis of alkaloids using Husson’s CN(R,5)-method
diethyl acetal and reductive removal of the cyano group with lithium in liquid ammonia furnishes 212, which is converted into enone 213 upon aciolytic cleavage of the O,O-acetal and Horner reaction with dimethyl 2-oxopropylphosphonate. Under acidic conditions, the iminium ion generated by opening of the oxazolidine ring attacks the α-position of the enone. In a concomitant and completely stereoselective addition of methanol to the β-position, the tropinone ring system is formed. The methoxy group is eliminated to restore the enone after the auxiliary has been replaced by a methyl group in a reductive methylation (Scheme 37).

A slightly more complex but only monofunctional N-auxiliary was developed by Enders, who employed lithiated α-aminonitriles derived from (S,S)-2,2-dimethyl-5-N-methylamino-4-phenyl-1,3-dioxane as chiral acyl anion equivalents (Scheme 38).209–212 The auxiliary is the N-methyl derivative of the amine used by Weinges for the preparation of chiral α-amino acids in an asymmetric Strecker reaction.8,213 The latter compound is formed as a side product in an industrial synthesis of the antibiotic chloramphenicol. Outstandingly high enantio- and diastereoselectivities have been achieved in vinylogous additions yielding 1,4 dicarbonyl compounds after elimination of HCN from the primary addition products and hydrolysis of the resulting ketimines. This procedure not only circumvents the destructive removal of the auxiliary by periodate cleavage but even permits its recycling.

In their synthesis of the lignans (+)-hinokinin and cubebin dimethyl ether, Enders and Milovanovic used the vinylogous addition of the Strecker product obtained from auxiliary 217 and piperonal to 5H-furan-2-one for the installation of the first asymmetric center.214,215 The product was obtained in >98% diastereomeric excess and was subsequently α-alkylated with piperonal bromide to furnish the trans-configured 2,3-disubstituted butanolid 220, again in high diastereoselectivity.216 Removal of the chiral auxiliary under formation of the aryl ketone with aqueous silver nitrate and reductive removal of the carbonyl group in a reduction–hydrogenation sequence yielded (+)-hinokinin (222), which could be converted into (S,S)-
Auxiliary-controlled synthesis of lignans. Several other lignans have been prepared using this strategy.\textsuperscript{217–219}

Along the same lines, the Enders group has developed an asymmetric nucleophilic glyoxylation by means of the vinyllogous addition of a chiral 2-amino cyanoacetate to nitroolefins.\textsuperscript{220} The starting material \textsuperscript{224} was prepared by \textsuperscript{N}-alkylation of auxiliary \textsuperscript{217} with chloroacetoniitrile, \textalpha-deprotonation and acylation of the keteneiminate with di-tetrt-butyl dicarbonate. Reaction of the potassium salt of \textsuperscript{224} with nitroalkenes furnished the Michael adducts \textsuperscript{225} in high diastereoselectivity, which could be further improved by a chromatographic separation. Again, the auxiliary was removed by aqueous silver nitrate to give the \textalpha-keto-\gamma-nitro esters \textsuperscript{226} in high yield and with 91–98\% enantiomeric excess (Scheme 40, top).

A related organocatalytic asymmetric nucleophilic glyoxylation of \textalpha,\beta-unsaturated aldehydes with cyanoacetate \textsuperscript{227} was described by the same authors.\textsuperscript{222} Through iminium catalysis, the proline-derived organocatalyst \textsuperscript{228} directed the attack of the anion of \textsuperscript{227} to the electrophile, resulting in 83–87\% enantiomeric excess or 49–88\% diastereomeric excess for the camphanoyl-substituted products \textsuperscript{231}, respectively (Scheme 40, bottom).

Asymmetric 1,2-additions of metallated \textalpha-aminonitriles controlled by auxiliaries derived from (S)-proline have been used for the preparation of chiral \textalpha-hydroxy ketones with up to 97\% ee.\textsuperscript{223} In their asymmetric synthesis of the alkaloid (S)-(+)−coniine (\textsuperscript{238}), Hurvois and co-workers used an electrochemical oxidation\textsuperscript{223} to convert piperidine \textsuperscript{233} into aminonitrile \textsuperscript{234}.\textsuperscript{224} Subsequent lithiation and alkylation with propyl iodide furnished \textsuperscript{235} as a 9:1 mixture of diastereomers. The chiral benzyllic auxiliary permitted control of the following hydride reduction, furnishing the diastereomeric amines \textsuperscript{236} and \textsuperscript{237} in 8\% and 72\% isolated yield, respectively. After chromatographic separation, the auxiliary was removed from \textsuperscript{237} by catalytic hydrogenation to give the target compound. Overall, this efficient procedure allowed the synthesis of (+)-coniine from commercially available (S)-1-phenylethylamine in five steps and 35\% yield (Scheme 41). Similar cyanation–alkylation sequences have been employed by the same authors for the preparation of various cyclic alkaloids.\textsuperscript{225,226}
12 Conclusions

In summary, deprotonated α-aminonitriles have proven to be versatile building blocks that have been widely applied as synthetic equivalents for acyl anions and α-aminocarbanions. Although the nitrile group has been replaced by other acidifying substituents such as the benzotriazolyl moiety,227–231 its unparalleled anion-stabilizing capacity, combined with the convenient and economical preparation of α-aminonitriles, strengthens their role as attractive intermediates in the synthesis of a large variety of heterofunctionalized compounds. The minimal steric hindrance imposed by the rod-like cyano substituent and the high degree of stereofacial control exerted by some chiral auxiliaries permits the efficient preparation of stericly encumbered and enantiomerically pure products, respectively. The described advantages are likely to more than outweigh the manageable risk associated with the use of the toxic cyanide.

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