# Structure and Reactivity of Lithiated α-Amino Nitriles

**Dieter Enders*[a], Jochen Kirchhoff[a], Peter Gerdes[a], Dietrich Mannes[a], Gerhard Raabe[a], Jan Runsink[a], Gernot Boche[b], Michael Marsch[b], Hubertus Ahlbrecht[c], and Horst Sommer[c]**

Institut für Organische Chemie, Rheinisch-Westfälische Technische Hochschule[a],
Professor-Pirlet-Straße 1, D-52074 Aachen, Germany
Fax: (internat.) + 49(0)241/8888127
E-mail: Enders@RWTH-Aachen.de

Fachbereich Chemie, Philipps Universität[b],
Hans-Meerwein-Str., D-35032 Marburg, Germany
Fax: (internat.) + 49(0)6421/288917
E-mail: Boche@ps1515.chemie.uni-marburg.de

Institut für Organische Chemie, Justus Liebig Universität[c],
Heinrich-Buff-Ring 58, D-35392 Gießen, Germany
Fax: (internat.) + 49(0)641/9934309
E-mail: Hubertus.Ahlbrecht@org.chemie.uni-giessen.de

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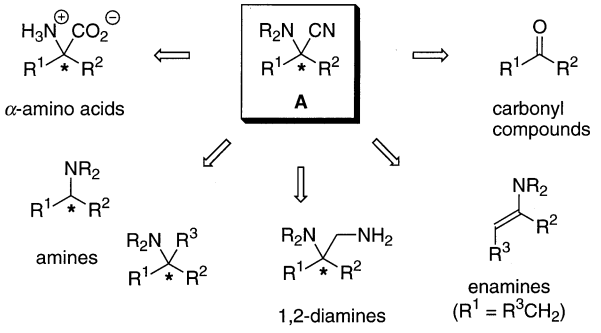
Investigations aimed at elucidating the structure of lithiated α-amino nitriles **B** have led to the identification of *N*-lithio α-amino nitrile anions as characteristic structural features. Their preparations, crystal structures, and solution structures under the reaction conditions, are described. X-ray crystal structure analyses of crystalline **3** and (*S,S*)-**4** reveal the presence of dimeric aggregates **B4** with $C_i$ symmetry, held together by four-membered NLiNLi rings, coordinatively saturated at lithium by four THF ligands. The crystal structure of (*S,S*)-**6** shows polymeric aggregation with dimeric subunits similar to those of **3** and (*S,S*)-**4**. The solution structure has been investigated by IR and Raman spectroscopy of **2**, (*S,S*)-**4** and (*S,S*)-**6**, by NMR spectroscopy of **3**, (*S,S*)-**5** and (*S,S*)-**6**, and by cryoscopic measurements of (*S,S*)-**6** in THF. Trapping experiments complement the results. In THF, which constitutes the principal reaction medium, the lithiated amino nitriles **B** are found to exist as monomeric species **B6** between −110 and +25°C. In less polar solvents, higher aggregation is presumed. NMR spectroscopic studies of **3** show that the favored orientations of the amine and phenyl groups are similar to their conformations in the solid state. In the light of the results obtained, a transition state is proposed to account for the relative topicity observed in the 1,4-additions of enantiopure lithiated α-amino nitriles (*S,S*)-**4**, (*S,S*)-**5**, and (*S,S*)-**6** to Michael acceptors.

## Introduction

Due to their broad range of synthetic applications, α-amino nitriles **A** play an important role in organic chemistry[1]. The presence of an amino- and a nitrile group, and thus a latent carbonyl function, offers synthetic approaches to a variety of different classes of compounds (Scheme 1), including natural products and bioactive compounds. For historical reasons, nearly 150 years after the introduction of the Strecker reaction[2], syntheses of α-amino acids should be mentioned in this context. Thus, hydrolysis of enantiomerically pure[3], or enantioselective hydrolysis of racemic α-amino nitriles[4], leads to enantiomerically pure α-amino acids. Moreover, amines can easily be obtained by hydride or carbanion substitution of the cyanide function employing sodium borohydride reduction[5] or the Bruylants reaction conditions[6][7], respectively. In this manner, following the latter route, *tert*-butylation of amines is possible[8]. Reduction of α-amino nitriles with lithium aluminium hydride leads to 1,2-diamines[9], whereas upon heating of **A** ($R^1$ = $CH_2R^3$) enamines[10] or α-amino ketones[11] are formed by dehydrocyanation. Furthermore, various methods have been described for α-amino nitrile cleavage to give the corresponding carbonyl compounds[1][12], which normally represent the starting materials for the generation of **A** (see also the umpolung of aldehydes as described below).

Scheme 1. Synthetic applications of α-amino nitriles **A** in organic synthesis

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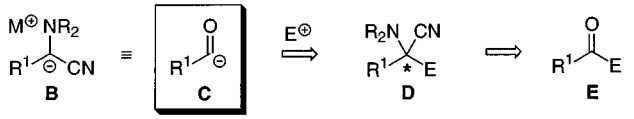
Besides this synthetic potential, the importance of α-amino nitriles as probable building blocks in the evolution of bioorganic molecules is worthy of a mention. Based on Miller's experiment aimed at imitating the atmospheric conditions on the prehistoric earth[13], Eschenmoser et al. discuss simple α-amino nitriles **A** as prebiotic precursors of porphyrins, corrins including vitamin $B_{12}$, nicotinic acids and even nucleotides[14].

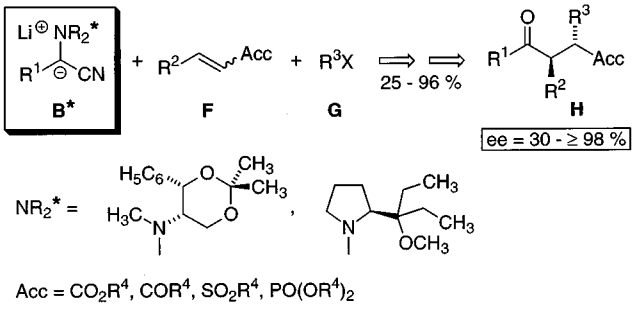
The extraordinary synthetic versatility stems from the use of metallated α-amino nitriles **B** as masked acyl anion equivalents **C** for the umpolung of carbonyl compounds to non-classical $d^1$-reactivity[15] (Scheme 2). Thus, by reactions with electrophilic reagents to form the adducts **D** followed by cleavage of the amino nitrile moiety to form the ketones **E**, many nucleophilic acylations have been accomplished[16].Using the appropriate electrophiles, alkylations, acylations, epoxide-, aldehyde-, and Michael additions have been successfully carried out[16].

Scheme 2. Lithiated α-amino nitriles **B** as acyl anion equivalents **C**



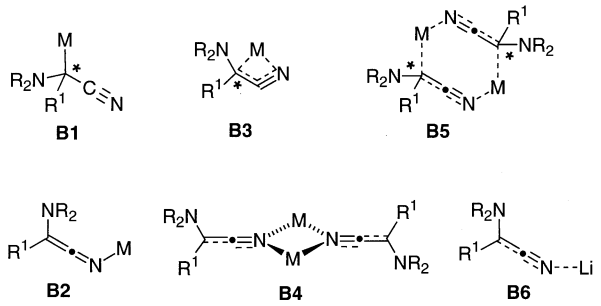
There has been great interest in asymmetric syntheses with lithiated α-amino nitriles **B***, containing enantiopure amine auxiliaries. Reactions with Michael acceptors **F** give substituted 4-oxo-esters, -ketones, -sulfones, and -phosphonates, usually in high yields, and with up to essentially complete asymmetric inductions[7][17][18][19] (Scheme 3). By trapping the intermediate lithiated adducts with electrophiles **G**, tandem Michael addition/α-alkylation or α-aldol reactions, respectively, have been successfully carried out[17c][17d]. Asymmetric 1,2-additions of **B*** to aldehydes, resulting in the enantioselective synthesis of α-hydroxyketones (*ee* = 10 to ≥ 97%), were among the first asymmetric nucleophilic acylation techniques to be developed in the early 1980s[7][16a][20][21].

Scheme 3. Enantioselective Michael additions with chiral α-amino nitriles **B***



In contrast to the many synthetic applications, little is known about the structure of metallated α-amino nitriles **B** and the mechanism of their nucleophilic attack on electrophiles. In principle, different structural types can be proposed, analogous to the situation with the related and previously reported nitrile-stabilized carbanions (Figure 1)[22]. In analogy to structural examinations of other organolithium compounds[23], two central issues need to be addressed: The position of the metal atom, and the degree of aggregation. *C*-metallated (**B1**), *N*-metallated (**B2**) or bridged monomers (**B3**), and *N*-metallated (**B4**) or mixed *C,N*-metallated dimers (**B5**) are the most realistic possible structural types. Unsolved questions relate to the preferred conformation of the amino group and the group $R^1$ (cf. structure determinations of lithiated aminobenzyl and benzyl compounds[24]) and to the distribution of the negative charge in the lithiated nitrile moiety. For example, **B6** represents the lithio ketene iminate structural form of **B2**.

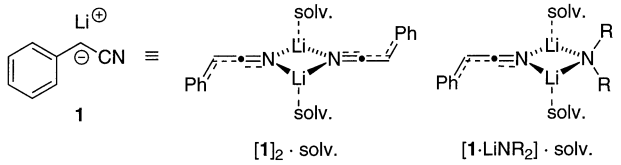
Figure 1. Possible structural types of lithiated α-amino nitriles **B**



Pertinent information concerning the crystal and solution structures of metallated nitriles can be gleaned from the extensive investigations on lithiated phenylacetonitrile **1** (Figure 2). In the solid state, **1** was found to exist as an *N*-lithiated α-cyano anion $[\mathbf{1}\cdot\text{tmeda}]_2\cdot C_6H_6$, stabilized by tetramethylethylenediamine as a ligand, and with co-crystallizing benzene[22b][25a]. This structural type was also detected in diethyl ether/toluene (1:2) by $^6$Li-/$^{15}$N-NMR spectroscopic methods[26], while in more polar solvents such as DMSO, THF, or THF/HMPA, *C*- or *N*-metallated monomers and solvent-separated ion pairs are postulated[27]. Using an excess of lithio amide base for the deprotonation of phenyl acetonitrile, the mixed aggregates [**1**·LDA·2 tmeda] in the crystal[28] and [**1**·LHMDS·2 tmeda] in toluene are formed[26].

We report here on the results of investigations into the structure and reactivity of lithiated α-amino nitriles.

Figure 2. Structures of lithiated phenylacetonitrile **1**

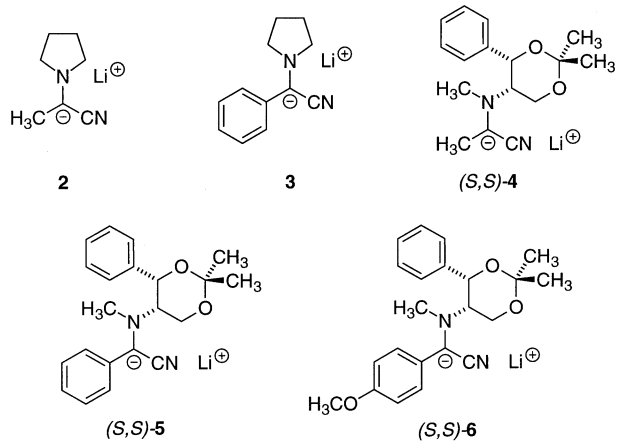


## Results and Discussion

Having successfully carried out nucleophilic asymmetric acylations[17][20], we wanted to understand in more detail the mechanism of the reaction of chiral, lithiated α-amino nitriles **B*** with electrophiles. Therefore, knowledge of their structure was essential. For this purpose, the lithiated α-amino nitriles **2**–**6** were examined (Figure 3). (*S,S*)-**4**, (*S,S*)-**5**, and (*S,S*)-**6** represent the hitherto most commonly used nucleophiles for asymmetric acylation, containing the sec-

ondary amine (*S,S*)-2,2-dimethyl-5-methylamino-4-phenyl-1,3-dioxane as chiral auxiliary[29]. For the simplification of analytical data, the pyrrolidine compounds **2** and **3** were also investigated.

Figure 3. Investigated lithiated α-amino nitriles **2**−**6**




**Crystal Structures**

From concentrated ethereal solutions, the aromatic lithiated compounds **3**, (*S,S*)-**5**, and (*S,S*)-**6** were crystallized and their structures were determined by X-ray crystal diffractometry at low temperature. In the solid state, **3** and (*S,S*)-**5**, crystallized from THF, were found to exist as dimeric *N*-lithiated α-cyano anions containing a four-membered $Li_2N_2$-ring as a bridging unit (Figures 4 and 5). This structural type is akin to that of $[\mathbf{1}\cdot\text{tmeda}]_2\cdot C_6H_6$[25]. The coordination sphere of each lithium atom is completed by two solvent ligands, so that $[\mathbf{3}\cdot 2\ \text{THF}]_2$ and $[(S,S)\text{-}\mathbf{5}\cdot 2\ \text{THF}]_2$ result as the smallest subunits. While $[\mathbf{3}\cdot 2\ \text{THF}]_2$ is $C_i$-symmetric with regard to the center of the $Li_2N_2$-square, $[(S,S)\text{-}\mathbf{5}\cdot 2\ \text{THF}]_2$ is dissymmetrically aggregated and therefore has only approximate $C_i$ symmetry. (*S,S*)-**6** was crystallized from diethyl ether. The polymeric crystal structure of $[(S,S)\text{-}\mathbf{6}\cdot OEt_2]$ contains dimeric *N*-lithiated α-cyano anion subunits, similar to those of $[\mathbf{3}\cdot 2\ \text{THF}]_2$ and $[(S,S)\text{-}\mathbf{5}\cdot 2\ \text{THF}]_2$. The polymeric aggregation results from the coordination of three anion units to each lithium, two *N*-connected via the α-cyano anion functionality and one *O*-connected via the *p*-methoxy group of the anisyl residue. One further ether molecule leads to tetracoordination at the lithium (Figure 6). The torsion of the α-cyano anion functionalities out of the $Li_2N_2$ plane in $[(S,S)\text{-}\mathbf{5}\cdot 2\ \text{THF}]_2$ and $[(S,S)\text{-}\mathbf{6}\cdot OEt_2]$, resulting in a slightly pyramidal configuration at the nitrogens, is reminiscent of that in the crystal structure of the dimeric triphenylphosphane/trihydroborane-substituted, *N*-lithiated α-cyano anion[30]. In all three crystal structures (Figures 4, 5, and 6), the same conformations of the aromatic and the amine groups are found. The aromatic ring systems are planar and the electron pair of the amino group is antiperiplanar to the linear *N*-lithiated α-cyano anion functionality. This favored conformation should allow optimal mesomeric phenyl stabilization of the negative charge and minimization of the repulsive destabilization by the lone pair of the amine.

Figure 4. Crystal structure of $[\mathbf{3}\cdot 2\ \text{THF}]_2$

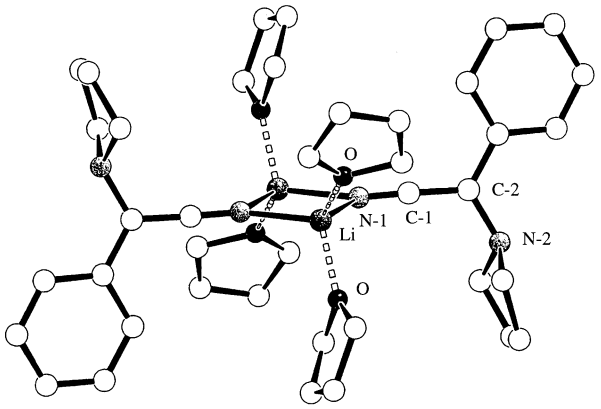



Figure 5. Crystal structure of $[\mathbf{5}\cdot 2\ \text{THF}]_2$

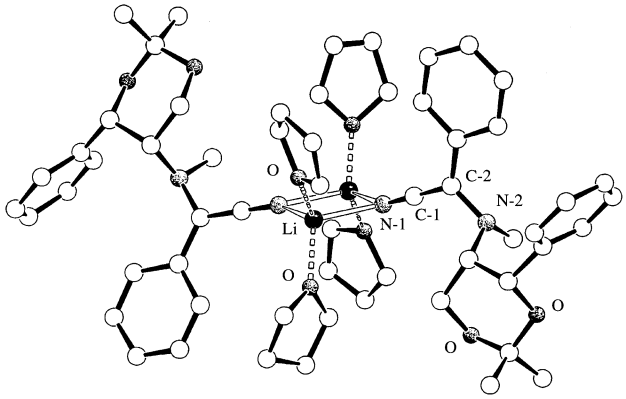
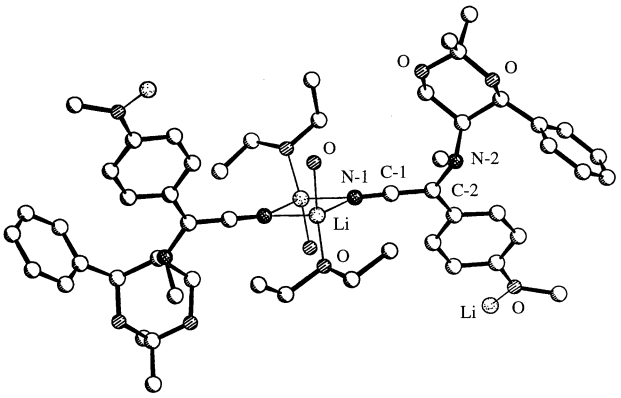


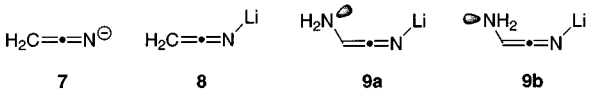

Figure 6. Crystal structure of $[\mathbf{6}\cdot OEt_2]$




The characteristic bond distances and angles in $[\mathbf{3}\cdot 2\ \text{THF}]_2$, $[(S,S)\text{-}\mathbf{5}\cdot 2\ \text{THF}]_2$, and $[(S,S)\text{-}\mathbf{6}\cdot OEt_2]_\infty$, are summarized in Table 1. Of primary interest is the α-cyano anion moiety, which is almost linear (177−179°). Quantum-chemical calculations[22a][31] on model compounds of the α-cyano "anions" **7**, **8**, and **9** (Figure 7, Table 1) reveal a partial double-bond character of the C−C bond (136−138 pm) and a slight triple-bond character of the C−N bond (117−120 pm). For this reason, a structure of type **B6** (Figure 1) better illustrates the delocalization of the negative

charge along the lithio ketene iminate moiety than the localized structure **B2**. In fact, the $C^1C^2$ bond distances (136−138 pm) and the $C^1N^1$ bond distances (116.9−119.6 pm) of the lithiated α-amino nitriles given in Table 1 indicate that they are almost exactly intermediate between the relevant standard values ($C^1C^2$ single bond: 144 pm, $C^1C^2$ double bond: 133 pm; $C^1N^1$ triple bond: 113 pm, $C^1N^1$ double bond: 124 pm). Thus, these structures are in accordance with those of the lithiated nitriles described previously[22][25][26][27][28].

Figure 7. Model compounds **7**−**9** for quantum-chemical calculations




X-ray structure analyses of the non-lithiated amino nitrile (*S,S,S*)-**6-H** and of the amino nitrile−methyl crotonate adduct (*S,S,R,R*)-**10** were also performed (Figure 8). (*S,S,S*)-**6-H** was formed from *p*-methoxybenzaldehyde, the enantiopure amine auxiliary[29] and potassium cyanide in water[17c]. The crude product **6-H** was found to exist as a 2:1 epimeric mixture of the (*R*)- and (*S*)-configured amino nitrile. Crystallization from ethanol yielded predominantly the (*S*)-epimer (91%, *de* = 88% or, depending on the crystallization conditions, 78%, *de* ≥98%). According to the literature, the equilibration at the amino nitrile center proceeds by a second-order asymmetric transformation via an immonium cyanide intermediate[3][32]. For further asymmetric transformations, both epimers could be used since the chirality information at the amino nitrile center is lost upon deprotonation (see below). Reaction of (*S,S*)-**6** with (*E*)-methyl crotonate at −78°C proceeded with 90% diastereoselectivity and furnished enantiomerically pure (*S,S,R,R*)-**10** in 52% yield after crystallization from diethyl ether[7][17a]. The (*R*)-configurations of the newly generated stereogenic centers, the amino nitrile (C-2) and the β-ester carbons (C-23), are based on the known absolute configuration of the chiral auxiliary. The crystal structure determinations of the amino nitrile adducts of (*S,S*)-**6** with cyclohex-2-enone[17b][17c] and with 5,6-dihydropyran-2-one[17e] have been described previously.

Figure 8. Crystal structures of (*S,S,S*)-**6-H** and (*S,S,R,R*)-**10**

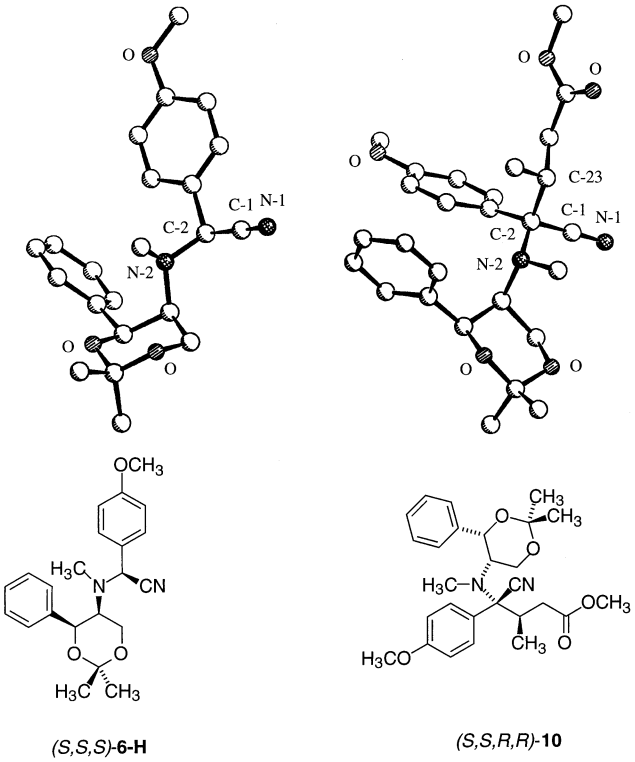



Table 1. Characteristic bond distances and angles of the lithiated nitriles **1**[25][28], **3**, **5**, and **6** determined by X-ray structure analysis, and of **7**−**9**[22a][31] derived from ab initio calculations. Quantum-chemical calculations of **7** and [**8**·2 $H_2O$]$_2$ were carried out at the MP2/6-31+G*//HF/6-31+G* level, and those of **8**, [**8**]$_2$, **9a**, and **9b** at the MP2/6-31G*//HF/6-31G* level

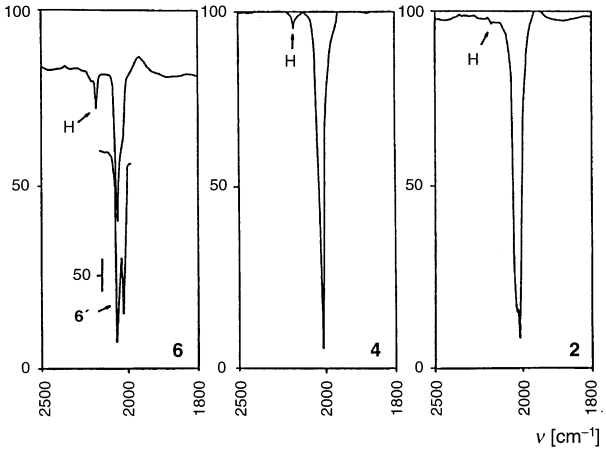
| compound | bond distances [pm] $C^1C^2$ | $C^1N^1$ | $N^1Li$ | bond angles [°] $C^2C^1N^1$ | $LiN^1Li'$ | $N^1LiN^{1'}$ |
|---|---|---|---|---|---|---|
| [**1**·tmeda]$_2$·$C_6H_6$[25] | 138 | 115 | 204 | 178.4 | 80.9 | 98.2 |
| [**1**·LDA·2 tmeda][28] | 138.3 | 117.3 | 207.5 | 179.5 | 80.0 | 99.2 |
| | | | 210.9 | | 82.7 | 98.1 |
| [**3**·2 THF]$_2$ | 136.7 | 116.9 | 199.1 | 177.0 | 82.3 | 97.7 |
| | | | 205.5 | | | |
| [**5**·2 THF]$_2$ | 136.1 | 118.2 | 203 | 179.3 | 80.4 | 98.6 |
| | 137.7 | 119.6 | 209 | 179.1 | 80.3 | 100.6 |
| | | | 206 | | | |
| | | | 200 | | | |
| [**6**·$OEt_2$] | 136.5 | 118.9 | 209.0 | 176.9 | 83.8 | 94.4 |
| | 136.6 | 118.4 | 206.0 | 179.1 | 85.4 | 96.4 |
| | | | 206.1 | | | |
| | | | 202.7 | | | |
| **7**[22a] | 143.0 | 115.4 | | 175.8 | | |
| **8**[31] | 133.2 | 118.2 | 176.2 | 180.0 | ($C^1N^1Li$: 180.0) | |
| [**8**]$_2$[31] | 132.5 | 119.0 | 194.2 | 180.0 | 78.8 | 101.2 |
| [**8**·2 $H_2O$]$_2$[22a] | 133.6 | 120.4 | 210.8 | | | |
| **9a**[31] | 133.5 | 118.1 | 176.1 | 179.2 | ($C^1N^1Li$: 172.7) | |
| **9b**[31] | 133.4 | 118.3 | 176.2 | 179.6 | ($C^1N^1Li$: 178.4) | |

**Structure in Solution**

A prerequisite for an understanding of the diastereofacial selectivity of electrophilic substitutions using lithiated α-amino nitriles is a knowledge of the "anion" structure in solution. To this end, the reaction solutions, i.e. the lithiated α-amino nitrile in THF, were examined by vibrational and NMR spectroscopic methods.

An interpretation of the experimental IR spectra by means of ab initio calculations has been presented previously[31]. The IR spectra were measured in THF solution under argon at room temperature. Of primary interest are the CN multiple-bond stretching frequencies between 2000 and 2100 $cm^{-1}$. In Figure 9, the 1800−2500 $cm^{-1}$ regions of the IR spectra of **2**, (*S,S*)-**4**, and (*S,S*)-**6** are shown. The characteristic intense Li-α-cyano anion bands were measured at 2061 $cm^{-1}$ for (*S,S*)-**6** and at 2016 $cm^{-1}$ for (*S,S*)-**4**. The IR absorption of **2** showed a split peak at 2019 and 2034 $cm^{-1}$. Similarly, the shoulder at 2025 $cm^{-1}$ in the spectrum of (*S,S*)-**6** was enhanced to form a second band after the sample was left to stand at room temperature for several hours (**6′**). These experimental wavenumbers match the theoretical values calculated for the model compounds **8** and **9**[31] by scaling with an empirical factor of 0.89[33].

Figure 9. IR spectra of **2**, **4**, and **6** in THF at room temperature. Absorptions labelled 'H' at around 2220 $cm^{-1}$ are due to the corresponding non-lithiated compound, generated by hydrolysis of the Li species. Spectra were recorded immediately after mixing, **6′** after being kept at room temperature for 4 hours




The theoretical calculations on lithiated acetonitrile (**8**) led to a 50 $cm^{-1}$ lower wavenumber for the dimeric lithio α-cyano anion (2245.1 $cm^{-1}$) as compared to that for the monomeric structural type (2298.9 $cm^{-1}$)[31]. In accordance with this difference, the lower wavenumbers may be assigned to the dimeric structure type and the higher frequencies to the monomeric lithiated α-cyano anion. It can thus be assumed that at room temperature in THF, the lithiated α-amino nitriles exist in a monomeric as well as a dimeric form, these being in equilibrium. Because of its high symmetry, the dimeric $D_{2h}$-symmetric structure should have an active Raman vibration, in contrast to the $C_{2v}$-symmetric monomeric species. Attempts to detect this Raman frequency were, however, unsuccessful, probably because of the low concentrations of the ethereal solutions (2−5%). At higher concentrations, the lithiated amino nitriles precipitated. A Raman spectrum of a highly concentrated suspension of (*S,S*)-**6** in THF showed a weak band at 2134 $cm^{-1}$[18].

More detailed information concerning the structure in solution was obtained by NMR spectroscopic measurements on **3**, (*S,S*)-**5**, and (*S,S*)-**6** in THF. The α-cyano function could be assigned from the chemical shifts of the relevant carbon nuclei at δ = 69 and δ = 142. By means of a COLOC experiment[34] on (*S,S*)-**6**, a $^2J_{CH}$ long-range coupling between the anionic carbon and the neighbouring equatorial dioxan hydrogen atom was detected. In Figures 10 and 11, sections of the $^{13}C$- and $^1H$-NMR spectra of **3** at room temperature and at reaction temperature (−80°C) are shown.

Figure 10. $^{13}C$-NMR spectrum of **3** in [$D_8$]THF at room and reaction temperature (−80°C)

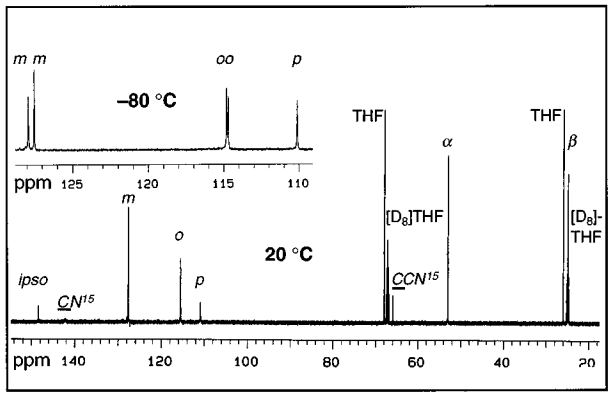
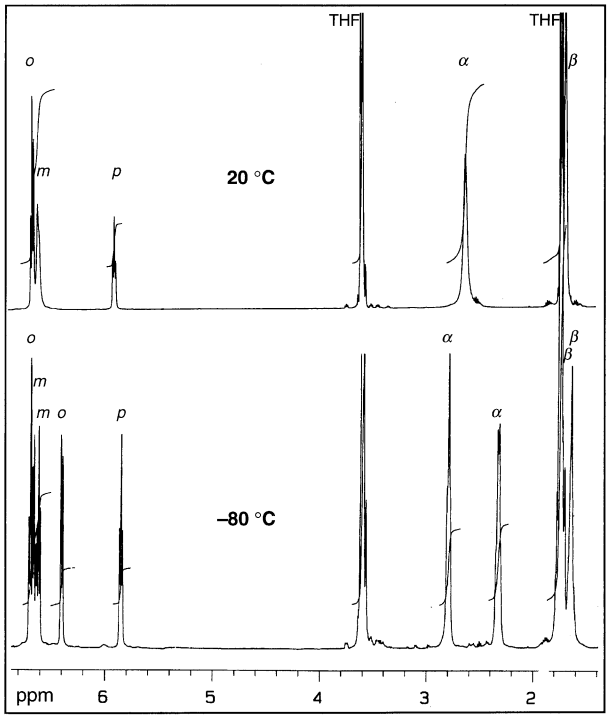
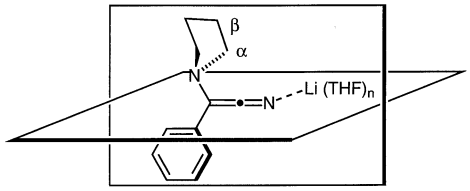



Figure 11. $^1H$-NMR spectrum of **3** in [$D_8$]THF at room and reaction temperature (−80°C)



The remarkable high-field shifts of the *para* carbons (δ ≈ 110), the *ortho* carbons (δ ≈ 115) and the *para* hydrogens (δ ≈ 5.8) in the spectra of **3** and (*S,S*)-**5** indicate a mesomeric distribution of the negative charge into the phenyl ring. Similarly, in the spectra of (*S,S*)-**6**, the proton and carbon signals of the anisyl group are shifted to higher fields. A coplanar orientation with the α-cyano anion functionality is necessary for the participation of the aromatic ring system in the electron delocalization. Furthermore, in the case of **3**, a signal splitting of isotopical nuclei is seen on lowering the temperature. The differentiation of each *ortho* and *meta* carbon and hydrogen, respectively, at lower temperatures is consistent with a hindered rotation of the phenyl group, resulting in a preferred coplanar conformation. In the low-temperature $^1$H-NMR spectrum of **3**, discrete α- and β-pyrrolidinyl proton signals are detected, in accordance with a preferred vertical orientation of the pyrrolidine ring, with magnetically distinct *syn*- and *anti*-oriented hydrogen atoms in relation to the α-cyano anion group. The resulting favored conformation of **3** in THF, as given in Figure 12, exactly matches the structure in the solid state (Figure 4).

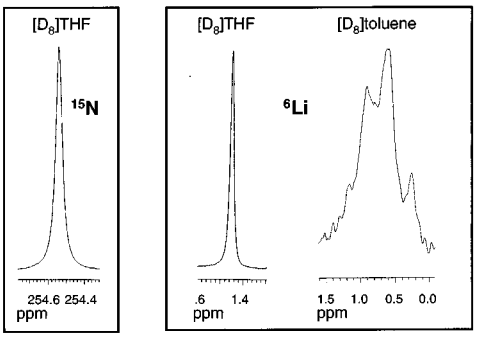
Figure 12. Predominant conformation of **3** in [D$_8$]THF at −80°C




It is thus concluded that in solution the preferred orientation of the aromatic ring systems is coplanar with the $C_1-C_2$ bond and that the amine lone pair is oriented antiperiplanar to the α-cyano anion function, corresponding to the conformations observed in the crystal structures.

In order to confirm the results concerning the aggregation state as derived from the IR investigations, a sample of $^6$Li,$^{15}$N-labelled α-cyano anion **3** was examined in a 0.5 M [D$_8$]THF solution. [$^{15}$N,$^6$Li]-**3** was obtained by deprotonation of [$^{15}$N]-**3-H** with $^6$Li-labelled lithium diethyl amide in THF. The amino nitrile [$^{15}$N]-**3-H** was prepared by reaction of pyrrolidine with benzaldehyde and commercially available 98% isotopically labelled [$^{15}$N] potassium cyanide. For a monomeric structure-type, a $^6$Li doublet and a $^{15}$N triplet was expected, whereas a $^6$Li triplet and a $^{15}$N quintuplet would correspond to dimeric aggregation. Depending on the Li−N bond character and the aggregation state, the coupling constants were expected to be in the range of 3−7 Hz[23e][26]. Unfortunately, however, only singlets were observed in [D$_8$]THF solution at temperatures between +25 and −110°C, both in the $^6$Li- and in the $^{15}$N-NMR spectra (Figure 13). This lack of any heteronuclear coupling between lithium and the corresponding anion might be attributed to fast intermolecular exchange processes in THF. In the case of lithium amides[23f][35] and lithio phenylacetonitrile[26], no coupling was found in THF either, in contrast to the situation in less polar solvents such as diethyl ether and toluene. Consequently, [$^{15}$N,$^6$Li]-**3** was also examined in [D$_8$]toluene, to which a small amount of [D$_8$]THF had been added for solubilization, such that a 0.05 M solution could be prepared. The $^1$H-NMR spectrum of this sample indicated the coexistence of different structural types, while the $^6$Li-NMR spectrum showed a broad complex signal (Figure 13).

Figure 13. $^6$Li- and $^{15}$N-NMR spectra of **3** at −80°C




The degree of aggregation was finally determined by means of cryoscopic measurements on (*S,S*)-**6** in THF, according to the method of Bauer and Seebach[36]. (*S,S*)-**6** was crystallized from diethyl ether, filtered, precisely weighed, and dissolved in a defined amount of pure THF. With a 0.015 M solution, a freezing point difference $\delta T$ with respect to pure THF of 0.029°C was measured, while a 0.05 M solution led to a difference $\delta T$ of 0.098°C. From these data, aggregation states of $n = 0.94$ and $n = 0.96$, respectively, could be derived. Thus, at the freezing point of THF ($\psi = -108.5$°C), the lithiated amino nitriles under discussion exist as monomers with a slightly ionic character and are thus represented by the monomeric ketene iminate structure-type **B2**, or more precisely, **B6**.

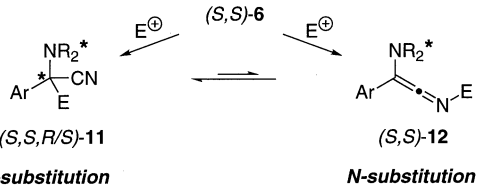
#### Reactivity and Stereoselectivity

The synthetic potential of the lithiated α-amino nitriles **B** as masked acyl anion equivalents **C** has already been reviewed[16][17][18][19][20][21] (Schemes 2 and 3). By reaction with electrophiles, e.g. alkyl halides, aldehydes or Michael acceptors, the *C*-substituted amino nitrile adducts **D** are obtained. In accordance with their structure as *N*-lithiated α-cyano anions, metallated amino nitriles exhibit an ambident character. Therefore, both the soft carbon and the hard nitrogen atom represent nucleophilic centers and *C*- and *N*-substitution is possible, as described previously for silylations of related metallated silyl cyanohydrins[37].

Treatment of (*S,S*)-**6** with e.g. methyl iodide, acetaldehyde, or cyclohexenone[17b][17c], resulted in the exclusive formation of *C*-substituted adducts (*S,S,R*/*S*)-**11**. Furthermore, each differently enriched epimeric mixture of (*S,S,R*/*S*)-**6-H** led upon deprotonation to (*S,S*)-**6**, and thus to asymmetric additions with the same diastereomeric excesses of (*S,S,R*/*S*)-**11**. When hard electrophiles were used, such as acetyl chloride, TMSCl, or even TMS-triflate, mainly the *N*-substituted ketene imines (*S,S*)-**12** were formed (Scheme 4). In these cases, the IR spectra of the

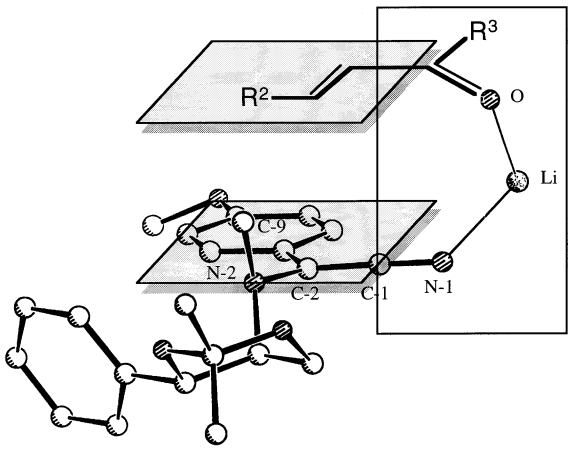
crude reaction mixtures showed a strong acetyl ketene imine or trimethylsilyl ketene imine band at around 1925 or 1960 $cm^{-1}$, respectively. By means of NMR spectroscopy, a mixture of *C*- and *N*-substituted products was detected, these being in a thermodynamically controlled equilibrium. After allowing the mixtures to stand for several days at 4°C, only the more stable *C*-substituted adducts could be detected. Depending on the strength of the electrophile, different ratios of (*S,S,R*/*S*)-**11**/(*S,S*)-**12** were detected in the crude reaction mixtures, e.g. 60:40 with AcCl, 70:30 with TMSCl, and 25:75 with TMSOTf.

Scheme 4. *C* versus *N* substitution by reaction of lithiated α-amino nitrile (*S,S*)-**6** with electrophiles (Ar = *p*-methoxyphenyl)



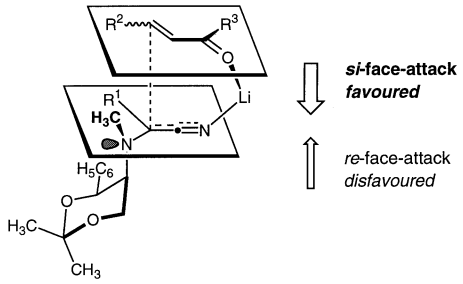

With a knowledge of their structure, a mechanism for the stereoselective reactions of chiral lithiated α-amino nitriles **B*** can be proposed. Under our reaction conditions, monomeric *N*-lithiated α-cyano anions **B6** with preferred conformations of the aromatic ring and the amine function similar to the orientations determined from the crystal structures are assumed. Based on the stereochemical outcome of the asymmetric Michael additions[17] and the X-ray structure analyses of (*S,S*)-**5** and (*S,S*)-**6**, attack of the lithiated α-cyano anions containing (*S,S*)-2,2-dimethyl-5-methylamino-4-phenyl-1,3-dioxan[29] as chiral auxiliary at α,β-unsaturated carbonyl compounds is envisaged. Any electrophilic attack at the trigonal-planar anionic carbon would be diastereoselectively directed towards the *si*-face by the sterically demanding chiral auxiliary. Figure 14 shows the proposed transition state of the diastereofacial approach of a Michael acceptor towards the sterically less hindered *si*-face of the monomer (*S,S*)-**6**, with its structure taken from the X-ray plot. Upon reaction, the favored (*R*)-configuration at the amino nitrile center results.

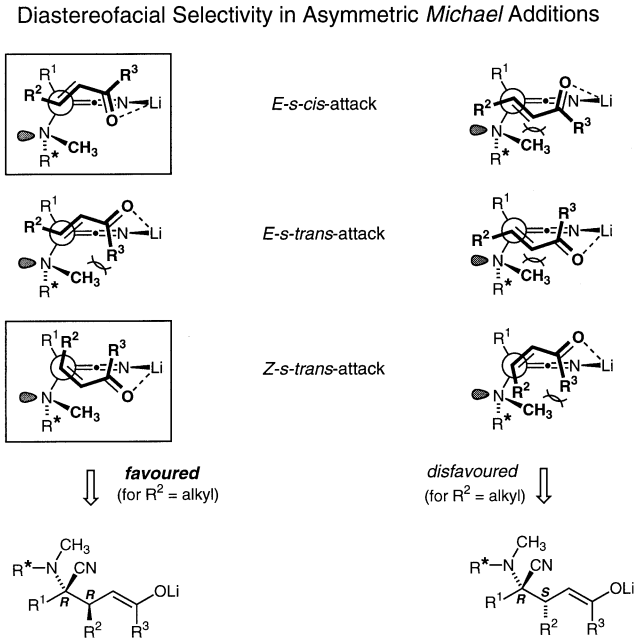
Figure 14. Diastereofacial less hindered *si*-face attack of a Michael acceptor on (*S,S*)-**6**




The *si*-face attack of the enone probably begins with a complexation of the carbonyl oxygen to the lithium by fast solvent/electrophile exchange. The relative topicity of the conjugate addition is then directed by the steric interactions of the prochiral Michael acceptors, with the *N*-methyl group (C-9) of the chiral amine pointing upwards. In Figure 15, different possible approaches from the *si*-face are drawn in the Newman projection. Clearly, those transition states that allow for a maximum distance between the *N*-methyl group and the electrophile should be favored. In the cases of (*E*)-*s-cis* and (*Z*)-*s-trans* isomeric Michael acceptors, this condition is clearly fulfilled if the enone reacts with the α-cyano anion at its *re*-face, resulting in the formation of the (*R,R*)-configured adduct. For an (*E*)-*s-trans* enone, a favored transition state cannot be predicted, and (*Z*)-*s-trans* enones have to this date not been employed in these asymmetric Michael additions.

Figure 15. Proposed transition state, relative topicity, and overall stereochemical outcome of *si*-face attacks of Michael acceptors on chiral lithiated amino nitriles




The mechanism outlined above requires a rather static behavior of the nucleophile, significant steric repulsions, and a lithium-mediated attraction between the reactants. It accounts for the absolute configuration of the main isomeric adduct obtained upon asymmetric conjugate ad-

dition. These configurations are (*R,R*) for $R^2$ = alkyl and (*R,S*) for $R^2$ = aryl (change of CIP priority)[7][17][18][19].

In summary, detailed information concerning the structure of lithiated α-amino nitriles **B** in the solid state and in solution has been collected and a mechanism for their stereoselective reactions, specifically asymmetric Michael additions, has been proposed. For the first time, several crystal structures of lithiated α-amino nitriles are reported. These show **3** and (*S,S*)-**5** to be dimeric lithiated α-cyano anions and (*S,S*)-**6** to be a polymeric aggregate with equivalent dimeric subunits. IR and NMR spectroscopic studies, as well as cryoscopic measurements in THF, prove **B** to exist as essentially monomeric species (**B2**, or more precisely **B6**). In less polar solvents, higher aggregation is presumed. The results presented here should help in the design of even more efficient methods for asymmetric nucleophilic acylation.

This work was supported by the *Deutsche Forschungsgemeinschaft* [Leibniz Prize and Sonderforschungsbereich 380 (Aachen) as well as 360 (Marburg)] and by the *Fonds der Chemischen Industrie*. We thank *Boehringer Mannheim GmbH* for providing us with "L-Acetonamin" and *Bayer AG*, *BASF AG*, *Degussa AG* and *Hoechst AG* for the donation of chemicals.

## Experimental Section

The metallations, crystallizations, and all further treatments and measurements were carried out using standard Schlenk techniques. Tetrahydrofuran (THF) was freshly distilled from potassium, diethyl ether from sodium under argon. Reagents of commercial quality were used from freshly opened containers or purified by common methods. The α-amino nitriles, in particular (*S,S,S*)-**6-H**[7][17c] and the α-amino nitrile Michael adducts, in particular (*S,S,R,R*)-**10**[17a][17b][17c][17d], were prepared according to the literature. − IR: Perkin-Elmer FT-IR 1750. − $^1$H NMR (500 MHz/300 MHz, TMS in $CDCl_3$ as external standard), $^{13}$C NMR (125 MHz/75 MHz, TMS in $CDCl_3$ as external standard), $^6$Li NMR (75 MHz, $^6$LiCl in $D_2O$ as external standard), $^{15}$N NMR (50 MHz, CH3$^{15}$NO2 in [$D_8$]THF as external standard): Varian Unity 500/Varian VXR 300 or Gemini 300. − Cryoscopic measurements: Apparatus according to Bauer and Seebach[36], digital thermometer: Systemtechnik S1224 (range −120 to +120°C, precision ±0.001°C, 100 mV/°C).

*X-ray Structure Determination of* **3**, *(S,S)*-**5**, *(S,S)*-**6**, *(S,S,S)*-**6-H**, *and (S,S,R,R)*-**10** [38]: Single crystals of [**3**·2 THF]$_2$ and [**5**·2 THF]$_2$ were grown from tetrahydrofuran. Specimens suitable for structure analysis were selected under an argon atmosphere. These crystals were then transferred to the goniometer head of an Enraf-Nonius CAD4 diffractometer under a protecting stream of argon and mounted on top of a glass fibre by means of a droplet of high-vacuum grease. Data were collected under a stream of cooled nitrogen at the temperatures given in Table 2. 25 reflections were used to determine cell constants, which were then refined in a least-squares process. The structures were solved using direct methods as implemented in the Xtal3.2 program package[39], employing GENSIN[40] to generate structure-invariant relationships and GENTAN[41] for the general tangent phasing procedure. Further details of the X-ray structure determinations are given in Table 2. The solid-state structures of [**3**·2 THF]$_2$, [**5**·2 THF]$_2$, [**6**·$EtO_2$]$_\infty$, and (*S,S,R,R*)-**10** are depicted in Figures 4, 5, 6, and 8, respectively.

*General Procedure 1 (GP 1) for the Preparation of the IR Samples:* A solution of α-amino nitrile **B-H** (5 mmol) in THF (5 ml) was treated with a solution of LDA (5.5 mmol) in THF/hexane (13 ml) at −78°C. After stirring for 30 min., the mixture was allowed to warm to room temperature. By means of a syringe, an aliquot of the solution was then transferred into the cell, which had been purged with argon.

*General Procedure 2 (GP 2) for the Preparation of the NMR Samples:* 39 mg (0.53 mmol) of diethylamine in 0.5 ml of THF was treated with 1.0 equivalent of *n*-butyllithium in *n*-hexane at −78°C. In the case of [$^{15}$N,$^6$Li]-**3**, [$^6$Li]-*n*-propyllithium in *n*-pentane was used. The solution was warmed to 0°C for 30 min., then cooled again to −78°C, and added dropwise to a solution of α-amino nitrile **B-H** (0.5 mmol) in THF (2 ml) at −78°C. After stirring for 30 min. at −40°C, the solvent and the amine were evaporated in vacuo at 0°C. At this temperature, the solid residue was diluted with [$D_8$]THF. The colored solution was transferred under argon via a syringe into an NMR tube with a Schlenk top, which was then sealed in vacuo.

*N-Lithio(methyl)(pyrrolidino)ketene Imine* (**2**): 0.62 g (5 mmol) of **2-H**[7] was deprotonated with 5.5 mmol of LDA according to GP 1. − IR (THF): $\tilde{\nu}$ = 2034, 2019 cm$^{-1}$ (s, C=N).

*[$^{15}$N]N-Lithio(phenyl)(pyrrolidino)ketene Imine* (**3**): 94 mg (0.5 mmol) of [$^{15}$N]-**3-H**[7] was deprotonated with 0.53 mmol of [$^6$Li]lithium diethylamide according to GP 2. − $^1$H NMR ([$D_8$]THF, *T* = 25°C): δ = 1.71 (br. m, 4 H, $NCH_2CH_2$), 2.64 (br. m, 4 H, $NCH_2$), 5.90 (t, *J* = 6.7 Hz, 1 H, $H_{para}$), 6.61 (br. m, 2 H, $H_{meta}$), 6.65 (d, *J* = 7.0 Hz, 1 H, $H_{ortho}$), 6.66 (d, *J* = 8.2 Hz, 1 H, $H_{ortho}$). − $^1$H NMR ([$D_8$]THF, *T* = −80°C): δ = 1.65 (br. m, 2 H, $NCH_2CH_2CH_2$), 1.72 (br. m, 2 H, $NCH_2CH_2CH_2$), 2.33 (q, *J* = 7.7 Hz, 2 H, $CH_2NCH_2$), 2.80 (t, *J* = 7.9 Hz, 2 H, $CH_2NCH_2$), 5.85 (t, *J* = 6.9 Hz, 1 H, $H_{para}$), 6.40 (d, *J* = 8.2 Hz, 1 H, $H_{ortho}$), 6.61 (t, *J* = 7.6 Hz, 1 H, $H_{meta}$), 6.65 (t, *J* = 7.6 Hz, 1 H, $H_{meta}$), 6.70 (d, *J* = 8.2 Hz, 1 H, $H_{ortho}$). − $^{13}$C NMR (CH-coupled, [$D_8$]THF, *T* = 25°C): δ = 25.0 (m, $NCH_2CH_2$), 53.0 (ttm, *J* = 136.0, 4.8 Hz, $NCH_2$), 66.0 (d, $^2J_{CN}$ = 1.9 Hz, *C*=C=N$^{15}$), 111.0 (dtt, *J* = 158.5, 6.5, 1.6 Hz, $C_{para}$), 115.6 (dt, *J* = 154.7, 6.5 Hz, $C_{ortho}$), 127.7 (dd, *J* = 151.9, 7.6 Hz, $C_{meta}$), 142.1 (d, $^1J_{CN}$ = 19.5 Hz, C=N$^{15}$), 148.4 (t, *J* = 6.9 Hz, $C_{ipso}$). − $^{13}$C NMR ([$D_8$]THF, *T* = −80°C): δ = 24.2 ($NCH_2CH_2$), 53.2 ($NCH_2$), 66.0 (d, $^2J_{CN}$ = 1.9 Hz, *C*=C=N$^{15}$), 110.1 ($C_{para}$), 114.7, 114.8 ($C_{ortho}$), 127.5, 127.9 ($C_{meta}$), 138.5 (d, $^1J_{CN}$ = 19.5 Hz, C=N$^{15}$), 148.3 ($C_{ipso}$). − $^6$Li NMR ([$D_8$]THF, *T* = 25°C/−80°C): δ = −0.30/1.45 (s). − $^{15}$N NMR ([$D_8$]THF, *T* = 25°C/−80°C): δ = 252.6/254.5 (s).

*(4S,5S)-N-Lithio-[N′-(2,2-dimethyl-4-phenyl-[1,3]dioxan-5-yl)-N′-methylamino]methylketene Imine* [(*S,S*)-**4**]: 1.62 g (5 mmol) of (*S,S*/*R,S*)-**4-H**[7] was deprotonated with 5.5 mmol of LDA according to GP 1. − IR (THF): $\tilde{\nu}$ = 2016 cm$^{-1}$ (s, C=N).

*(4S,5S)-N-Lithio-[N′-(2,2-dimethyl-4-phenyl-[1,3]dioxan-5-yl)-N′-methylamino]phenylketene Imine* [(*S,S*)-**5**]: 168 mg (0.5 mmol) of (*S,S*/*R,S*)-**5-H**[17c] was deprotonated with 0.53 mmol of lithium diethylamide according to GP 2. − $^1$H NMR ([$D_8$]THF, *T* = 25°C): δ = 1.42 (br. s, 3 H, $CCH_3$), 1.45 (br. s, 3 H, $CCH_3$), 2.70 (br. s, 3 H, $NCH_3$), 2.92 (br. m, 1 H, NCH), 4.04 (dd, *J* = 12.1, 3.3 Hz, 1 H, $CH_2O$), 4.73 (dm, *J* = 12.1 Hz, 1 H, $CH_2O$), 5.12 (dm, *J* = 3.6 Hz, 1 H, CHPh), 5.83 (br. t, *J* = 7.0 Hz, 1 H, $H_{para}$), 5.60−6.60 (br. m, 1 H, $H_{ortho}$), 6.48 (br. m, 2 H, $H_{meta}$), 6.74 (br. d, *J* = 7.4 Hz, 1 H, $H_{ortho}$), 7.18−7.49 (complex, 5 H, aromatic H). − $^{13}$C NMR ([$D_8$]THF, *T* = 25°C): δ = 19.0 ($CCH_3$), 29.9 ($CCH_3$), 40.9 ($NCH_3$), 62.3 (NCH), 62.8 ($CH_2O$), 70.9 (*C*=C=N), 75.8 (*C*HPh), 98.8 ($CO_2$), 111.3 ($C_{para}$), 115.7 (br, $C_{ortho}$), 126.5 ($C_{para}$),

Table 2. Crystallographic data of $[\mathbf{3}\cdot 2\ THF]_2$, $[\mathbf{5}\cdot 2\ THF]_2$, $[\mathbf{6}\cdot EtO_2]_\infty$, (*S,S,S*)-**6-H**, and (*S,S,R,R*)-**10**

| compound | $[\mathbf{3}\cdot 2\ THF]_2$ | $[\mathbf{5}\cdot 2\ THF]_2$ | $[\mathbf{6}\cdot EtO_2]_\infty$ | (*S,S,S*)-**6-H** | (*S,S,R,R*)-**10** |
|---|---|---|---|---|---|
| emp. form. | $(C_{20}H_{29}O_2N_2Li)_2$ | $(C_{29}H_{39}O_4N_2Li)_2$ | $(C_{30}H_{45}O_5N_2Li)_2$ | $C_{22}H_{26}O_3N_2$ | $C_{26}H_{34}O_5N_2$ |
| form. mass | 672.82 | 973.17 | 1041.29 | 366.46 | 454.57 |
| radiat. | Cu-$K_\alpha$ | Cu-$K_\alpha$ | Cu-$K_\alpha$ | Cu-$K_\alpha$ | Cu-$K_\alpha$ |
| λ [A] | 1.54179 | 1.54179 | 1.54184 | 1.54184 | 1.54184 |
| cryst. syst. | monoclinic | monoclinic | monoclinic | monoclinic | orthorhombic |
| space. gr. (No.) | $P2_1/_n$ (14) | $P2_1$ (4) | $P2_1$ (4) | $P2_1$ (4) | $P2_12_12_1$ (19) |
| $Z$ | 4 | 2 | 2 | 2 | 4 |
| $a$ [Å] | 13.927(1) | 10.952(3) | 18.635(2) | 9.973(1) | 9.777(1) |
| $b$ [Å] | 10.452(1) | 18.472(2) | 9.207(2) | 18.320(1) | 11.713(4) |
| $c$ [A] | 14.265(4) | 14.206(1) | 19.719(14) | 11.205(1) | 22.659(4) |
| α [°] | 90.0 | 90.0 | 90.0 | 90.0 | 90.0 |
| β [°] | 104.76(1) | 106.37(1) | 116.60(2) | 98.150(4) | 90.0 |
| γ [°] | 90.0 | 90.0 | 90.0 | 90.0 | 90.0 |
| $V$ [Å$^3$] | 2008.0 | 2757.5 | 3025.1 | 2026.5 | 2594.9 |
| dens. [g·cm$^{-3}$] | 1.113 | 1.172 | 1.143 | 1.201 | 1.194 |
| temp. [K] | 230 | 213 | 184 | 293 | 293 |
| abs. coeff. [cm$^{-1}$] | 5.2 | 5.8 | 6.1 | 6.4 | 6.7 |
| abs. corr. | none | none | none | none | none |
| meas. reflns. | 5303 | 6214 | 6393 | 3763 | 5639 |
| indep. reflns. | 4346 | 5154 | 6150 | 3488 | 3249 |
| $R_{int.}$ | 0.0547 | 0.0144 | 0.0126 | 0.1260 | 0.0256 |
| obs. reflns. | 2999[a] | 4470[a] | 5910 | 3261 | 3099 |
| $F(000)$ | 728 | 1048 | 1128 | 784 | 1000 |
| ind. range *(h, k, l)* | ±17, 13, 17 | ±13, 23, 17 | −18/16, ±9, −9/19 | 10, ±19, ±11 | −9/0, ±12, −6/24 |
| par. ref. | 227 | 641 | 701 | 495 | 314 |
| $R$ | 0.081 | 0.066 | 0.0395[b] | 0.051[b] | 0.030[b] |
| $R_w$ | 0.092 | 0.062 | 0.1046[c] | 0.129[c] | 0.089[c] |
| $w$ | $\sigma^{-2}$ | $\sigma^{-2}$ | p:0.0633, q:15704[d] | 0.1037/0[d] | 0.418/0.2875[d] |
| hole/peak [e·Å$^{-3}$] | 0.4/+0.4 | −0.4/+0.5 | −0.2/+0.4 | −03/0.25 | −0.13/0.13 |
| progr. used | XTAL 3.2 | XTAL 3.2 | SHELXL-93 | SHELXL-93 | SHELXL-93 |

[a] $I > 2\cdot\sigma(I)$. − [b] Observ. refl. − [c] On $F^2$, all reflns. − [d] $w = 1/[\sigma^2(F_0)^2 + {}_pP)^2 + {}_qP]$; $P = (F_0^2 + 2\ F_i^2)/3$.

126.9, 127.6 ($C_{ortho/meta}$), 127.3 (br, $C_{meta}$), 142.1 ($C_{ipso}$), 144.8 (C=N), 147.2 ($C_{ipso}$).

*(4S,5S)-N-Lithio-[N′-(2,2-dimethyl-4-phenyl-[1,3]dioxan-5-yl)-N′-methylamino]-4-methoxyphenylketene Imine* [(*S,S*)-**6**]: 1.83/0.183 g (5.0/0.5 mmol) of (*S,S,R*/*S*)-**6-H**[17c] was deprotonated with 5.5/0.55 mmol of LDA according to GP 1/GP 2, respectively. − IR (THF): $\tilde{\nu}$ = 2061 cm$^{-1}$ (s, C=N), 2025 (sh., m, C=N). − $^1$H NMR ([D$_8$]THF, $T$ = 25°C): δ = 1.45 (br. s, 6 H, $CCH_3$), 2.72 (br. m, 1 H, NCH), 2.75 (br. s, 3 H, $NCH_3$), 3.51 (s, 3 H, $OCH_3$), 4.03 (dd, $J$ = 11.8, 3.0 Hz, 1 H, $CH_2O$), 4.67 (dm, $J$ = 11.8 Hz, 1 H, $CH_2O$), 5.12 (d, $J$ = 3.0 Hz, 1 H, CHPh), 6.10 (br. d, $J$ = 8.4 Hz, 2 H, 3-H anisyl), 6.30 (br. d, $J$ = 8.4 Hz, 2 H, 2-H anisyl), 7.19 (t, $J$ = 7.2 Hz, 1 H, $H_{para}$), 7.28 (t, $J$ = 7.4 Hz, 2 H, $H_{meta}$), 7.42 (br. d, $J$ = 7.4 Hz, 2 H, $H_{ortho}$). − $^{13}$C NMR ([D$_8$]THF, $T$ = 25°C): δ = 19.1 (br., $CCH_3$), 30.1 (br., $CCH_3$), 41.2 (br., $NCH_3$), 55.8 ($OCH_3$), 62.0 (NCH), 62.9 ($CH_2O$), 69.3 (*C*=C=N), 75.8 (*C*HPh), 98.9 ($CO_2$), 114.4 (C-2 anisyl), 117.3 (C-3 anisyl), 126.7 ($C_{para}$), 127.0 (br., $C_{ortho}$), 127.8 ($C_{meta}$), 139.9 (br, C-1 anisyl), 142.1 ($C_{ipso}$), 150.7 (C-4 anisyl), 154.5 (C=N). − In a cryoscopy apparatus according to ref.[36], 0.73 g (2 mmol) of (*S,S,R*/*S*)-**6-H**[17c] was treated with 2.1 mmol LDA in $Et_2O$ (25 ml) at −78°C. After stirring for 1 h, *n*-hexane (50 ml) was added and the mixture was stirred for a further 30 min. The resulting crystals were filtered off and washed with four portions of *n*-hexane (6 ml). After drying in vacuo at −20°C, a precisely weighed amount of THF was added at −60°C and the solution was frozen and thawed. − $n$ = 0.94 ± 0.06 ($c$ = 14.58, δ$T$ = 0.029°C), 12% ionic, 88% M. − $n$ = 0.96 ± 0.02 ($c$ = 50.21, δ$T$ = 0.098°C), 8% ionic, 92% M.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