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Cyclization of Zincated α-*N*-Homoallylamino Nitriles: A New Entry to Enantiopure 2,3-Methanopyrrolidines

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Dedicated to Professor Carmen Najera on the occasion of her 60th birthday

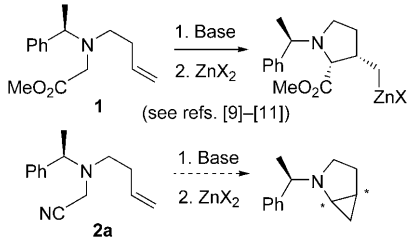
Abstract: Stereoselective cyclization of zincated α-*N*-homoallylamino nitriles has been developed. Following treatment with lithium diisopropylamide (LDA) and transmetalation with zinc bromide, α-*N*-(1-phenylethyl)-*N*-homoallylamino nitriles lead to 2,3-methanopyrrolidines in moderate to good yields (up to 66%) and excellent selectivities (up to >98:2). With substrates derived from α-branched homoallylic amines, a stereospecific inversion of the homoallylic stereogenic center was observed. To account for this, a mechanistic rationale involving the formation of zincioiminium ions from zincated α-amino nitriles is put forward. 2,3-Methanopyrrolidines should then arise from a sequence involving an aza-Cope rearrangement providing a configurationally stable (2-azoniaallyl)zinc species that then undergoes a [3+2] cycloaddition reaction.

Keywords: cyclization · enantioselectivity · metalation · sigmatropic rearrangement · ylides

Introduction

Metalated α-amino nitriles are well-known nucleophiles that react with a range of electrophiles including alkyl or acyl halides, epoxides, aldehydes, and C–C multiple bonds.[1] Lithiated α-amino nitriles, which are easily obtained by deprotonation of the parent α-amino nitriles, have been widely used in organic synthesis and, more specifically, in asymmetric synthesis.[2] Accordingly, their structure and reactivity have been extensively studied.[3] To a lesser degree, sodium and potassium derived metalated α-amino nitriles have also been considered and have proven to be synthetically useful. In contrast, very little is known about zincated α-amino nitriles which, to the best of our knowledge, have almost never been used in organic synthesis.[4,5]

Inspired by literature reports on base-induced inter-[6] and intramolecular[7] additions of metalated α-amino nitriles to unactivated alkynes, and as part of our ongoing project on the intramolecular carbometalation of unactivated alkenes by zinc enolates,[8] we became interested in zincated α-*N*-homoallylamino nitriles. Zinc enolates obtained from enantiopure α-*N*-homoallylamino esters such as **1** by lithium diisopropylamine (LDA)-mediated deprotonation/transmetalation sequence have been shown to lead to the formation of 3-zinciomethyl prolines with excellent stereoselectivity (Scheme 1).[9–11] We reasoned that if, in a similar way, a stereoselective carbozincation took place starting from zincated α-*N*-homoallylamino nitriles, such as **2a**, it would provide bifunctional 2-cyano-3-(zinciomethyl)pyrrolidines bearing



Scheme 1. Projected approach to methanopyrrolidines from α-*N*-homoallylamino nitriles.

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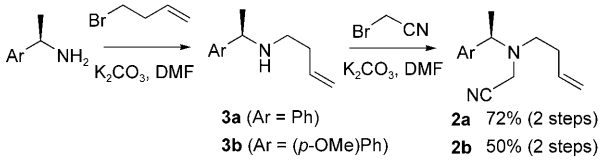
both an electrophilic α-amino nitrile moiety and a nucleophilic alkylzinc moiety. As for previously disclosed analogous cyclizations of ω-stannyl appendages on *N*-acyloxyiminium ions,[12] we then anticipated an intramolecular displacement of the cyano group through the well-known Bruylants reaction between α-amino nitriles and organometallic nucleophiles, which has been reported, in particular, with organozinc reagents.[13–16] If successful, our approach would thus offer a new entry to enantiopure 2,3-methanopyrrolidines (Scheme 1), which are interesting compounds[12,17] that are still challenging to prepare in spite of recent elegant approaches based on the intramolecular Kulinkovich–de Meijere reaction.[18]

Results and Discussion

Deprotonation studies: We initiated our studies by looking at unsubstituted α-*N*-homoallylamino nitriles **2a** and **2b** as precursors. Starting from enantiopure (*R*)-1-phenylethylamine or (*R*)-1-(4-methoxyphenyl)ethylamine, products **2a** and **2b** were obtained in 72 and 50% yield, respectively, after a two-step sequence involving two subsequent alkylations, first with bromobutene and then with bromoacetonitrile (Scheme 2).

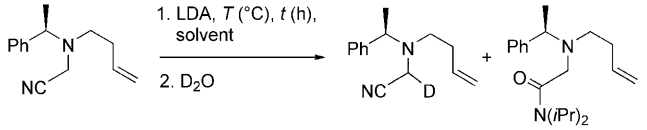


Scheme 2. Synthesis of α-*N*-homoallylamino nitriles **2a** and **2b**.

Building on our previous experience with α-amino esters, we intended to access the zincated amino nitriles by lithiation of the amino nitriles with LDA, followed by transmetalation with a zinc salt. However, because difficulties in the deprotonation of hindered α-amino nitriles either due to a lack of reactivity or to competitive addition of the base to the nitrile moiety have been reported,[4] we decided to first secure the metalation procedure by studying the product distribution obtained by deprotonation of **2a** followed by performing a deuterium quench (D_2O; Table 1).

Whereas complete metalation was achieved after 1 h at −80 °C in THF using 2.2 equivalents of LDA (Table 1, entry 1), the use of diethyl ether as solvent was problematic. At −60 °C (Table 1, entry 2), product **4**, resulting from the addition of LDA to the nitrile group, was the major product observed after hydrolysis. Fortunately, the ratio of deprotonation over addition increased with increasing temperature (Table 1, entries 2–4) and clean metalation was obtained by carrying out the reaction at 0 °C (Table 1, entry 4). Under these conditions, 2.2 equivalents of LDA proved necessary to achieve complete deprotonation; when 1.2 equivalents were used, 25% of unreacted (non-deuterated) starting material **2a** was recovered (Table 1, entry 5). We thus established two lithiation procedures: Method A (LDA (2.2 equiv), THF, −80 °C, 1 h), and Method B (LDA (2.2 equiv), Et_2O, 0 °C, 1 h).

Table 1. Deprotonation of **2a** with LDA.



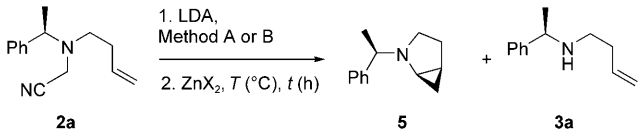
2a **2a-D** **4**

Entry	LDA [equiv]	Solvent	*T* [°C]	*t* [h]	Ratio[a] **2a**/**2a-D**/**4**
1	2.2	THF	−80	1	0:100:0
2	2.2	Et_2O	−60	1.5	0:25:75
3	2.2	Et_2O	−40	0.5	0:50:50
4	2.2	Et_2O	0	1	0:100:0
5	1.2	Et_2O	0	1	25:75:0

[a] Determined by ^{1}H NMR spectroscopic analysis.

Cyclization of α-*N*-homoallylamino nitriles: With the appropriate metalation procedures in hand, we studied the cyclization reactions (Table 2). No formation of 2,3-methanopyrrolidine **5** was observed following treatment of amino nitrile **2a** with 2.2 equivalents of LDA in Et_2O at 0 °C and further stirring at room temperature. In contrast, and to our delight, addition of 4 equivalents $ZnBr_2$ following the deprotonation led to the formation of methanopyrrolidine **5** in 32% yield, essentially as a single diastereoisomer (95:5 d.r.) (Table 2, entry 1). ^{1}H NMR spectroscopic analysis of the crude product revealed the presence of several side products, however, only amine **3a**, which formed in 30%, could be identified.

Table 2. Cyclization reactions from **2a** following deprotonation with LDA.



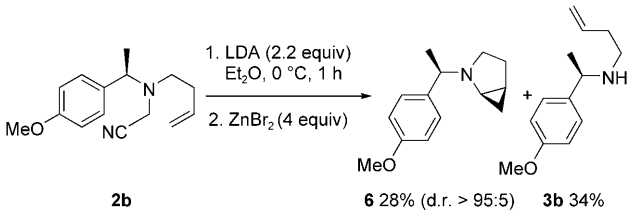
2a **5** **3a**

Entry	Method	ZnX_2 [equiv]	*T* [°C]	*t* [h]	**5** (d.r.)[a] [%][b]	**3a** [%][c]
1	A[d]	$ZnBr_2$ (4)	0 to RT	1.5	32 (95:5)	30
2	B[e]	$ZnBr_2$ (4)	−80 to RT	1.5	45 (77:23)	17
3	B[e]	ZnI_2 (4)	−80 to RT	2	40 (70:30)	20
4	B[e]	BuZnI·LiI[f] (4)	−80 to RT	2.5	<10 (nd)	60
5	A[d]	$Zn(CN)_2$ (4)	0 to RT	18	<10	<10
6	–[g]	$Zn(NiPr_2)_2$ (1.6)	0 to RT	4	14 (40:60)	16[h]

[a] Determined by ^{1}H NMR spectroscopic analysis of the crude material. [b] Combined yield of isolated diastereoisomers. [c] Isolated yield. [d] Method A: LDA (2.2 equiv), Et_2O, 0 °C, 1 h. [e] Method B: LDA (2.2 equiv), THF, −80 °C, 1 h. [f] Prepared by mixing BuLi with ZnI_2. [g] Reaction carried out in THF with a 2:1 mixture of $LiNiPr_2/ZnBr_2$. [h] 24% of starting material was recovered.

In particular, no starting material was recovered. It is important to note that, to obtain ^{1}H NMR spectra of sufficient clarity, the reaction mixture had to be stirred in the presence of ethanolamine for 1 h during workup to remove zinc salts that, otherwise, led to broadening and shifting of the signals. Encouraged by these results and seeking improved yields, we studied the influence of several reaction parameters. A standard amount of zinc salt (4 equiv) was chosen because it was noticed that lower quantities led to lower diastereoselectivities and had little impact on the yield and product distribution. In all cases, ^{1}H NMR spectroscopic analysis of the crude reaction mixture revealed the presence of amine **3a** and several other unidentified side products. Unless otherwise stated in Table 2, no starting material was recovered. Conducting the reaction in THF afforded a slight increase in yield (45%), although a significant decrease in selectivity was observed (77:23 d.r.) (Table 2, entry 2). Whereas similar results were observed using ZnI_2 (40% yield and 70:30 d.r.) (Table 2, entry 3), the reaction failed to produce the desired cyclization compound when BuZnI and $Zn(CN)_2$ were used (Table 2, entries 4–5). Interestingly, formation of methanopyrrolidine **5** was observed, albeit in only 14% yield, when $Zn(NiPr_2)_2$ was used without any additional base (Table 2, entry 6).

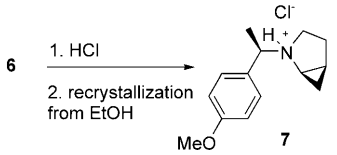
Changing the stereodirecting group from a phenyl-ethylamino to a 4-methoxyphenyl-ethylamino group had little influence on the reaction outcome starting from **2b**; methanopyrrolidine **6** was obtained in 28% yield and excellent selectivity (d.r. >95:5) (Scheme 3).



2b **6** 28% (d.r. > 95:5) **3b** 34%

Scheme 3. Cyclization of substrate **2b**.

The absolute configuration of the newly created centers in **6** was determined by X-ray crystallographic analysis of its hydrochloride salt **7** (Scheme 4, Figure 1).[19] The absolute configuration of **5** was inferred from this result. It is worth noting that the sense of induction brought about by the stereodirecting phenylethylamino group was found to be opposite to the sense observed previously for the carbocyclization of α-*N*-homoallylamino esters.[9–11]



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Scheme 4. Hydrochloride salt formation from **6** for X-ray analysis.

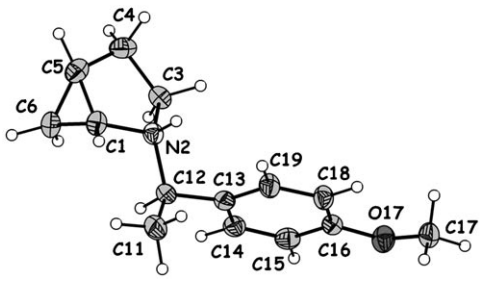
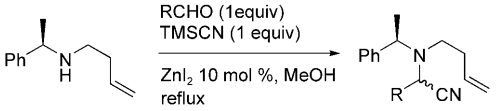


Figure 1. ORTEP view of **7**.

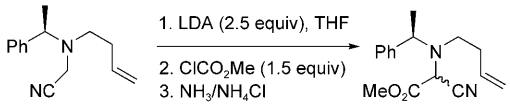
Although rather disappointing in terms of yield, we nevertheless decided to explore the scope of this new cyclization procedure. We first considered substrates bearing a substituent α to the nitrile group. Compounds **8** and **9** were readily accessed through the Strecker reaction between amine **3a**, trimethylsilyl cyanide (TMSCN) and either ethanal or cyclohexylcarboxaldehyde, respectively (Scheme 5).[20] Compound **10**, which is both an α-amino ester and an α-amino nitrile, was prepared in 72% yield by alkylation of amino nitrile **2a** with methylchloroformate (Scheme 6). In all cases, the products were isolated and used as mixtures of two diastereoisomers.



3a

R = Me **8** 44% (50:50 d.r.)
R= *c*Hex **9** 55% (60:40 d.r.)

Scheme 5. Preparation of substrates **8** and **9**.

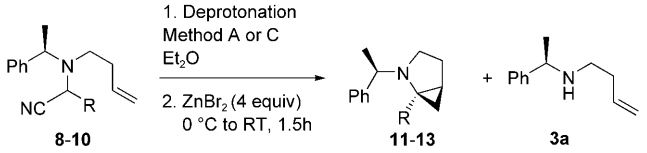


2a **10** 72% (53:47 d.r.)

Scheme 6. Preparation of substrate **10**.

Treatment of alkyl-substituted aminonitriles **8** and **9** under the previously developed conditions resulted in the formation of methanopyrrolidines **11** and **12** with a significant increase in yield (75–80%) with respect to unsubstituted aminonitriles (Table 3, entries 1 and 2). Interestingly, formation of the free amine **3a** was nearly completely suppressed. Unfortunately, the diastereoselectivity of the reaction dropped, and diastereoisomeric ratios of 75:25 were observed. LDA did not deprotonate substrate **10**, presumably because the acidic proton was too sterically hindered. Metalation was finally effected using 2.2 equivalents of sodium hydride. Following deprotonation, addition of $ZnBr_2$ and usual workup led to methanoproline **13** in 67% isolated yield but, very disappointingly, only as a 55:45 diastereoisomeric mix-

Table 3. Cyclization from substrates **8–10** bearing a substituent α to the CN group.



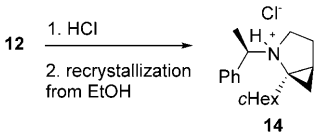
8-10 11-13 3a

Entry	Method	Substrate	R	Product	Yield (d.r.)[a] [%][b]	3a [%][c]
1	A[d]	**8**	Me	**11**	75 (75:25)	10
2	A[d]	**9**	*c*-Hex	**12**	80 (75:25)	10
3	C[e]	**10**	CO_2Me	**13**	67 (55:45)[f]	<5

[a] Determined by ^{1}H NMR spectroscopic analysis of the crude material. [b] Combined yield of isolated diastereoisomers. [c] Isolated yield. [d] Method A: LDA (2.2 equiv), Et_2O, 0 °C, 1 h. [e] Method C: NaH (2.2 equiv), Et_2O, RT, 1 h. [f] Stereochemistry of the major product was not established.

ture (Table 3, entry 3). Again, only small amounts of free amine **3a** were formed.

The absolute configuration of the newly created centers of the major products were also determined by X-ray crystallographic analysis of the hydrochloride salt **14** obtained from **12** (Scheme 7, Figure 2).[21] The same sense of induction brought by the phenylethylamino group was also observed in the unsubstituted case.



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Scheme 7. Hydrochloride salt formation from **12** for X-ray analysis.

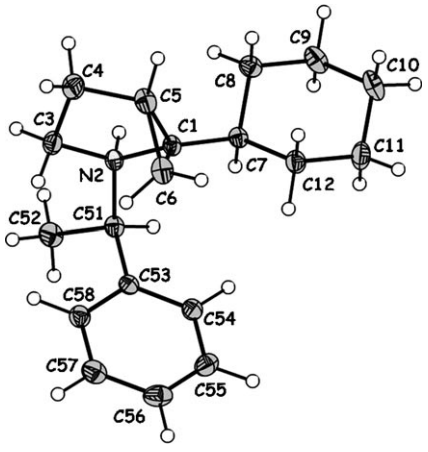
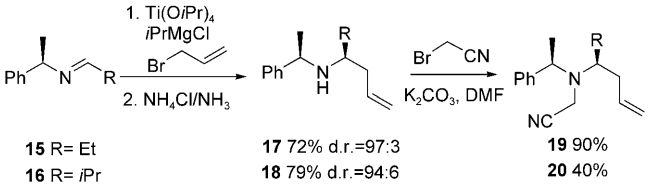


Figure 2. ORTEP view of **14**.

Cyclization of α-*N*-homoallylamino nitriles bearing a substituent in the homoallylic position: We next investigated the influence of a substituent in the homoallylic position. Following a procedure reported by Gao and Sato,[22] enantiomerically pure amines **17** and **18** were prepared in good yields by the diastereoselective addition of allyltitanium to imines **15** and **16**, respectively (Scheme 8). Alkylation with bromoacetonitrile afforded the corresponding α-amino nitriles, which were isolated in nearly diastereomerically pure form (d.r. >98:2).



15 R= Et
16 R= *i*Pr

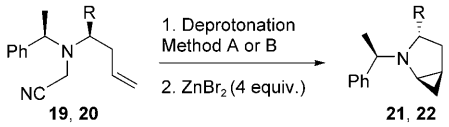
17 72% d.r.=97:3
18 79% d.r.=94:6

19 90%
20 40%

Scheme 8. Preparation of substrates **19** and **20**.

Initially, when the deprotonation–transmetalation–cyclization procedure was carried out in Et_2O starting from **19**, methanopyrrolidine **21** was obtained in excellent selectivity (95:5 d.r.) but, again, in quite poor yield (30%; Table 4, entry 1). Fortunately, in this case, changing the solvent to THF proved to be highly beneficial; under these conditions the yield was increased to 66% without loss of diastereoselectivity (Table 4, entry 2). With substrate **20**, which bears an isopropyl group, a similar 71% yield was obtained, again with a 95:5 diastereomeric ratio (Table 4, entry 3).

Table 4. Cyclization from substrates **19** and **20**.

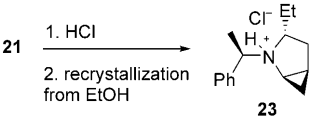


19, 20 21, 22

Entry	Method	Substrate	R	Product	Yield (d.r.)[a] [%]
1	A[b]	**19**	Et	**21**	30[c] (95:5)
2	B[d]	**19**	Et	**21**	66[c] (96:4)
3	B[d]	**20**	*i*Pr	**22**	71[e] (95:5)

[a] Determined by ^{1}H NMR spectroscopic analysis of the crude material. [b] Method A: LDA (2.2 equiv), Et_2O, 0 °C, 1 h. [c] Combined yield of isolated isomers. [d] Method B: LDA (1.2 equiv), THF, −80 °C, 1 h. [e] Yield determined by ^{1}H NMR spectroscopy based on analysis of the crude mixture with biphenyl as internal standard. Problematic separation from side products resulted in 43% isolated yield.

As described previously, to determine the absolute configuration of the newly created centers of **21**, X-ray analysis of its hydrochloride salt **23** was performed (Scheme 9, Figure 3).[23] The same sense of induction observed for the unsubstituted case was also found with regard to the (*R*)-1-phenylethylamino stereodirecting group but, to our surprise,



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Scheme 9. Hydrochloride salt formation from **21** for X-ray analysis.

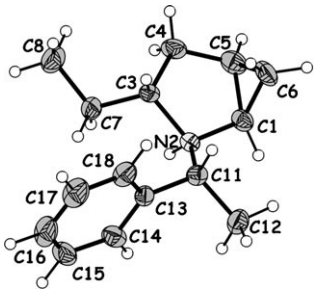
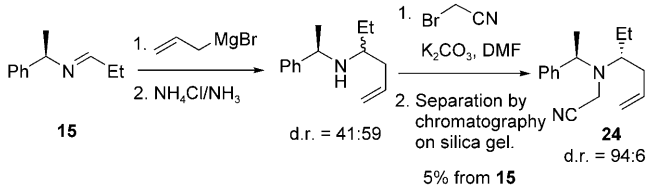


Figure 3. ORTEP view of **23**.

an inversion of the homoallylic stereogenic center was detected. Furthermore, when these results are compared with the analogous carbocyclization of *N*-homoallyl α-amino esters,[11] it can be seen that not only is the sense of induction of the stereodirecting group opposite, but the diastereoselectivity is also much higher (96:4 here versus 40:60, in the case of proline formation) and the relative configuration between the substituents of the pyrrolidine ring is opposite (*trans* here versus *cis* for the major carbocyclization product).

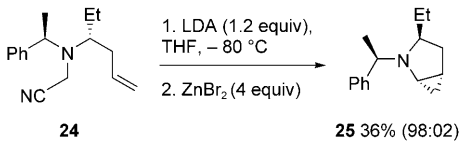
So that the relative influence of each stereogenic center during the cyclization could be determined, we decided to prepare α-amino nitrile **24**, having a relative configuration opposite to that of **19** (Scheme 10). Allylation of imine **15**



Scheme 10. Preparation of substrate **24**.

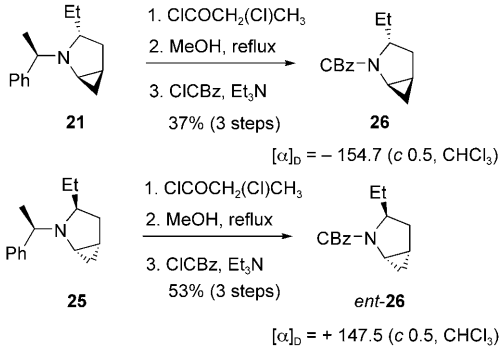
with allyl Grignard followed by alkylation of the resulting mixture of amines with bromoacetonitrile led to a 41:59 mixture of amino nitriles **19** and **24**. Careful separation by silica-gel flash chromatography allowed compound **24** to be isolated in nearly diastereomerically pure form (94:6 d.r.).

With compound **24** in hand, the cyclization procedure was carried out and methanopyrrolidine **25** was obtained in 36% yield in practically diastereomerically pure form (98:02 d.r.; Scheme 11). As evidenced by their different NMR spectra, two diastereomeric methanopyrrolidines were obtained starting from **19** and **24**. NOE experiments carried out with



Scheme 11. Cyclization from substrate **24**.

methanopyrrolidine **25** showed a *trans* relative configuration between the ethyl and the cyclopropyl groups, implying a relative configuration between the methyl group of the (*R*)-1-phenylethylamino moiety and the cyclopropyl group opposite to that observed for **21**. The structure of **25** was further secured by removal of the nitrogen protecting group, because, in so doing, two enantiomeric compounds (**26** and *ent*-**26**) were obtained starting, respectively, from **21** and **25** (Scheme 12). Thus, in conclusion, the reaction of phenyl-

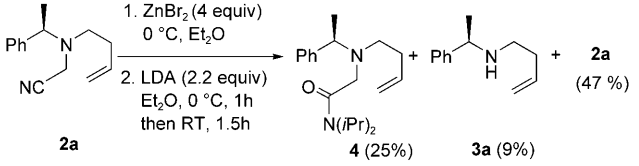


Scheme 12. Stereochemical correlation for products **21** and **25**.

ethylamino-derived *N*-homoallylamino nitriles substituted at the homoallylic position is stereospecific; it proceeds with inversion of configuration of the homoallylic center and affords methanopyrrolidines with a *trans* relationship between the cyclopropyl and the homoallylic substituents.

Mechanistic considerations: The unexpected stereochemical outcome of the cyclization reactions involving α-*N*-homoallylamino nitriles substituted at the homoallylic position led us to rule out a mechanistic rationale involving a carbocyclization/intramolecular Bruylants reaction (see path A, Scheme 14 below), because this route could not account for the stereospecific inversion of the homoallylic center.

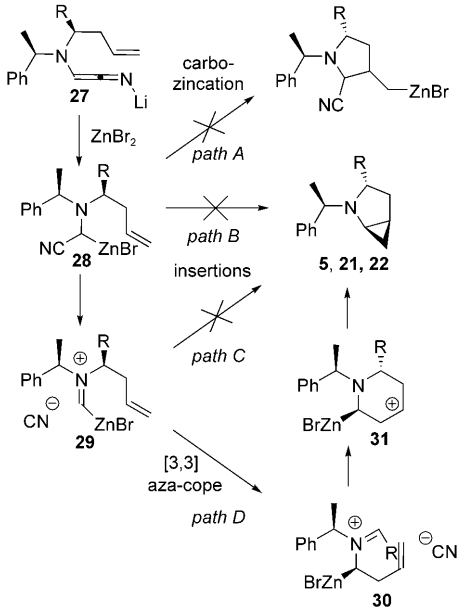
Because α-amino nitriles are potential iminium ion precursors in the presence of Lewis acids,[24] we decided to make sure that metalation was, as anticipated, the first step of the cyclization sequence leading to methanopyrrolidine formation. We thus carried out a test reaction in which zinc bromide was added prior to addition of LDA (Scheme 13). No cyclization was detected. Along with 47% of unreacted starting material, the only products isolated were compound **4**, resulting from the addition of LDA to **2a**, and small amounts of amine **3a**. From a mechanistic standpoint, this



Scheme 13. Reaction with **2a**, reversing the reagent addition order.

result suggests that methanopyrrolidine formation only arises from the metalated amino nitrile, whereas formation of amine **3a** can occur by reaction of the starting amino nitrile with the zinc salt (iminium formation and hydrolysis).

Accordingly, starting from lithiated amino nitriles **27** (Scheme 14; for the sake of clarity only the formation of



Scheme 14. Mechanistic rationales for methanopyrrolidine formation from lithiated α-*N*-homoallylamino nitriles.

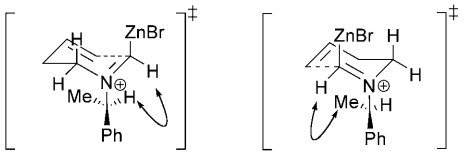
methanopyrrolidines **5**, **21**, and **22** are depicted), one can envision that addition of the zinc salt will first result in a transmetalation to afford the zincated derivative **28** (probably C-metalated as observed for other zincated nitriles).[25,26] The Lewis acidic salt can then assist the departure of the cyano group to lead to the metalated iminium salt **29**, which is a species that has precedents in literature.[27–29] From this point, several possibilities can be considered. First, the postulated zincioiminium ion **29** (or the parent zincated α-amino nitrile) is a carbenoid species. Because both intra-[27e,30] and intermolecular[27a–d,31] cyclopropanations of α-amino carbenes or carbenoids have been reported, trapping of a carbenoid or carbene intermediate by the pendant homoallylic chain is a possible pathway that may account for the formation of methanopyrrolidines (paths B or C, Scheme 14). However, as in the case of the carbocyclization mechanism, this possibility can be excluded because it cannot explain the stereospecific inversion of the homoallylic center. Nevertheless, this highly reactive intermediate might be involved in degradation pathways and side reactions and, hence, could lead to the observed moderate yields.

Alternatively, the zincioiminium intermediate could undergo a 2-aza-Cope[32–34] rearrangement and thus lead to the (2-azoniaallyl)zinc species **30**.[35] A [3+2] intramolecular cycloaddition[36] would then afford the observed methanopyrrolidines. Formation of an azomethine ylide from **30**, which would then undergo cycloaddition,[37] cannot be ruled out completely in presence of halides (or cyanide).[38] However, this possibility is considered unlikely because intramolecular dipolar cycloadditions of azomethine ylides bearing such a short tether have not previously been reported, to the best of our knowledge.[37] Thus, we prefer to consider a more plausible sequence involving the addition of the pendant alkene onto the iminium moiety[34a,39] of **30** to afford **31**, followed by anionic annulation[40] by reaction between the organozinc and the formed cationic center (path D, Scheme 14).

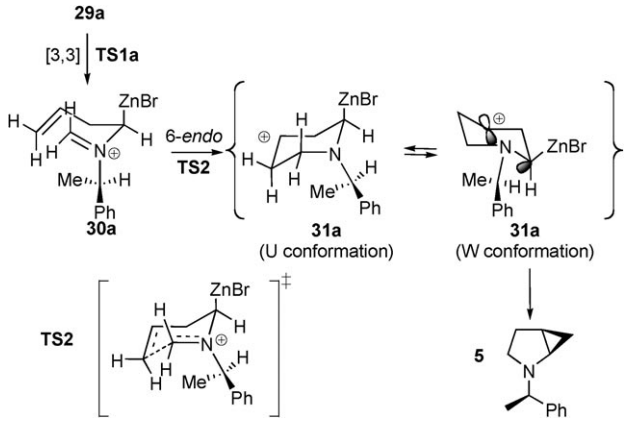
The stereochemical outcome of the cyclization reactions can be rationalized on the basis of this mechanism. The stereospecific inversion of the homoallylic center observed in the cyclization procedure can only be explained if a chirality transfer takes place from **29** to the zincated azomethine imine ylide **30**, and if the latter is configurationally stable during the time scale of the reaction.[41] The configuration of the (2-azoniaallyl)zinc intermediate depends both on the configuration of the zincioiminium ion and on the preferred six-center chair-like transition state for the aza-Cope rearrangement.[42,43] Furthermore, according to Polniaszek and co-workers' studies[44] on additions to *N*-acyliminum ions bearing an α-methylbenzyl group,[45] in the most reactive conformation the phenyl group is perpendicular to the plane of the C=N double bond to maximize the interaction between the σ* of the C–Ph bond and the π* of the π system. As a consequence, two possible chair-like diastereomeric transition states for the aza-Cope rearrangement are to be considered for a given configuration of the reacting zincioiminium ions.

In the case of substrate **2a** (and **2b**) bearing no homoallylic substituent, the observed product arises from a path involving the aza-Cope rearrangement of the (*E*)-zincioiminium ion via **TS1a**. A probable explanation is that formation of the (*E*)-zincioiminium ion is favored over that of the *Z* isomer to minimize steric repulsive interactions between the zinc moiety and the bulkier α-methylbenzyl group.[33d] Transition-state **TS1a** should be lower in energy than **TS1b** as a consequence of a more favorable allylic interaction between the iminium proton and the hydrogen (in **TS1a**) compared with the methyl group of the α-methylbenzyl moiety (for **TS1b**).[46]

Through **TS1a**, 3,3-sigmatropic rearrangement leads to ylide **30a** (Scheme 15). Although no previous reports on the reactivity of (2-azoniaallyl)zinc species have been disclosed,



TS1a TS1b

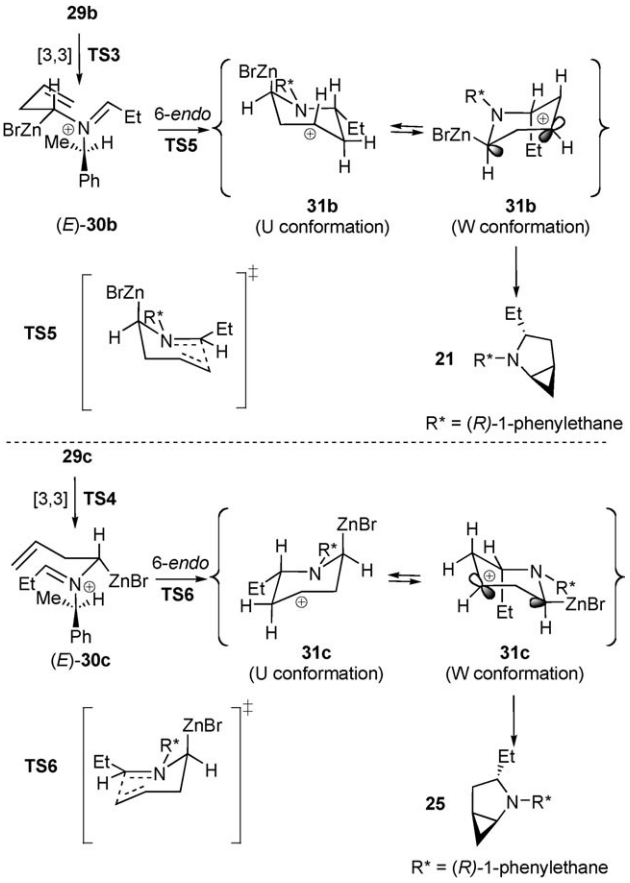


Scheme 15. Proposed rationale for the stereochemical outcome of the synthesis of **5**.

we hypothesize that the subsequent alkene addition follows Linderman's model[47] for nucleophilic additions to α-silyl- and stannyl oxocarbenium ions, which has also been used to rationalize the behavior of [3+2] cycloadditions involving (2-azoniaallyl)stannanes.[38] Hence, cyclization to **31a** should take place via transition-state **TS2**, wherein the iminium adopts a favored conformation involving a hyperconjugative interaction between the Zn–C bond and the neighboring electron-deficient iminium π system.[48] From **31a**, methanopyrrolidine **5** can then be produced by anionic cyclization, resulting in cyclopropane formation. For reaction of the carbanionic center with the carbocation to occur, the Zn–C bond and the p orbital of the cation must adopt a W conformation to enable back-lobe orbital overlap (Scheme 15).[49] This requirement accounts for the stereoselective formation of the cyclopropyl group, provided that the organozinc intermediate **31a** is configurationally stable on the reaction time scale.

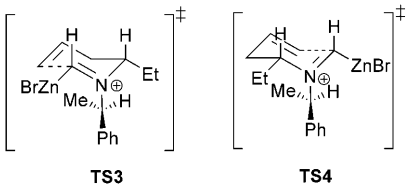
It should be noted that the stereochemical outcome of the reactions starting from substrates **8** and **9**, bearing a substituent α to the nitrile, is also consistent with this picture. Indeed, the formation of the *E* isomer of the zincioiminium should be less selective as a consequence of a lower difference in bulk between the zinc atom and the alkyl group. This might be one of the reasons (though perhaps not the only one) for the overall loss of stereoselectivity noted.

In the case of substrates bearing a substituent in the homoallylic position, such as **19** and **24**, there is no clear difference of bulk between the nitrogen substituents (α-(ethyl)homoallyl versus α-methylbenzyl), so one would also expect iminium ion formation to be less selective. The excellent selectivity nevertheless obtained must then arise from the stereoselectivity of the aza-Cope rearrangement. Indeed, the observed outcome is consistent with preferred transition states **TS3** and **TS4** wherein both the homoallylic substituent and the zinc moiety adopt less hindered pseudo-equatorial positions. Based on Linderman's model, 5-*endo* cyclization of **30b** or **30c** then occurs through **TS5** or **TS6**, respectively, to produce **31b** or **31c**, which is configurationally stable on



Scheme 16. Proposed rationale for the stereochemical outcome of the synthesis of **21** and **25**.

the timescale of the reaction. Intramolecular cyclopropanation involving a W conformation then stereoselectively affords methanopyrrolidine **21** or **25** (Scheme 16).



Conclusion

We have developed a new stereoselective cyclization reaction that provides enantiopure 2,3-methanopyrrolidines from zincated α-*N*-homoallylamino nitriles in moderate to good yields. In addition to the synthetic potential offered by this new approach, the analysis of the stereochemical outcome of the reaction has provided evidence for an unexpected mechanistic behavior. To account for the stereospecific inversion of the homoallylic stereogenic center for substrates bearing a substituted homoallylic side chain, we pro-

pose that zincated α-amino nitriles are new zincioiminium ion precursors. We believe that this approach will foster new developments in the chemistry of zincated iminiums. In the particular case of α-*N*-homoallylamino nitriles, a subsequent aza-Cope rearrangement takes place to afford previously unreported (2-azoniaallyl)zinc intermediates,[50] which lead to 2,3-methanopyrrolidines after a [3+2] cycloaddition process. Remarkable features of this mechanism include a chirality transfer through an asymmetric aza-Cope rearrangement, which is rather uncommon,[51] and the formation of a metalated azomethine-ylide that is configurationally stable on the timescale of the subsequent reaction. Additional mechanistic studies are underway in our group to fully understand the [3+2] process and will be reported in due course.

Experimental Section

General information: Experiments involving organometallic compounds were carried out in dried glassware under a positive pressure of dry N_2. Liquid nitrogen was used as a cryoscopic fluid. A three-necked, round-bottomed flask equipped with an internal thermometer, a septum cap and a nitrogen inlet was used. Anhydrous solvents were distilled to remove stabilizers and dried with a double column purification system. Zinc bromide (98%) was melted under dry N_2 and, immediately after cooling to RT, was dissolved in anhydrous Et_2O or THF. All other reagents and solvents were of commercial quality and were used without further purification. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker AVANCE 400 spectrometer fitted with a BBFO probe or with a Bruker ARX 200 spectrometer fitted with a dual probe (^{13}C/^{1}H). Chemical shifts are reported in δ units relative to an internal standard of residual chloroform ($\delta=7.27$ ppm for ^{1}H NMR spectra and $\delta=77.16$ ppm for ^{13}C NMR spectra). IR spectra were recorded with a diamond ATR spectrometer. High-resolution mass spectra (HRMS) were obtained with a Finnigan MAT 95 instrument. Elemental analyses were performed at the Service de Microanalyses de l'Université Pierre et Marie Curie - Bat F - case 55–4 place Jussieu - 75252 Paris Cedex 05.

Cyclization of α-aminonitriles (Method A): Typical procedure (Compound 5; Table 2, entry 1): Diisopropylamine (0.31 mL, 2.2 mmol) was added at RT to *n*BuLi (0.94 mL, 2.2 mmol). Once a gummy mixture formed, anhydrous Et_2O (0.5 mL) was added and the solution was cooled to 0°C. A solution of **2a** (214 mg, 1.0 mmol) in anhydrous Et_2O (4 mL) was added dropwise. After 1 h of stirring at 0°C, $ZnBr_2$ (1.0 M in Et_2O, 4.0 mL, 4.0 mmol) was added in one portion. The reaction mixture was allowed to warm to RT and stirred for 2 h. An aqueous solution of NH_4Cl/NH_3 (2:1; 10 mL) and ethanolamine (1 mL) were added. The biphasic mixture was stirred vigorously for 30 min before the aqueous layer was extracted with Et_2O (3×10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography afforded **5** as a yellow oil (60 mg, 32%, d.r.=95:05). Further purification by flash chromatography afforded a stereochemically pure sample. $[\alpha]_D^{20}=+6.9$ ($c=0.94$ in chloroform); ^{1}H NMR (200 MHz, $CDCl_3$, 25°C, TMS): $\delta=7.32$–7.20 (m, 5H), 3.24 (q, $J=6.6$ Hz, 1H), 2.91 (dt, $J=5.9$, 2.9 Hz, 1H), 2.58–2.48 (m, 1H), 2.00–1.84 (m, 1H), 1.81–1.62 (m, 2H), 1.49 (d, $J=6.4$ Hz, 3H), 1.46–1.32 (m, 1H), 0.75–0.69 (m, 1H), 0.13 ppm (dt, $J=8.4$, 5.9 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, 25°C, TMS): $\delta=144.3$, 126.8, 125.7, 125.4, 62.8, 46.7, 37.7, 25.3, 22.3, 13.9, 0.0 ppm; IR (neat): $\tilde{\nu}=2931$, 1947 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{13}H_{18}N$: 188.14338 [M^+−H]; found: 188.14320.

Cyclization of α-aminonitriles (Method B): Typical procedure (Compound 21; Table 4, entry 2): Diisopropylamine (0.17 mL, 1.2 mmol) was added at RT to *n*BuLi (2.4 M in hexane, 0.50 mL, 1.2 mmol). Once a gummy mixture formed, anhydrous THF (1.5 mL) was added and the solution was cooled to −80°C. A solution of **19** (242 mg, 1 mmol) in anhydrous THF (1.5 mL) was added and, after 1 h of stirring at −80°C, $ZnBr_2$ (1.0 M in anhydrous THF, 4.0 mL, 4.0 mmol) was added dropwise, and the cooling bath was removed and replaced by a water bath. Once the solution reached RT, the bath was removed and the mixture was stirred at RT for 2 h. An aqueous solution of NH_4Cl/NH_3 (2:1; 10 mL) and ethanolamine (1 mL) were added. The biphasic mixture was stirred vigorously for 30 min before the aqueous layer was extracted with ethyl acetate (3×10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Purification by flash chromatography afforded **21** as a yellow oil (142 mg, 66%, d.r.=96:4). Further purification by flash chromatography afforded a stereochemically pure sample. $[\alpha]_D^{20}=-100.7$ ($c=1.03$ in chloroform); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C, TMS): $\delta=7.41$ (d, $J=7.0$ Hz, 2H), 7.32–7.21 (m, 3H), 3.64 (q, $J=6.6$ Hz, 1H), 2.75 (dt, $J=5.9$, 2.8 Hz, 1H), 2.36–2.29 (m, 1H), 2.11–2.07 (m, 1H), 1.70 (ddd, $J=12.5$, 9.4, 5.3 Hz, 1H), 1.52 (d, $J=6.8$ Hz, 3H), 1.33–1.27 (m, 1H), 1.11–1.01 (m, 1H), 0.96–0.85 (m, 1H), 0.67 (t, $J=7.4$ Hz, 3H), 0.69–0.65 (m, 1H), 0.21 ppm (dt, $J=5.5$, 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C, TMS): $\delta=145.9$, 128.2, 127.7, 126.8, 61.1, 60.5, 39.5, 34.5, 27.8, 19.0, 12.7, 10.6, 5.5 ppm; IR (neat): $\tilde{\nu}=2958$, 1638, 1492, 1454, 1112, 952, 701 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $C_{15}H_{22}N$: 216.17468 [M^+−H]; found: 216.17420.

Acknowledgements

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[23] X-ray crystal data of compound **23**·H_2O: $C_{15}H_{24}ClNO$; $M_w = 269.82$; colorless sticks; crystal size $0.20 \times 0.20 \times 0.40$ mm; orthorhombic; space group $P2_12_12_1$; $Z = 4$; $a = 7.470(6)$, $b = 8.590(7)$, $c = 25.586(16)$ Å, $\alpha = 90.000$, $\beta = 90.000$, $\gamma = 90.000°$; $V = 1642(2)$ Å^3; $\rho_{calcd} = 1.09$ g cm^{-3}; $\lambda = 0.710690$ Å ($Mo_{K\alpha}$); $\mu = 2.24$ cm^{-1}; KAPPA type diffractometer; temperature 295 K; θ range 1.0–25.0°; min/max $h = 0/8$, min/max $k = 0/10$, min/max $l = 0/30$; 1719 collected reflections, 1693 independent, 1110 used, 173 parameters; $R = 0.0729$ ($R = \Sigma||F_0| - |F_c||/\Sigma|F_0|$), $Rw = 0.0782$ ($Rw = [\Sigma w(||F_0| - |F_c||)^2/\Sigma wF_0^2]^{1/2}$), goodness of fit = 0.888, max/min $\Delta\rho = 0.60/-0.31$ e Å^{-3}. CCDC-777552 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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