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A comparative study of the stereoselective addition of trimethylsilyl cyanide and diethylaluminum cyanide to chiral cyclic nitrones

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Abstract—The mild cyanating agent trimethylsilyl cyanide adds with total stereoselectivity to α-alkoxy cyclic nitrones to afford the corresponding *trans*-hydroxyaminonitriles. The addition of Lewis acids to precomplexing the nitrones does not affect the stereoselectivity of these additions significantly. In all of the cases examined, excellent yields of diastereomerically homogeneous products were obtained. On the other hand, the use of diethylaluminum cyanide as cyanating agent leads to low diastereoselectivities. Both NMR studies and theoretical calculations show that whereas the addition of trimethylsilyl cyanide takes place through a concerted mechanism, in the addition of diethylaluminum cyanide, a complex is formed prior to the intramolecular delivery of the cyanide ion.

1. Introduction

In recent years, considerable progress has been made in the stereocontrolled 1,2-addition of carbon nucleophiles to chiral non-racemic nitrones under the influence of a Lewis acid.[1]

In particular, nucleophilic additions to α-alkoxy aldonitrones **1** take place with *syn* selectivity[2] when the reaction is carried out in the absence of any additive or in the presence of Lewis acids such as $ZnBr_2$ or $MgBr_2$ (Scheme 1).

On the other hand, the use of Et_2AlCl (DEAC) as a precomplexing agent gives rise to *anti* adducts preferentially, thus rendering the reaction stereodivergent.

A notable exception to this behavior is the addition of cyanide: irrespective of the reagent used or the presence of additives, the reaction invariably gives rise to *syn* adducts.[3] Nitrones **1** can only be obtained in the *Z*-form, the most stable configuration for aldonitrones (with the exception of those having an electron-withdrawing group at the nitrone carbon atom), which is also assumed to be the reactive species. Consequently, it is not possible to study the reactivity of the corresponding *E*-isomers (Scheme 2).

In order to carry out a comparative study on hydrocyanation of nitrones, we consider nitrones **2**[4] as close substrates to **1**, but possessing two important structural differences: (i) nitrones **2** are cyclic and (ii) they are blocked into an *E*-configuration.

Although the hydrocyanation of cyclic imines[5] and iminium salts[6] as well as other endocyclic C=N bonds[7] has been reported before, only a handful of reports of hydrocyanation of cyclic nitrones have appeared in the literature.[8] Moreover, only a couple of examples have been reported for cyanide addition to chiral hydroxylated nitrones while this work was in progress, but a detailed and unified study is lacking.[8a,9]

Herein, we disclose our results from cyanide additions to the enantiopure nitrones **2a**–**d** and racemic **2e** (Fig. 1). These nitrones can be easily prepared from L-malic acid **2a**,**b**,[10] L-tartaric acid **2d**[11] and arabinose **2e**[4a,12] as

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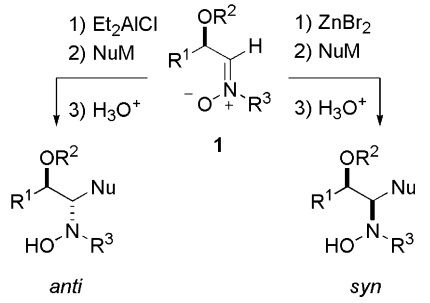
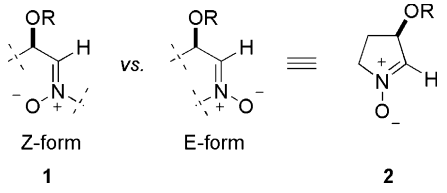


Scheme 1.



Scheme 2.

described before. Nitrone **2c** has been appositely synthesized for this study in analogy to **2a** and **2b** (see Section 4). We undertook the investigation of the addition of two representative cyanating agents, i.e. trimethylsilyl cyanide and diethylaluminum cyanide. A parallel between these reagents has been established: whereas TMSCN only acts as the cyanide-transfer reagent and additives can be used, Et_2AlCN can play both the roles of additive and cyanide-transfer reagent at the same time. Both NMR and computational studies have also been carried out to aid interpretation of the experimental results.

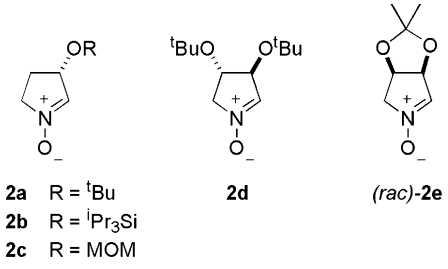


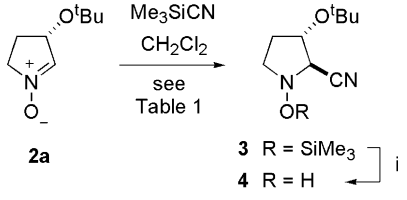
Figure 1. α-Alkoxy nitrones **2**.

Synthetically, the interest in this reaction lies in the cyanide adducts being precursors of proline derivatives and of chiral 1,2-diamines.

2. Results and discussion

2.1. Trimethylsilylcyanide additions

The addition of trimethylsilyl cyanide to nitrone **2a** was the first reaction to be examined. Thus, the nitrone was treated with 1.0 equiv. of the reagent at ambient temperature in dichloromethane as a solvent. The addition product **3** was isolated in quantitative yield as a single *trans* isomer[13] after evaporation of the solvent no purification being necessary (Table 1, entry 1). The ^1H NMR spectrum of **3** showed two sets of signals when recorded at 22°C. When the solution was heated to 55°C they coalesced to a single, well-resolved set of resonances, whereas cooling the sample restored the spectrum to its original condition, thus suggesting the existence of a dynamic equilibrium which could be attributed to nitrogen inversion according to previous theoretical and experimental investigations.[14] However, the presence of bulky groups linked to the hydroxylamine oxygen means that an equilibrium between rotamers around the N–O bond[15] cannot be discarded.[16] Further treatment of compound **3** with 5% methanolic citric acid gave rise quantitatively to the free hydroxylamine **4** (Scheme 3). Since compound **4** was obtained as a single isomer, we can reasonably assume that the observed ratio at the free hydroxylamine stage reflects the diastereoselectivity of the addition step.



Scheme 3. Reagents: (i) 5% citric acid, MeOH.

The *trans* relative stereochemistry has been established for CN with respect to O′Bu by ^1H NMR analysis. Indeed, in a NOESY spectrum, cross peaks H-2/H-5α,

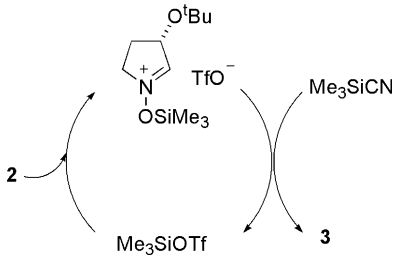
Table 1. Trimethylsilyl cyanide addition to nitrone **2a**[a]

Entry	Equiv.	Additive (equiv.)	Time	Yield (%)[b]	*trans*:*cis*[c]
1	1.0	None	16 h	100	>20:1
2	3.0	None	2 h	100	>20:1
3	1.0	TMSOTf (1.0)	5 min	100	>20:1
4	1.0	Et_2AlCl (1.0)	5 min	100	>20:1
5	1.0	TMSOTf (0.2)	5 min	100	>20:1
6	1.0	Et_2AlCl (0.2)	5 min	100	>20:1

[a] Further treatment with 5% methanolic citric acid of the crude mixtures afforded free hydroxylamines. No purification was necessary.
[b] All reactions showed quantitative yield.
[c] Only one isomer could be detected by NMR noise-to-signal ratio.

H-3/H-4β, H-4α/H-5α and H-4β/H-5β were observed; hence *R* configuration at the newly created stereogenic center was assigned.

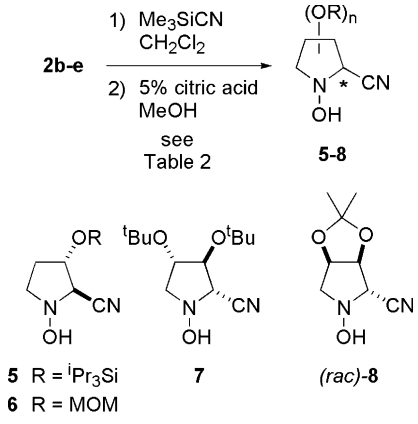
Using an excess of trimethylsilyl cyanide the reaction time shortened considerably (Table 1, entry 2). Since trimethylsilyl triflate (TMSOTf) and diethylaluminum chloride (DEAC) are considered to be effective activating agents for nitrones towards nucleophilic additions,[17] we also examined the addition of trimethylsilyl cyanide to **2a** in the presence of such additives.[18] Using 1.0 equiv. of either TMSOTf or DEAC considerably accelerates the reaction such that a 5 min reaction time was only required for total conversion (Table 1, entries 3 and 4). The action of those activating agents was shown to be catalytic since the same results were obtained when the reaction was carried out in the presence of 20 mol% of additive (Table 1, entries 5 and 6). The proposed catalytic cycle for the reaction in the presence of TMSOTf is illustrated in Scheme 4; a similar cycle may be proposed with DEAC.



Scheme 4.

It is of interest to compare the above results with that reported for a structurally similar TBDMS protected hydroxypyrroline *N*-oxide.[8a] In that case, the TMSOTf catalyzed addition of TMSCN was reported to afford a mixture of *trans* and *cis* *N*-hydroxypyrrolidines with a poor 1.5:1 diastereoselectivity. It is unclear if this outcome, which contrasts with the complete stereoselectivity observed by us, is a result of the different reaction procedure employed. However, when the reaction was performed with cyanides, a complete stereoselectivity was also observed,[8a] as it was by the authors of a recent patent.[9]

Next, we took the best systems, catalytic TMSOTf or DEAC, and surveyed nitrones **2b–e** in the cyanosilylation reaction using these Lewis acids as additives, in comparison with the reaction in absence of any additive (Scheme 5). The results are shown in Table 2 and establish the generality of the complete stereoselective cyanation previously proved with nitrone **2a**. The crude mixture was treated in all instances with 5% methanolic citric acid in order to obtain the free hydroxylamine **5–8**.



Scheme 5.

It is noteworthy that the reactions were extremely clean, the products were obtained essentially pure without the need to resort to chromatographic purification. In all cases, only a single isomer could be detected by HPLC and NMR. The relative stereochemistries at C-2/C-3 of the pyrrolidine ring could be inferred from NOE experiments as before. In the case of hydroxypyrrolidine (*rac*)-**8** a single X-ray crystal structure

Table 2. Trimethylsilyl cyanide addition to nitrones **2b–e**[a,b]

Entry	Nitrone	Additive (equiv.)	Time	Yield (%)[c]	*trans*:*cis*[d]
1	**2b**	None	16 h	100	>20:1
3		TMSOTf (1.0)	5 min	100	>20:1
4		TMSOTf (0.2)	5 min	100	>20:1
5		Et_2AlCl (1.0)	5 min	100	>20:1
6		Et_2AlCl (0.2)	5 min	100	>20:1
8	**2c**	TMSOTf (0.2)	5 min	100	>20:1
9		Et_2AlCl (0.2)	5 min	100	>20:1
11	**2d**	TMSOTf (0.2)	5 min	100	>20:1
12		Et_2AlCl (0.2)	5 min	100	>20:1
14	**2e**	TMSOTf (0.2)	5 min	100	>20:1
15		Et_2AlCl (0.2)	5 min	100	>20:1

[a] All reactions were carried out in CH_2Cl_2 at 25°C with 1.0 equiv. of TMSCN.
[b] Further treatment with 5% methanolic citric acid of the crude mixtures afforded free hydroxylamines. No purification was necessary.
[c] All reactions showed quantitative yield.
[d] Only one isomer could be detected by NMR noise-to-signal ratio.

analysis was accomplished, which confirmed the structural assignment (Fig. 2).[19]

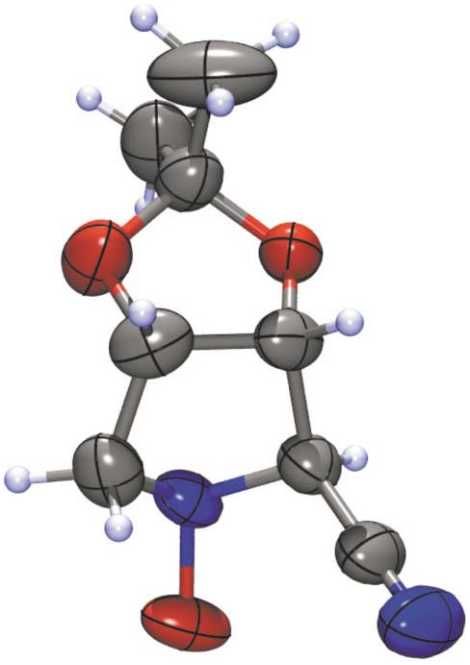


Figure 2. Perspective view (ORTEP) of (*rac*)-**8**. Non-hydrogen atoms are drawn as 50% thermal ellipsoids while hydrogens are drawn at an arbitrary size. Only the atoms refined with anisotropic thermal parameters are drawn with the principal axes indicated; the isotropic atoms are represented as simple circles.

The stereoselective cyanosilylation of **2a** was followed using NMR spectroscopy. Upon injecting a CD_2Cl_2 solution of TMSCN (1.0 equiv.) into a CD_2Cl_2 solution of nitrone **2a** at 20°C, the ^1H NMR spectrum was immediately recorded, at which time only the signals corresponding to nitrone **2a** (without variation of displacement) and TMSCN were observed. Upon ageing the reaction mixture for suitable periods the reagents afforded the corresponding product of the reaction.

In order to obtain information concerning the structures of the nitrone-additive complexes, ^1H NMR analysis of the mixture of equimolar amounts of nitrone **2a** and the Lewis acid was carried out (Fig. 3). The mixtures were prepared at −20°C by injecting CD_2Cl_2 solutions of the corresponding Lewis acid into an NMR tube containing a CD_2Cl_2 solution of **2a**. The ^1H NMR spectra were immediately recorded and they showed, in both cases (TMSOTf and DEAC) considerable deshielding of several protons.[20] Therefore the structures of complexes **A** and **B** were formulated as indicated in Fig. 3.

It is particularly revealing that the signal of the azomethine proton H_a of uncomplexed nitrone **2a** shifts downfield from 6.71 to 8.20 or 7.80 ppm upon complexation with TMSOTf or DEAC, respectively. Moreover, whereas the addition of a second equivalent of TMSOTf has no effect, the addition of a second equivalent of DEAC effected additional deshielding of H_a (7.90 ppm); two species were observed upon the addition of 1.5 equiv. DEAC. Thus, the formation of complex **C** with a 2:1 stoichiometry DEAC:nitrone can be postulated.

The reaction of TMSOTf-activated nitrone with 1.0 equiv. of TMSCN proceeded with the immediate disappearance of the complex. Upon injection of the cyanating agent and immediate recording of the spectrum only silylated hydroxylamine **3** could be detected. A similar result was observed when the nitrone was activated with DEAC. It proved impossible (even on cooling the mixture to −60°C) to record the progress of the reaction due to its extremely high rate.

At this stage, two major findings can be emphasized: (i) only starting materials and final products can be detected in the reaction of **2a** with TMSCN either in the absence of any additive or in the presence of Lewis acids and (ii) the resonances of the azomethine proton undergo a large downfield shift upon complexation of the nitrone functionality. These observations will be of importance for supporting the rationale for the cyanosilylation that is presented in the mechanistic section.

2.2. Diethylaluminum cyanide additions

The results of the addition of Et_2AlCN to nitrone **2a** are summarized in Table 3. We screened a variety of conditions in the hope of obtaining information about the reaction.

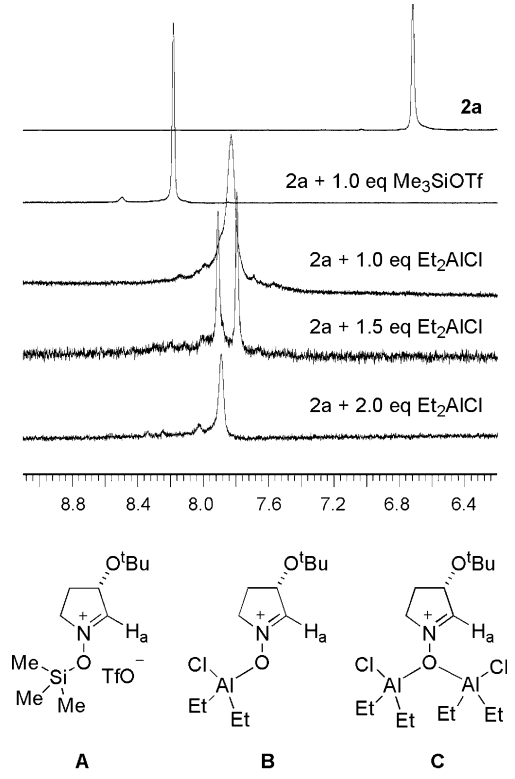


Figure 3. Partial NMR spectra, showing the signal corresponding to Ha, of **2a** upon the addition of Lewis acids.

Table 3. Diethylaluminum cyanide additions to nitrone **2a**[a]

Entry	Additive (equiv.)	Solvent	Time	Yield (%)[b]	*trans*:*cis*
1	None	CH_2Cl_2	2 h	100	66:33
2	None	CH_2Cl_2	1 h	100	70:30
3	None	CH_2Cl_2	30 min	100	75:25
4	None	CH_2Cl_2	5 min	100	90:10
5	None	CH_2Cl_2	[d]	100	90:10
6	None	THF	2 h	100	60:40
7	None	CH_2Cl_2	2 h	100	68:32[c]
8	None	THF	2 h	100	63:37[c]
9	TMSOTf (1.0)	CH_2Cl_2	5 min	100	90:10
10	Et_2AlCl (1.0)	CH_2Cl_2	5 min	100	86:14
11	TMSOTf (1.0)	CH_2Cl_2	15 min	100	85:15
12	Et_2AlCl (1.0)	CH_2Cl_2	15 min	100	80:20
13	TMSOTf (1.0)	CH_2Cl_2	30 min	100	78:22
14	Et_2AlCl (1.0)	CH_2Cl_2	30 min	100	72:28
15	TMSOTf (1.0)	CH_2Cl_2	1 h	100	69:31
16	Et_2AlCl (1.0)	CH_2Cl_2	1 h	100	67:33
17	TMSOTf (1.0)	CH_2Cl_2	2 h	100	69:31
18	Et_2AlCl (1.0)	CH_2Cl_2	2 h	100	67:33

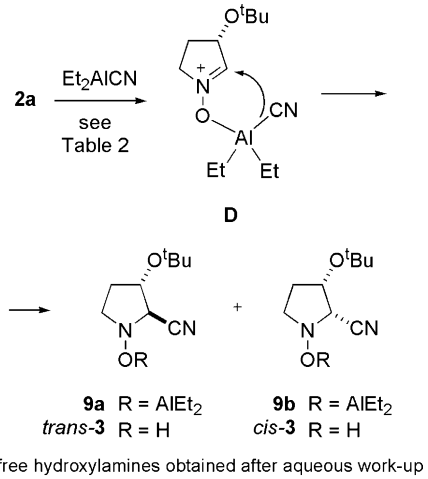
[a] All reactions were carried out at 25°C with 1.0 equiv. of Et_2AlCN.
[b] All reactions showed quantitative yield.
[c] 3.0 equiv. of Et_2AlCN were used.
[d] The reaction was quenched prior to the immediate addition of the nitrone which was made to react for 10 min.

Thus, a solution of nitrone **2a** in CH_2Cl_2 was treated with 1.0 equiv. of Et_2AlCN and the mixture was stirred at 0°C. Quenching of the reaction was made by addition of a saturated aqueous sodium bicarbonate solution. Surprisingly, rather different diastereoselectivities were obtained depending on the time of the reaction (Table 3, entries 1–4). This result might be due to the reversibility of the reaction. However, in an independent experiment a *cis*/*trans* 2:3 mixture of hydroxylamines **4** was placed in CH_2Cl_2 in the presence of aqueous $NaHCO_3$ containing 'quenched' Et_2AlCN. After 2 days the spectroscopic (^1H NMR) analysis of the mixture showed the same 2:3 ratio. The same experiment was repeated with pure *trans* and *cis* hydroxylamines, no variation of the diastereomeric purity being observed. Furthermore, these results show that epimerization of the hydroxylamines did not occur and, in consequence, the reversibility of the cyanide addition can be discarded, at least under these conditions.

Moreover, when a solution of Et_2AlCN in CH_2Cl_2 was treated with saturated aqueous sodium bicarbonate and the resulting mixture was treated with a solution of **2a** in CH_2Cl_2 (Table 3, entry 5) the reaction was complete after 15 min and a diastereoselectivity of 9:1 was obtained. This experiment clearly indicates that 'free' cyanide anion, produced after quenching is actual nucleophile when reaction of Et_2AlCN is not complete. These observations are in agreement with the previously reported addition of cyanides to a particular nitrone **2** (R = TBS).[8a,9]

From these experiments it can be concluded that at least 2 h are needed for the Et_2AlCN addition to reach completion. Low selectivities were observed and no better results were obtained on using an excess of Et_2AlCN or on changing the solvent of the reaction (Table 3, entries 6–8).

The efficiency of TMSOTf and DEAC as activating agents was lower than for the addition of TMSCN, probably due to the necessity of formation of a reactive complex in the case of Et_2AlCN addition (Scheme 6). As will be considered in more detail in the mechanistic section, those results suggest that such a complex would be less favored if an electron pair of the nitrone oxygen is compromised with the Lewis acid.



Scheme 6.

In order to estimate some rate enhancement of the reaction it was quenched at different times. After 5 min it was found a higher selectivity for the TMSOTf-promoted reaction (Table 3, entry 9) than that activated with Et_2AlCl (Table 3, entry 10). The same trend was

Table 4. Diethylaluminum cyanide additions to nitrone **2b–e**[a]

Entry	R	Additive (equiv.)	Time (h)	Yield (%)[b]	*trans*:*cis*
1	**2b**	None	2	100	66:33
2		TMSOTf (1.0)	1	100	70:30
3		Et_2AlCl (1.0)	1	100	72:28
4	**2c**	None	2	100	70:30
5		TMSOTf (1.0)	1	100	68:32
6		Et_2AlCl (1.0)	1	100	67:33
7	**2d**	None	2	100	65:35
8		TMSOTf (1.0)	1	100	60:40
9		Et_2AlCl (1.0)	1	100	62:38
10	**2e**	None	2	100	78:22
11		TMSOTf (1.0)	1	100	75:25
12		Et_2AlCl (1.0)	1	100	72:28

[a] All reactions were carried out in CH_2Cl_2 at 25°C with 1.0 equiv. of Et_2AlCN.
[b] All reactions showed quantitative yield.

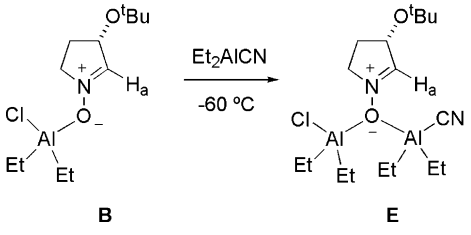
maintained after 15 min, 30 min, 1 and 2 h (Table 3, entries 11–18) at which time one can estimate that the reaction is finished. These results confirmed a slight Lewis acid activation for the Et_2AlCN addition, the TMSOTf-promoted reaction being slower than the Et_2AlCl promoted one. *It can be concluded that a higher reaction rate leads to lower diastereoselectivity*.

The hydrocyanation with Et_2AlCN was extended to nitrones **2b–e**; the results are summarized in Table 4. The observed diastereoselectivities were similar to those observed for **2a** and similar slight enhancement of the reaction rates were observed upon activation with Lewis acids. Thus, the presence of TMSOTf or DEAC speeds up the reaction, although diastereoselectivities remain practically the same. Moreover, the selectivity is mainly inferred by the vicinal alkoxy group, remaining almost the same for all nitrone substrates and only slightly increasing for the *cis* configured diol **2e** and decreasing for the *trans* **2d**, as expected.

Unambiguous evidence for the formation of an initial complex between nitrone **2a** and Et_2AlCN was obtained by carrying out a ^1H NMR study of the complexation in Scheme 6 in CD_2Cl_2. In all cases, freshly prepared Et_2AlCN was used, obtained by the reaction of trimethylsilyl cyanide and diethylaluminum chloride in dry CH_2Cl_2.[21]

Upon injecting a CD_2Cl_2 solution of Et_2AlCN (1 equiv.) into a CD_2Cl_2 solution of nitrone **2a** at –60°C the ^1H NMR spectrum was immediately recorded. The signal of the azomethine proton shifted downfield from 6.71 ppm (nitrone) to 7.70 ppm, thus indicating the formation of complex **D** in a similar way to the addition of Et_2AlCl. The complex showed broad signals, probably due to either nitrogen inversion or presence of rotamers around the N–O bond (see discussion above).[14–16] To this respect, it proved impossible to record the spectrum at temperatures above 0°C, because under these conditions irreversible C–C bond formation set in simultaneously. At –60°C there is no C–C bond formation for at least 1 h. Aging the reaction by warming to 0°C showed gradual disappearance of complex **D** with concomitant formation of new species to which structures **9** were tentatively assigned. After 2 h the spectrum did not show any additional change, therefore it is experimentally proved that the use of only 1.0 equiv. of Et_2AlCN consumes completely the nitrone, giving a quantitative yield of the product. For shorter reaction times the reaction is complete after quenching as a consequence of the free cyanide liberated upon aqueous treatment of the reaction mixture.

On the assumption that in the presence of additives the formation of the final adducts occurs by nucleophilic attack to the coordinated nitrone, we hoped that addition of Et_2AlCN in the presence of DEAC would allow us to detect an intermediate containing a nitrone bridging ligand between two aluminum atoms (in a similar way to that found when 2 equiv. of DEAC were added to **2a** to form complex **C**—see above). Indeed, it was possible to observe that the signal for the azomethine proton of Et_2AlCl complexed nitrone **B** shifts upfield from 7.80 to 7.86 ppm upon addition of Et_2AlCN at –60°C, thus indicating the formation of complex **E** (Scheme 7). This observation could not be confirmed in the case of the TMSOTf activated nitrone because the otherwise sharp lines of complex **A** became broad even at low temperatures.



Scheme 7.

Both TMSOTf- and DEAC-promoted reactions proceeded more rapidly than those carried out in the absence of any additive, the former being slower than the latter. Moreover, relative rates between activated and non-activated reactions with TMSCN and Et_2AlCN indicated a higher efficiency of the activation

in the case of TMSCN addition. These observations provided considerable insight into the two-step (complex formation and cyanide transfer) mechanism of the addition of Et_2AlCN to nitrones **2** illustrated in Scheme 6.

Reaction retardation for the TMSOTf-promoted Et_2AlCN addition with respect to the Et_2AlCl-promoted reaction is consistent with lower availability of the remaining electron-pair of the nitrone oxygen for the crucial complexation with the aluminum atom of the cyanating reagent. Thus, it can be postulated an internal delivery of CN from complexes **D** or **E** for Et_2AlCN in contrast to the external delivery occurring in reactions with TMSCN.

2.3. Computational studies

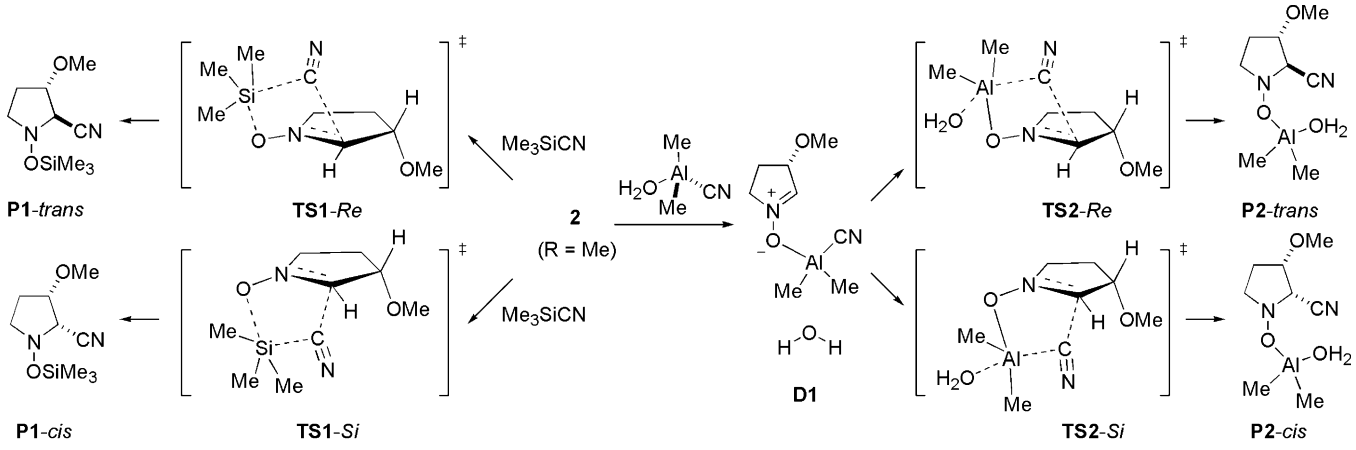
To investigate the origin of the stereoselectivity of the cyanation reactions we carried out a theoretical study using semiempirical and DFT methods. Semiempirical calculations were performed with MOPAC 2000[22] and DFT calculations were carried out with Gaussian98.[23] All stationary points were optimized first at the semiempirical AM1 method,[24] then moved to Gaussian98 and optimized without any restriction at the B3LYP/6-31G(d)[25] level of theory. Vibrational frequencies were calculated (1 atm, 298.15 K) for all B3LYP/6-31G(d) optimized structures and used, unscaled, to compute both ZPVE and activation energies. Intrinsic reaction coordinate (IRC) analysis[26] was performed to verify that the transition structures connect reactants and products. Graphical animations of the imaginary frequencies (transition vectors) for all transition structures and IRC calculations ensured that the motions were appropriate for converting reactants to products and for verifying the reaction path.[27] The only simplification of the calculations consisted of replacement of the *tert*-butyl group of the nitrone and the ethyl groups of the Et_2AlCN by methyl groups in all cases. So, the calculated reactions were those between nitrone **2** (R = Me) and Me_2AlCN or TMSCN. A molecule of water was also included in the study of the reaction with Me_2AlCN in order to simulate the presence of the solvent.

Calculations were carried out with the most stable conformer of the nitrone. The calculated reaction paths are depicted in Scheme 8. For the addition of TMSCN two transition structures, **TS1-*Re*** and **TS1-*Si***, were located. The geometries of these stationary points and the nitrone are depicted in Fig. 4.[28] The total and relative energies as well as selected geometrical parameters are summarized in Table 5.

The transition structure corresponding to a *Re* attack, **TS1-*Re***, is more stable (3.74 kcal/mol) than **TS1-*Si*** (corresponding to the *Si* attack), the former having a relatively high energy barrier (37.25 kcal/mol), which is in agreement with a slow reaction even at ambient temperature. The IRC calculations confirm that transition structures connect **2** and the corresponding products and no intermediate stable complexes (minima of energy) having a pentacoordinate silicon atom were found following the reaction path. Such a pentacoordinated silicon atom was found only in the transition structures in agreement with previous calculations for nucleophilic additions of silyl ketene acetals to nitrones.[29]

The lengths of the forming C–C bonds in **TS1-*Re*** and **TS1-*Si*** are 2.26 and 2.31 Å, respectively. The lengths of the Si–O distances in **TS1-*Re*** and **TS1-*Si*** are 1.84 and 1.83 Å, respectively, thus showing that the Si–O bond formation is more advanced than the C–C bond formation (even when the forming bond lengths are compared with typical values of the stated bonds, i.e. C–C and Si–O).

In the case of the addition of Me_2AlCN the reaction proceeds through a two-step mechanism, in agreement with experimental observations and as illustrated in Scheme 6. The first step corresponds to the formation of a stable complex **D1** (8.45 kcal/mol below the reactants for DFT calculations) without energy barrier, through the displacement of the molecule of solvent (water) by the nitrone. The conformational analysis of **D1** (by rotation of N–O and O–Al bonds) give us clues to understand the experimentally observed ^1H NMR spectra which presented broad signals at −60°C. Very



Scheme 8.

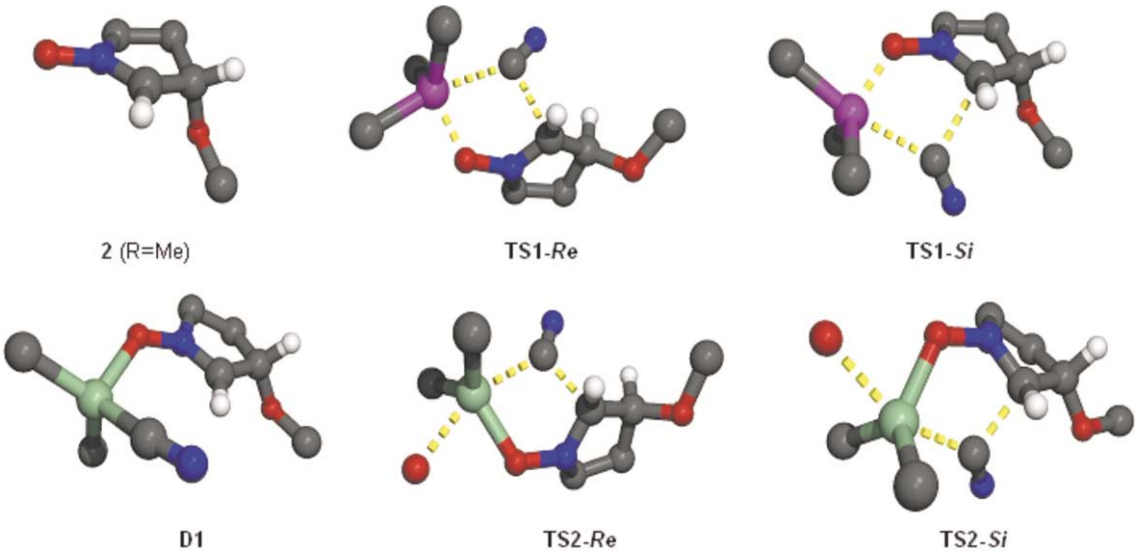


Figure 4. B3LYP/6-31G(d) optimized structures of important stationary points of the TMSCN and Me_2AlCN additions to **2** (R = Me). Some hydrogen atoms have been omitted for clarity. For selected geometrical data see Table 5.

Table 5. Total free energies, relative free energies and selected bond lengths (in Å), for the stationary points of the nucleophilic additions of TMSCN and Me_2AlCN to **2** (R = Me)

	AM1		B3LYP/6-31G(d)		Geometric parameters[a]				
	Total energy[b]	Relative energy[b]	Total energy[c]	Relative energy[b]	C–C[d]	C–N[e]	N–O[e]	C–X[f]	O–X[f]
2 (R = Me)	−23.21	–	−400.946434	–	–	1.31	1.258	–	–
Me_3SiCN	−27.20	–	−502.039177	–	–	–	–	1.88	–
$Me_2AlCN{\cdot}H_2O$	−70.94	–	−491.513985	–	–	–	–	1.96	2.06
TS1-*Re*	−7.04	43.37[g]	−902.926255	37.25[g]	2.26	1.30	1.34	2.49	1.84
TS1-*Si*	−2.60	47.81[g]	−902.920290	40.99[g]	2.31	1.30	1.34	2.53	1.83
P1-*trans*	−77.37	−26.96[g]	−903.002184	−10.40[g]	1.47	1.49	1.46	–	1.71
P1-*cis*	−74.84	−24.43[g]	−903.000895	−9.59[g]	1.47	1.48	1.46	–	1.71
D1[j]	−97.80	−3.65[h]	−892.474878	−8.45[h]	–	1.29	1.31	2.01	1.94
TS2-*Re*	−70.88	26.92[i]	−892.438060	22.48[i]	1.97	1.34	1.35	2.32	1.91 (2.18)
TS2-*Si*	−64.79	33.01[i]	−892.429810	27.65[i]	2.00	1.33	1.35	2.28	1.92 (2.20)
P2-*trans*	−122.20	−28.05[h]	−892.488932	−17.89[h]	1.47	1.47	1.43	–	1.79 (2.03)
P2-*cis*	−119.74	−21.94[h]	−892.487750	−17.15[h]	1.47	1.48	1.43	–	1.80 (2.02)

[a] Only those corresponding to B3LYP/6-31G(d) optimized structures are given.
[b] kcal/mol.
[c] Hartrees.
[d] Referred to the forming C–C bond in transition structures.
[e] Referred to nitrone/hydroxylamine.
[f] X = Si for **TS1** and **P1**; X = Al for **D1**, **TS2** and **P2**; referred to nitrone oxygen; referred to coordinating water in brackets.
[g] Referred to **2**+Me_3SiCN.
[h] Referred to **2**+$Me_2AlCN{\cdot}H_2O$.
[i] Referred to complex **D1**.
[j] The energy corresponding to a molecule of water (−59.25 kcal/mol (AM1) and −76.406097 au (B3LYP/6-31G(d)) has been included for comparison of relative energies.

low energy differences (1–2 kcal/mol) are found when the PES defined by the two dihedral angles mentioned above was analyzed[30] (the most stable conformer is depicted in Fig. 5). The second step is the intramolecular delivery of cyanide via transition structures **TS2-*Re*** and **TS2-*Si*** to give *trans* and *cis* adducts, respectively. The energy barriers are 22.48 and 27.65 kcal/mol for **TS2-*Re*** and **TS2-*Si***, respectively and the *trans* adduct is more stable than the *cis* adduct. The final products are lower in energy than complex **D1**, indicating an exothermic transformation.

The lengths of the O–Al bonds change from 1.94 Å in the starting complex to 1.91 and 1.92 Å in the transition structures, showing a continuance of the O–Al bond during the rate-limiting step. The lengths of the C–C forming bonds in **TS2-*Re*** and **TS2-*Si*** are 1.97 and 2.00 Å, respectively.

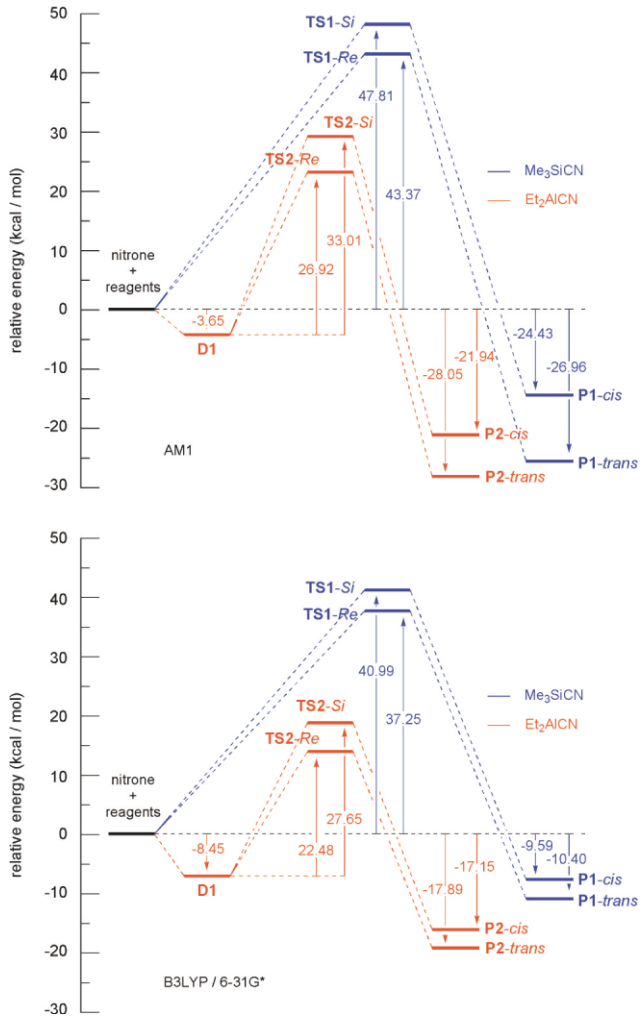


Figure 5. Energy profiles of the TMSCN (blue) and Me_2AlCN (red) additions to **2** (R = Me) at the AM1 and B3LYP/6-31G(d) level.

For the purpose of comparison, the energy profiles of the addition reactions of the two cyanating reagents are given in Fig. 5. These energetic differences are in agreement with experimental results concerning both selectivity (*Re* attack is preferred to *Si* attack) and reactivity (Me_2AlCN is more reactive than TMSCN). However, the selectivity differences observed between the two cyanating reagents are not well-described. It should be noted that for a quantitative evaluation of the diastereomeric ratio the B3LYP/6-31G(d) level of theory might not be sufficiently flexible to produce reliable energetics across the entire potential energy surface.

In conclusion, based upon these calculations we propose that TMSCN is added to nitrone **2** in a one-step process without formation of any stable intermediate, via transition states **TS1-*Re*** and **TS1-*Si***. In contrast, the addition of Et_2AlCN to **2** takes place via transition structures **TS2-*Re*** and **TS2-*Si*** formed from the intermediate complex **D1**, which has been detected by NMR.

3. Conclusions

A complete study of the hydrocyanation of α-alkoxy chiral non-racemic cyclic nitrones has been carried out. Additionally, a rationale for the cyanation of cyclic nitrones using TMSCN and Et_2AlCN has been given.

According to both theoretical and experimental observations, whereas TMSCN reacts through a concerted transition state, Et_2AlCN initially forms a complex, which evolves to the final product via intramolecular carbon-carbon bond formation. On the basis of intrinsic reactivity data, there is no doubt that Et_2AlCN behaves as an intramolecular cyanating agent.

A comparison of the results reported in the Tables for the two cyanating reagents employed under a variety of conditions clearly show that the stereoselectivity furnished by TMSCN is always considerably higher than that seen with Et_2AlCN. A study of the reaction profile by ^1H NMR and theoretical calculations allows us to assign this difference to the switch from an intermolecular to an intramolecular mode of addition on passing from TMSCN to Et_2AlCN.

Careful examination of the reaction conditions employed in this study allows us to raise a general warning when Et_2AlCN is used as a cyanating agent, to ensure that the addition is complete before quenching, the rate of addition being much slower than that of free cyanide.

From a practical point of view, virtually quantitative yields of adducts were obtained and complete stereoselectivity has been achieved in the addition of TMSCN with all the nitrones under study. Moreover, very short reaction times are attainable with the use of catalytic amounts of TMSOTf or DEAC and no separation technique is needed for recovery of hydroxylamine products. This study suggests that the same behavior will be displayed by at least all 3-oxy substituted pyrroline *N*-oxides, which makes their cyanation a general and valuable method for the synthesis of adducts of the type **3**. In turn, compounds **3** can be envisaged as useful intermediates for obtaining substituted prolines, as demonstrated by a recently patented work,[9] or chiral diamines usable as chelating ligands for metal complexation and related to those already employed in clinical trials with Pt-based anticancer agents.[31]

4. Experimental

The reaction flasks and other glass equipment were heated in an oven at 130°C overnight and assembled in a stream of Ar. All reactions were monitored by TLC on silica gel 60 F254; the position of the spots were detected with 254 nm UV light or by spraying with one of the following staining systems: 50% methanolic sulfuric acid, 5% ethanolic phosphomolybdic acid and iodine. Preparative centrifugally accelerated radial thin-layer chromatography (PCAR-TLC) was performed with a Chromatotron® Model 7924 T (Harrison Research, Palo Alto, CA, USA) and with solvents that

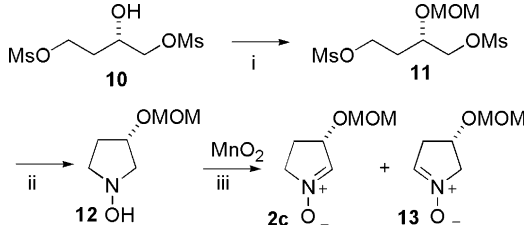
were distilled prior to use; the rotors (1 or 2 mm layer thickness) were coated with silica gel Merck grade type 7749, TLC grade, with binder and fluorescence indicator (Aldrich 34,644-6) and the eluting solvents were delivered by the pump at a flow-rate of 0.5–1.5 mL min^{-1}. Melting points were uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Varian Unity or on a Bruker 300 instrument in $CDCl_3$. Chemical shifts are reported in ppm (δ) relative to $CHCl_3$ ($\delta=7.26$) in $CDCl_3$. Optical rotations were taken at 25°C on a Perkin–Elmer 241 polarimeter. Elemental analysis were performed on a Perkin Elmer 240B microanalyzer. Nitrones **2a**,[10a] **2b**,[10b] **2d**[11] and **2e**[4a] were prepared as described. Diethylaluminum cyanide was prepared as described.[21]

4.1. Synthesis of 4-methoxymethoxy-3,4-dihydro-2*H*-pyrrole 1-oxide

The nitrone **2c** was synthesized following the procedure reported in Scheme 9.

4.1.1. Methanesulfonic acid 4-methanesulfonyloxy-3-methoxymethoxy-butyl ester, 11. A solution of methanesulfonic acid 2-hydroxy-4-methanesulfonyloxy-butyl ester **10**[32] (1.2 g, 4.57 mmol) in $CHCl_3$ (60 mL) was mixed with dimethoxymethane (9 mL, 101.7 mmol) and phosphorus pentoxide (4.5 g, 31.71 mmol) and stirred at room temperature for 45 min. The suspension was then cooled with ice and quenched by slow addition of a saturated Na_2CO_3 solution. The aqueous phase was washed with ether (3×30 mL) and the washings were added to the $CHCl_3$ solution. The organic phase was washed with brine, dried with Na_2SO_4, and concentrated. The crude reaction mixture was purified by passage on a short pad of silica gel (petroleum ether:ethyl acetate, 1:1) to afford pure **11** (1.41 g, 100%) as a colorless oil; $R_f=0.37$; $[\alpha]_D^{25}=-40$ (*c* 0.46, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.98–2.08 (s, 2H), 3.03 (s, 3H), 3.05 (s, 3H), 3.40 (s, 3H), 3.98 (dq, 1H, $J=6.6$, 4.4 Hz), 4.20–4.32 (m, 2H), 4.37 (t, 2H, $J=6.6$ Hz), 4.67–4.76 (AB system, 2H). ^{13}C NMR ($CDCl_3$) δ 31.5, 37.5, 37.6, 56.1, 65.6, 70.3, 71.9, 96.8. Anal. calcd for $C_8H_{18}S_2O_8$: C, 31.37; H, 5.93. Found: C, 31.20; H, 5.80%.

4.1.2. 3-Methoxymethoxy-pyrrolidin-1-ol, 12. A suspension of **11** (3.0 g, 9.43 mmol) and hydroxylamine hydrochloride (3.14 g, 45.24 mmol) in triethylamine (60 mL) was heated under reflux with vigorous stirring for 4 h. The suspension was concentrated and the remaining solid was washed thoroughly with ether (3×50 mL). The ethereal washings were concentrated and the residue was purified by flash column chromatography (petroleum ether:ethyl acetate, 3:1) to afford pure **12** (1.0 g, 66%) as a pale yellow oil. $R_f=0.51$; $[\alpha]_D^{25}=+17$ (*c* 2.2, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.56 (bs, 1H), 1.98, (bs, 1H), 2.65–3.05 (m, 5H), 3.09 (s, 3H), 4.1 (bs, 1H), 4.36 (AB system, 2H). ^{13}C NMR ($CDCl_3$) δ 29.8, 54.9, 57.1, 64.3, 75.3, 95.4. Anal. calcd for $C_6H_{13}NO_3$: C, 48.97; H, 8.90; N, 9.52. Found: C, 48.90; H, 8.80; N, 9.13%.



Scheme 9. *Reagents*: (i) $CH_3OCH_2OCH_3$, P_2O_5. (ii) NH_2OH. (iii) MnO_2.

4.1.3. 4-Methoxymethoxy-3,4-dihydro-2*H*-pyrrole 1-oxide. A solution of **12** (700 mg, 4.76 mmol) in CH_2Cl_2 (25 mL), cooled into an ice bath, was added with MnO_2 (472 mg, 5.26 mmol). The suspension was stirred at 0°C for 1 h, then at rt overnight. The suspension was filtered on a short pad of Celite and Na_2SO_4 and the solution concentrated. The crude reaction mixture contained the two regioisomeric nitrones **2c** and **13** in a 9:1 ratio. Separation by flash column chromatography (ethyl acetate:ethanol, 1:5) afforded pure nitrones **2c** (590 mg, 85%) as a colourless oil and **13** (100 mg, 14%) as a yellowish solid.

4.1.3.1. 4-Methoxymethoxy-3,4-dihydro-2*H*-pyrrole 1-oxide, 2c. $R_f=0.29$; $[\alpha]_D^{25}=-77$ (*c* 1.28, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.97–2.12 (m, 1H), 2.37–2.56 (m, 1H), 3.20 (s, 3H), 3.71 (ddd, 1H, $J=9.5$, 5.2, 5.1 Hz), 3.90–4.05 (m, 1H), 4.51 (AB system, 2H), 4.67 (d, 1H, $J=7.3$ Hz), 6.85, (s, 1H). ^{13}C NMR ($CDCl_3$) δ 27.8, 55.5, 60.9, 77.2, 99.0, 134.5. Anal. calcd for $C_6H_{11}NO_3$: C, 49.65; H, 7.64; N, 9.65. Found: C, 49.84; H, 7.36; N, 9.83%.

4.1.3.2. 3-Methoxymethoxy-3,4-dihydro-2*H*-pyrrole 1-oxide, 13. Mp 35–37°C. $R_f=0.11$; $[\alpha]_D^{25}=33$ (*c* 2.63, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.75 (dd, 1H, $J=19.4$, 1.5Hz), 3.03 (ddd, 1H, $J=19.4$, 6.6, 1.5 Hz), 3.35 (s, 3H), 3.92 (d, 1H, $J=14.6$ Hz), 4.15 (dd, 1H, $J=14.6$, 6.6 Hz), 4.51 (dq, 1H, $J=9.6$, 2.9 Hz), 4.67 (AB system, 2H), 6.85, (s, 1H). ^{13}C NMR ($CDCl_3$) δ 36.8, 55.2, 68.1, 70.6, 95.7, 132.8. Anal. calcd for $C_6H_{11}NO_3$: C, 49.65; H, 7.64; N, 9.65. Found: C, 49.55; H, 7.74; N, 9.45%.

4.2. (2*R*,3*S*)-3-*tert*-Butoxy-1-(trimethylsiloxy)-pyrrolidine-2-carbonitrile, 3

To a solution of nitrone **2** (0.157 g, 1 mmol) in CH_2Cl_2 (10 mL) was added trimethylsilyl cyanide (0.100 g, 1 mmol). The resulting solution was stirred at ambient temperature for 16 h, at which time the solvent was rotatory evaporated to afford pure **3** (0.256 g, 100%) as a colourless oil; $[\alpha]_D^{25}=-62$ (*c* 0.56, $CHCl_3$); ^1H NMR ($CDCl_3$, 55°C) δ 0.14 (s, 9H), 1.18 (s, 9H), 1.65 (ddd, 1H, $J=3.9$, 8.3, 12.7 Hz), 2.19 (dt, 1H, $J=8.3$, 12.7 Hz), 2.86–3.12 (m, 2H), 3.50 (d, 1H, $J=5.4$ Hz), 4.30–4.36 (m, 1H). ^{13}C NMR ($CDCl_3$, 55°C) δ –0.7, 28.2, 31.8, 57.1, 66.4, 73.9, 74.6, 114.4 Anal. calcd for $C_{12}H_{24}N_2O_2Si$: C, 56.21; H, 9.43; N, 10.92. Found: C, 56.49; H, 9.11; N, 11.25%.

4.3. Addition of trimethylsilyl cyanide to nitrones in the absence of Lewis acids. General procedure

To a solution of the corresponding nitrone (1 mmol) in CH_2Cl_2 (10 mL) was added trimethylsilyl cyanide (0.100 g, 1 mmol). The resulting solution was stirred at ambient temperature for 16 h, at which time the solvent was rotatory evaporated. The residue was taken up into 5% methanolic citric acid (10 mL) and the resulting mixture was stirred for 1 h, at which time saturated aqueous sodium bicarbonate (25 mL) was added. The reaction mixture was extracted with dichloromethane (3×15 mL) and the combined organic extracts were dried ($MgSO_4$) and evaporated to give the free hydroxylamines which did not need further purification.

4.3.1. (2*R*,3*S*)-3-*tert*-Butoxy-1-hydroxy-pyrrolidine-2-carbonitrile, 4. (0.184 g, 100%); oil; $[\alpha]_D^{25}=+20$ (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.14 (s, 9H), 1.69 (ddt, 1H, $J=13.4$, 8.6, 3.7 Hz), 2.22 (dq, 1H, $J=13.4$, 8.6 Hz), 3.06 (dt, 1H, $J=11.7$, 8.6 Hz), 3.18 (ddd, 1H, $J=11.7$, 8.1, 3.7 Hz), 3.58 (d, 1H, $J=5.9$ Hz), 4.33 (ddd, 1H, $J=8.9$, 5.9, 3.7 Hz), 7.41 (s, 1H, ex. D_2O). ^{13}C NMR ($CDCl_3$) δ 28.1, 31.6, 56.2, 67.7, 73.3, 74.9, 117.8. Anal. calcd for $C_9H_{16}N_2O_2$: C, 58.67; H, 8.75; N, 15.21. Found: C, 58.77; H, 8.63; N, 15.31%.

4.3.2. (2*R*,3*S*)-1-Hydroxy-3-(triisopropylsiloxy)-pyrrolidine-2-carbonitrile, 5. (0.285 g, 100%); oil; $[\alpha]_D^{25}=-37$ (*c* 0.27, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.05 (s, 21H), 1.68–1.72 (m, 1H), 2.28–2.31 (m, 1H), 3.20–3.24 (m, 2H), 3.73 (s, 1H), 4.63–4.66 (m, 1H), 6.48 (bs, 1H, ex. D_2O). ^{13}C NMR ($CDCl_3$) δ 6.8, 12.3, 27.8, 50.5, 62.1, 69.2, 118.2. Anal. calcd for $C_{14}H_{28}N_2O_2Si$: C, 59.11; H, 9.92; N, 9.85. Found: C, 59.22; H, 9.86; N, 9.97%.

4.3.3. (2*R*,3*S*)-1-Hydroxy-3-(methoxymethoxy)-pyrrolidine-2-carbonitrile 6. (0.173 g, 100%); oil; $[\alpha]_D^{25}=+9$ (*c* 0.22, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.79–2.01 (m, 1H), 2.20–2.44 (m, 1H), 3.07–3.34 (m, 2H), 3.43 (s, 3H), 3.85 (d, 1H, $J=4.4$ Hz), 4.37–4.50 (m, 1H), 4.69 (pseudo d, 2H, $J=1.5$ Hz), 5.62 (bs, 1H, ex. D_2O). ^{13}C NMR ($CDCl_3$) δ 28.7, 55.0, 55.2, 64.1, 77.7, 95.6, 117.7. Anal. calcd for $C_7H_{12}N_2O_3$: C, 48.83; H, 7.02; N, 16.27. Found: C, 48.88; H, 6.90; N, 16.15%.

4.3.4. (2*S*,3*S*,4*S*)-3,4-Di-*tert*-butoxy-1-hydroxy-pyrrolidine-2-carbonitrile, 7. (0.256 g, 100%); oil; $[\alpha]_D^{25}=-16$ (*c* 0.80, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.15 (s, 9H), 1.22 (s, 9H), 3.14 (dd, 1H, $J=10.3$, 4.4 Hz), 3.18 (dd, 1H, $J=10.3$, 6.4 Hz), 3.60 (d, 1H, $J=5.0$ Hz), 3.89 (ddd, 1H, $J=6.4$, 4.4, 3.4 Hz), 4.12 (dd, 1H, $J=5.0$, 3.4 Hz), 5.80 (bs, 1H, ex. D_2O). ^{13}C NMR ($CDCl_3$) δ 28.2, 28.6, 31.5, 56.4, 69.3, 74.0, 75.8, 76.2, 116.4. Anal. calcd for $C_{13}H_{24}N_2O_3$: C, 60.91; H, 9.44; N, 10.93. Found: C, 61.06; H, 9.38; N, 11.00%.

4.3.5. (2*R,3*S**,4*R**)-5-Hydroxy-2,2-dimethyl-tetrahydro-[1,3]dioxolo[4,5-c]pyrrole-4-carbonitrile, 8**. (0.184 g, 100%); white solid; mp 110–112°C; ^{1}H NMR ($CDCl_3$) δ 1.27 (s, 3H), 1.44 (s, 3H), 3.15 (dd, 1H, $J=11.4$, 4.8 Hz), 3.42 (d, 1H, $J=11.4$ Hz), 4.20 (s, 1H), 4.70–4.80 (m, 2H), 6.18 (bs, 1H, ex. D_2O). ^{13}C NMR ($CDCl_3$) δ 24.3, 25.8, 60.5, 62.9, 76.1, 80.1, 112.6, 114.8. Anal. calcd for $C_8H_{12}N_2O_3$: C, 52.17; H, 6.57; N, 15.21. Found: C, 52.21; H, 6.53; N, 15.18%.

4.4. Addition of trimethylsilyl cyanide to nitrones in the presence of Lewis acids. General procedure

To a solution of the corresponding nitrone (1 mmol) in CH_2Cl_2 (10 mL) was added the corresponding Lewis acid (1 mmol for stoichiometric reactions or 0.2 mmol for catalytic reactions). The resulting mixture was stirred for 5 min at ambient temperature, at which time trimethylsilyl cyanide (0.100 g, 1 mmol) was added. After stirring for 5 min, the solvent was rotatory evaporated. The residue was taken up into 5% methanolic citric acid (10 mL) and the resulting mixture was stirred for 1 h, at which time saturated aqueous sodium bicarbonate (25 mL) was added. The reaction mixture was extracted with dichloromethane (3×15 mL) and the combined organic extracts were dried ($MgSO_4$) and evaporated to give the free hydroxylamines which did not need further purification.

4.5. Addition of diethylaluminium cyanide to nitrones in the absence of Lewis acids. General procedure

To a solution of the corresponding nitrone (1 mmol) in CH_2Cl_2 (10 mL) was added diethylaluminium cyanide (0.111 g, 1 mmol). The resulting solution was stirred at ambient temperature (for time see Tables 3 and 4), at which time the reaction mixture was quenched by the addition of saturated aqueous sodium bicarbonate (15 mL). The resulting mixture was stirred for additional 5 min at ambient temperature and then extracted with CH_2Cl_2 (3×15 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated to give the crude mixture which was taken up into 5% methanolic citric acid (10 mL) and the resulting mixture was stirred for 1 h, at which time saturated aqueous sodium bicarbonate (25 mL) was added. The reaction mixture was extracted with dichloromethane (3×15 mL) and the combined organic extracts were dried ($MgSO_4$) and evaporated to give the pure mixture of free hydroxylamines. Separation of the diastereomers was performed by preparative centrifugally accelerated thin layer chromatography with a Chromatotron®.

4.6. Addition of diethylaluminium cyanide to nitrones in the presence of Lewis acids. General procedure

To a solution of the corresponding nitrone (1 mmol) in CH_2Cl_2 (10 mL) was added the corresponding Lewis acid (1 mmol for stoichiometric reactions or 0.2 mmol for catalytic reactions). The resulting mixture was stirred for 5 min at ambient temperature, at which time diethylaluminium cyanide (0.111 g, 1 mmol) was added. The reaction mixture was stirred at ambient temperature (for time see Tables 3 and 4), and then it was quenched by the addition of saturated aqueous sodium bicarbonate (15 mL). The resulting mixture was stirred for additional 5 min at ambient temperature and then extracted with CH_2Cl_2 (3×15 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated to

give the crude mixture which was taken up into 5% methanolic citric acid (10 mL) and the resulting mixture was stirred for 1 h, at which time saturated aqueous sodium bicarbonate (25 mL) was added. The reaction mixture was extracted with dichloromethane (3×15 mL) and the combined organic extracts were dried ($MgSO_4$) and evaporated to give the pure mixture of free hydroxylamines. Separation of the diastereomers was performed by preparative centrifugally accelerated thin layer chromatography with a Chromatotron®.

4.6.1. (2*S*,3*S*)-3-*tert*-Butoxy-1-hydroxy-pyrrolidine-2-carbonitrile, *cis*-4. (0.061 g, 33%); oil; $[\alpha]_D^{25}=+21$ (*c* 0.40, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.22 (s, 9H), 1.74–1.97 (m, 1H), 2.07–2.34 (m, 1H), 2.84 (dt, 1H, $J=10.3$, 8.8 Hz), 3.36 (ddd, 1H, $J=10.3$, 8.8, 4.4 Hz), 3.85 (d, 1H, $J=6.6$ Hz), 4.28 (ddd, 1H, $J=8.9$, 5.9, 3.7 Hz), 6.00 (s, 1H, ex. D_2O).^{13}C NMR ($CDCl_3$) δ 27.4, 31.3, 54.7, 64.4, 68.3, 74.5, 115.6. Anal. calcd for $C_9H_{16}N_2O_2$: C, 58.67; H, 8.75; N, 15.21. Found: C, 58.57; H, 8.80; N, 15.15%.

4.6.2. (2*S*,3*S*)-1-Hydroxy-3-(triisopropylsiloxy)-pyrrolidine-2-carbonitrile, *cis*-5. (0.094 g, 33%); oil; $[\alpha]_D^{25}=+15$ (*c* 0.10, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.05 (s, 21H), 1.83–1.86 (m, 1H), 2.26–2.28 (m, 1H), 2.95 (q, 1H, $J=8.3$ Hz), 3.92 (d, 1H, $J=6.8$ Hz), 4.60 (pseudo q, 1H, $J=6.5$ Hz), 6.12 (bs, 1H, ex. D_2O). ^{13}C NMR ($CDCl_3$) δ 6.8, 12.0, 32.8, 55.5, 65.7, 69.8, 115.7. Anal. calcd for $C_{14}H_{28}N_2O_2Si$: C, 59.11; H, 9.92; N, 9.85. Found: C, 59.34; H, 9.69; N, 9.91%.

4.6.3. (2*S*,3*S*)-1-Hydroxy-3-(methoxymethoxy)-pyrrolidine-2-carbonitrile, *cis*-6. (0.052 g, 30%); sticky oil; $[\alpha]_D^{25}=-50$ (*c* 0.10, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.93–2.17 (m, 1H), 2.24–2.47 (m, 1H), 2.87–3.05 (m, 1H), 3.35–3.45 (m, 1H), 3.46 (s, 3H), 3.96 (d, 1H, $J=5.9$ Hz), 4.31–4.47 (m, 1H), 4.74 (s, 2H), 5.34 (bs, 1H, ex. D_2O). ^{13}C NMR ($CDCl_3$) δ 30.1, 55.2, 56.2, 63.9, 73.9, 96.1, CN carbon undetected. Anal. calcd for $C_7H_{12}N_2O_3$: C, 48.83; H, 7.02; N, 16.27. Found: C, 48.80; H, 6.95; N, 16.10%.

4.6.4. (2*S,3*S**,4*R**)-5-Hydroxy-2,2-dimethyl-tetrahydro-[1,3]dioxolo[4,5-c]pyrrole-4-carbonitrile, *cis*-8**. (0.040 g, 22%); oil; ^1H NMR ($CDCl_3$) δ 1.31 (s, 3H), 1.54 (s, 3H), 2.80 (d, 1H, $J=11.4$ Hz), 3.47 (s, 1H), 3.55 (d, 1H, $J=11.4$ Hz), 3.60–3.62 (m, 1H), 4.73–4.76 (m, 2H, ex. 1H D_2O). ^{13}C NMR ($CDCl_3$) δ 24.7, 25.8, 61.7, 63.6, 76.6, 76.7, 112.8, 115.5. Anal. calcd for $C_8H_{12}N_2O_3$: C, 52.17; H, 6.57; N, 15.21. Found: C, 52.26; H, 6.68; N, 15.03%.

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