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Highly diastereoselective nucleophilic addition of organometallic reagents to 2-pyrrolidinyl nitrones: a semiempirical approach

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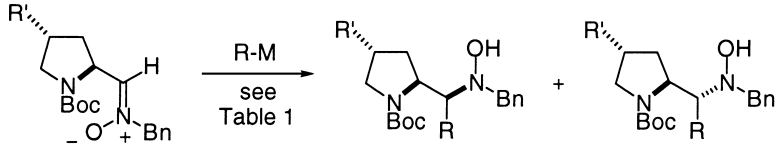
Abstract

2-Pyrrolidinyl nitrones **1** and **2** derived from L-proline and *trans*-4-hydroxy-L-proline, respectively, undergo nucleophilic additions of Grignard reagents and organolithium compounds with high *syn* selectivity, to yield enantiomerically pure pyrrolidinyl benzyl hydroxylamines. A rationale for the observed stereoselectivity based on semiempirical calculations is presented. © 1999 Elsevier Science Ltd. All rights reserved.

The diastereoselective addition of carbon nucleophiles to protected chiral non-racemic α-alkoxy and α-amino nitrones is a highly efficient method for the preparation of useful optically active secondary hydroxylamines.[1–4] As a part of our effort to develop new synthetic strategies based on the use of nitrones as electrophiles, we recently reported that α-amino monoprotected nitrones undergo nucleophilic additions of Grignard reagents with modest to good levels of *syn* selectivity.[5] This result, and parallel chemistry developed in our laboratory with L-serine derived nitrones,[6–8] suggested that analogous α-amino diprotected nitrones would exhibit enhanced diastereofacial *syn* selectivity. Here, we report that pyrrolidine-derived nitrones **1** and **2** undergo highly diastereoselective nucleophilic additions of organometallic reagents to afford the corresponding *syn* hydroxylamines as major adducts (Scheme 1). The mechanism of the addition is also discussed based on semiempirical PM3 MO calculations.



1 R' = H

2 R' = $^{t}BuPh_2SiO$

syn

3a - 16a

anti

3b - 16b

Scheme 1.

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Table 1
Diastereoselective addition of organometallic reagents to nitrones **1** and **2**[a]

entry	nitrone	R-M[b]	temp (°C) / time (h)	hydroxylamine[c]	syn : anti[d]	yield (%)[e]
1	**1**	PhMgBr	-60 / 2	**3**	>25 : 1	90
2	**1**	MeMgBr	-60 / 2	**4**	>25 : 1	87
3	**1**	EtMgBr	-60 / 2	**5**	>25 : 1	83
4	**1**	BnMgBr	-60 / 2	**6**	>25 : 1	72
5	**1**	VyMgBr	-60 / 2	**7**	4 : 1	93
6	**1**	AllMgBr	-60 / 2	**8**	3 : 1	91
7	**1**	TMSC≡CLi	-80 / 0.5	**9**	>25 : 1	93
8	**1**	$MeO_2CC{\equiv}CLi$	-80 / 0.5	**10**	>25 : 1	95
9	**2**	PhMgBr	-60 / 2	**11**	>25 : 1	91
10	**2**	MeMgBr	-60 / 2	**12**	>25 : 1	86
11	**2**	VyMgBr	-60 / 2	**13**	9 : 1	94
12	**2**	AllMgBr	-60 / 2	**14**	3 : 1	80
13	**2**	TMSC≡CLi	-80 / 0.5	**15**	>25 : 1	92
14	**2**	$MeO_2CC{\equiv}CLi$	-80 / 0.5	**16**	>25 : 1	90

[a] All reactions were performed by the addition of 1.5 equiv. of organometallic reagent to a 0.05 M solution of nitrone in THF followed by aqueous workup. [b] Ph: phenyl, Me: methyl, Et: ethyl, Bn: benzyl, Vy: vinyl, All: allyl, TMS: trimethylsilyl. [c] **a** and **b** refer to *syn* and *anti* series, respectively. [d] ratio determined by ^1H or ^{13}C NMR spectroscopy (300 MHz instrument) of the crude product. [e] isolated yield of both diastereomers.

The variety of experimental results obtained with nitrones **1** and **2** is summarized in Table 1. In a typical procedure the nitrone (1 mmol) was dissolved in THF (20 mL) cooled at the temperature indicated in Table 1 and then treated with the corresponding organometallic derivative (1.5 mmol), either commercially available Grignard reagents or freshly prepared organolithium derivatives. The whole reaction mixture was stirred until TLC indicated that the reaction was finished. Usual aqueous work-up (NH_4Cl) and column chromatography on silica gel gave the pure product.

In all cases the levels of asymmetric induction achieved are quite remarkable for such a simple process; the *syn* adducts were formed preferentially and only in the addition of vinyl and allyl magnesium bromides (Table 1, entries 5, 6, 11 and 12) could the minor diastereomer be observed.[†] In the other cases listed in Table 1 the minor diastereomer was not observed. In such instances the minimal diastereomeric ratio is given as >25:1, the limit of detectability by ^{13}C NMR spectroscopy.[‡]

The configurational assignments were surmised from the ^1H NMR spectra and by X-ray crystallography. The α-(*tert*-butoxycarbonylamino) hydroxylamines **3–16** constitute unique intramolecularly hydrogen-bonded systems in which stereochemical assignments of the newly formed stereogenic center can readily be made according to an empirical rule, i.e., coupling constants of *syn* isomers showed values of $^3J_{H,H}$ >9.0 Hz for the protons attached to the carbon atoms bearing the nitrogenated functionalities.[§] Moreover, the values of the coupling constants for the observed *anti* adducts **7b**, **8b**, **13b** and **14b** were calculated in the range of 2–4 Hz. However, ^1H NMR spectra of these compounds showed broad signals in a range of temperatures (from −40°C to 60°C); therefore, one cannot be confident on the

[†] In fact, it has been reported by other authors that allylation of chiral nitrones usually take place with low levels of diastereofacial selectivity. See the literature.[9–12]

[‡] This is the signal-to-noise limit of detection.

[§] See preceding paper.

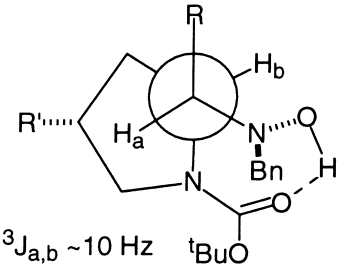

Figure 1. Preferred conformation of *syn* hydroxylamines **3**–**16**

coupling constant values obtained for those *anti* isomers. An X-ray analysis of compounds **3a**, **4a** and **13a** further confirmed their *syn* configuration. These crystallographic studies also showed the above-mentioned intramolecular hydrogen bond between the hydroxyamino group and the carbonyl oxygen of the carbamate group (Fig. 1).

Indeed, the possible origin of the diastereofacial selection is probably related to the strong intramolecular hydrogen bond between the hydroxyamino group and the carbamate carbonyl. This observation suggests the latter as the site for metal coordination in the transition state and thus, considering the coordinating capabilities of magnesium(II), one might expect that the intermediary Grignard reagent–nitrone complex takes an analogous conformation involving eight-membered chelation instead of the hydrogen bonding. In the hope of obtaining a good insight into the nucleophilic addition mechanism, we invoked the theoretical calculations at the restricted Hartree–Fock (RHF) level using the PM3 semiempirical SCF–MO method[¶] for the transition states in the nucleophilic reaction of methylmagnesium chloride with nitrone **1** (for simplicity the *N*-benzyl and *tert*-butyl groups were replaced with methyl groups).

According to the metal coordination proposed, in a similar way to the hydrogen bond interaction observed in the products, two genuine transition states $\mathbf{TS}_{syn}$ and $\mathbf{TS}_{anti}$, corresponding to the attack of the nucleophile by the *Si* and *Re* faces, respectively, were located (Fig. 2).[||] Critical points have been characterized by diagonalizing the Hessian matrices calculated for the optimized structures with respect to all structural variables; transition states have only one negative eigenvalue, the transition mode imaginary frequencies being −469.95 cm^{-1} for $\mathbf{TS}_{syn}$ and −435.18 cm^{-1} for $\mathbf{TS}_{anti}$. Also, starting from each transition state, both sides of the reaction path were investigated using the internal reaction coordinate (IRC) procedure. In both cases it could be verified that the transition states proceed from the reactants and give rise to the products.

An inspection of the transition state structures revealed that an eight-membered ring is formed and depending on the conformation of such a ring two approaches of the Grignard reagent are possible. Both the distance between the incoming methyl group and the nitrone carbon (2.383 Å and 2.443 Å for $\mathbf{TS}_{syn}$ and $\mathbf{TS}_{anti}$, respectively), and the bond orders calculated (0.157 and 0.152 for $\mathbf{TS}_{syn}$ and $\mathbf{TS}_{anti}$, respectively) clearly show an early transition state as expected for a nucleophilic addition reaction. The activation enthalpy ($\Delta H^{\ddagger}$) value of the reaction by the *Si* face (*syn* attack, $\mathbf{TS}_{syn}$, 24.01 kcal mol^{-1}) is significantly smaller than that by the *Re* face (*anti* attack, $\mathbf{TS}_{anti}$, 27.21 kcal mol^{-1}) by 3.2 kcal mol^{-1}. This calculation suggests that nucleophilic attack by the *Si* face leading to *syn* adducts should be two orders of magnitude larger than that by the *Re* face. This stands in excellent agreement with the experimental observations and confirms our previously proposed models.[13]

[¶] The PM3 calculations were carried out using the MOPAC 97 module as implemented in the ChemOffice™ package of programs (CambridgeSoft Corporation, Cambridge, MA, USA).

[||] Cartesian coordinates of **TS**s are available on request.

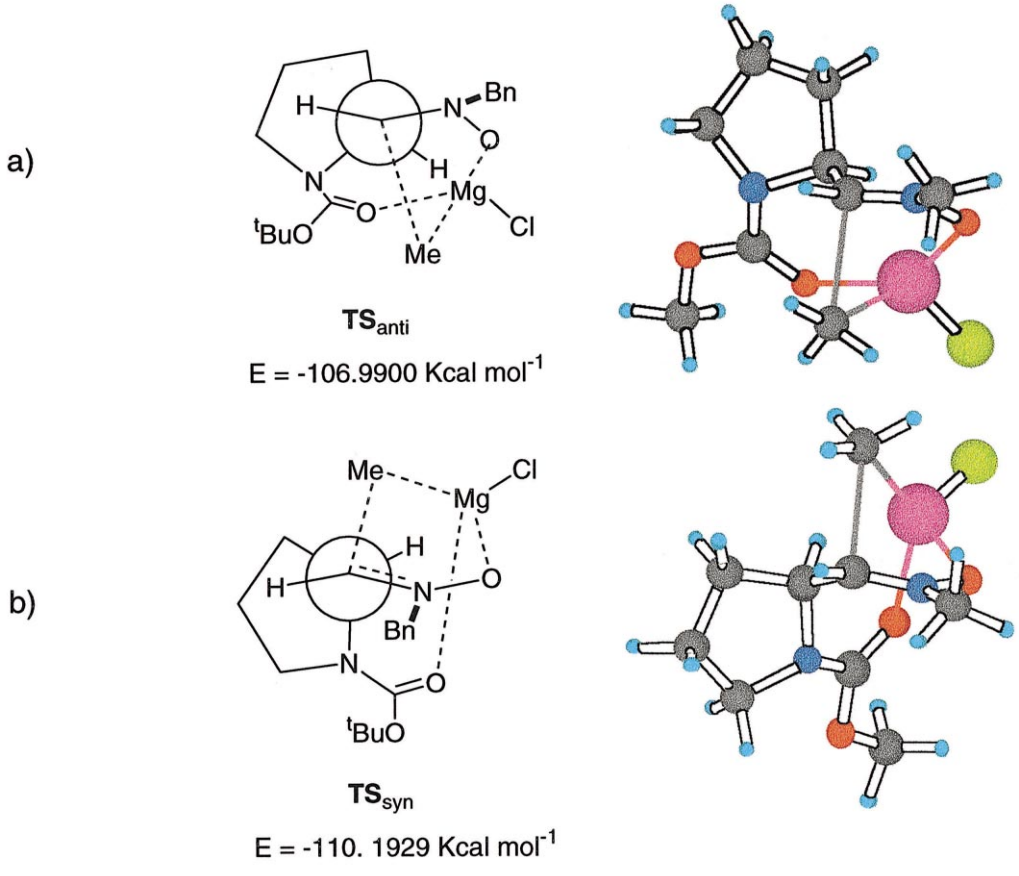

Figure 2. Transition state structures of the reaction of nitrone **1** with MeMgCl obtained at the PM3 level. (a) *Re* face approach, $\mathbf{TS}_{anti}$; (b) *Si* face approach, $\mathbf{TS}_{syn}$

In conclusion, the asymmetric addition of organometallic reagents to L-proline derived nitrones constitute a remarkably simple procedure for the construction of optically pure functionalized pyrrolidines. A key feature of the process is the high selectivity observed which can be explained on the basis of the corresponding transition states calculated at the PM3 level. Further studies of these pyrrolidinyl substituted hydroxylamines in asymmetric transformations including the synthesis of biologically interesting compounds are in progress in our laboratory.

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