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Stereoselective Additions of Grignard Reagents to Masked Imines and Iminium Ions.

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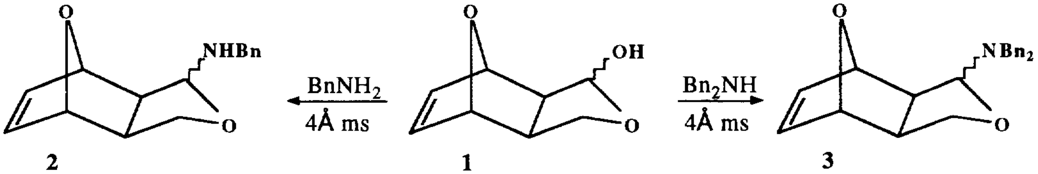
Abstract : Additions of organomagnesium bromides to the masked imine **2** or iminium ion **3** were found to be highly diastereoselective, and were shown to occur on the same diastereotopic face of the C=N bonds of these two compounds. Thermolysis of the aminoalcohols obtained gave rise to chiral allylic aminoalcohols of high synthetic potential.

The diastereoselective addition of organometallic reagents to the C=N bond of chiral imines and their derivatives is a very efficient method for the obtention of enantiomerically enriched aminocompounds.[1] We describe, in this note, preliminary results dealing with the addition of organomagnesium bromides to the masked imine **2** or iminium ion **3**,[2] which allows the preparation of unsaturated aminoalcohols of high synthetic potential. The procedure involves the reaction of the lactol **1** with benzylamine or dibenzylamine to afford the corresponding hemiaminals **2** and **3** which are then reacted with a Grignard reagent. A thermal retro Diels-Alder reaction leads to the desired allylic aminoalcohols.

The lactol **1** dissolved in dry tetrahydrofuran was reacted with an excess of benzylamine or dibenzylamine at 50°C to afford the corresponding aminocompounds **2** or **3** with excellent yields (95% and 90% respectively).



2 **1** **3**

Treatment of the compounds **2** and **3** with an excess of organomagnesium bromide (at least 4 equivalents are necessary to obtain a total reaction) gave respectively after hydrolysis the aminoalcohols **4a,b** or **6** (**a-d**) in good chemical yields and with excellent stereoselectivity (Table 1).

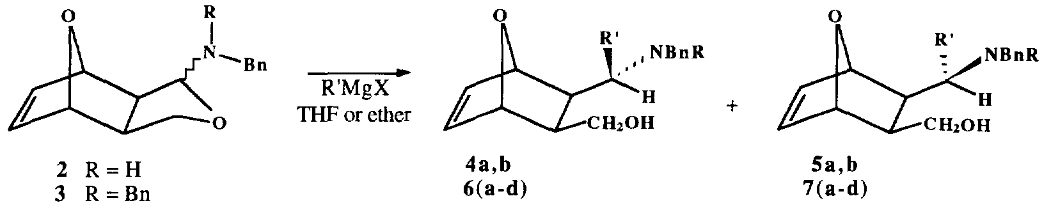


Table 1 : Diastereoselective addition of Grignard reagents to compounds **2** and **3**

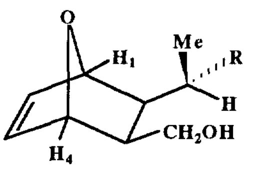
Entry	Substrate	R'	Time (h)^(a)	Products	Ratios^(b) **4**/**5** or **6**/**7**	Yields (%)^(c)
1	**2**	nButyl	18	**4a** + **5a**	94 / 6	85
2	**2**	Vinyl	24	**4b** + **5b**	95 / 5	83
3	**3**	nButyl	24	**6a** + **7a**	95 / 5	92
4	**3**	Vinyl	24	**6b** + **7b**	95 / 5	85
5	**3**	Methyl	24	**6c** + **7c**	85 / 15	90
6	**3**	Phenyl	48	**6d** + **7d**	>98 / 2	93

(a) All the reactions have been carried out at room temperature in a mixture of ether/THF : 50/50

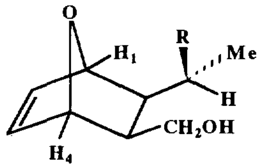
(b) Ratios estimated by ^1H NMR on the crude products : integration of the signals corresponding to the bridgehead protons

(c) Combined yields of diastereomers after purification by column chromatography

In contrast with similar additions to the corresponding lactol **1** [3] the sense or the degree of stereoselection was not affected by the change of solvent from THF to ether. The stereochemical outcome of this reaction appeared to be the same with the two aminocompounds **2** and **3** since in both cases the major products **4** or **6** arose from an approach of the organometallic reagent on the same face of the C=N double bond. Effectively the two monobenzyl amino alcohols **4a** and **4b** after treatment with benzyl bromide and potassium carbonate [4] in toluene/ethanol (1/1) at reflux were transformed directly into the dibenzylamino alcohols **6a** and **6b**. The stereochemistry of the major and the minor products were assigned by ^1H NMR spectroscopy by comparison of the chemical shifts of the bridgehead protons H_1 and H_4. In all the cases, the two singlets due to this protons were at higher field for **4** and **6** than for **5** and **7** and they could be compared with the chemical shifts of the same protons of the corresponding diols of known stereochemistry.[3a] An example is given below :

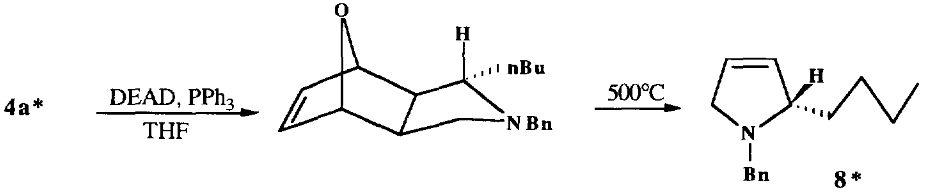


R = OH, δ H_1, H_4 = 4.62, 4.75 ppm
R = NBn_2, δ H_1, H_4 = 4.50, 4.75 ppm

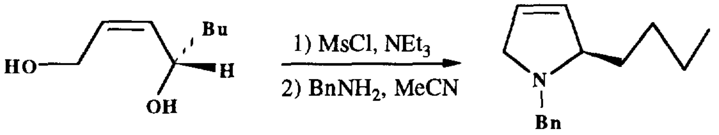


R = OH, δ H_1, H_4 = 4.93, 5.08 ppm
R = NBn_2, δ H_1, H_4 = 4.93, 5.56 ppm

This stereochemistry has been confirmed for **4a*** arising from enantiomerically pure lactol **1*** by chemical transformation (Mitsunobu cyclisation followed by a retro Diels-Alder reaction) to the (2*S*)-pyrroline **8***, $[\alpha]_D^{20}$ = +93 (c=0.5, $CHCl_3$) ; ee = 97% (chiral VPC, Cidex B column).



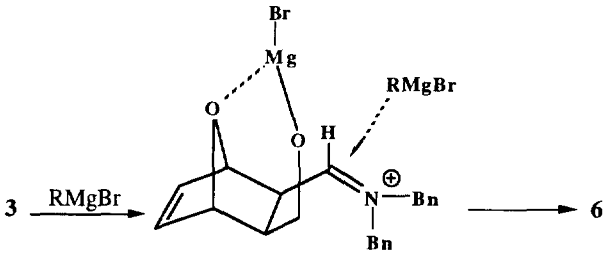
Effectively, the sign of optical rotation of this pyrroline proved to be the opposite of the sign of optical rotation of the (2*R*)-pyrroline obtained from the diol **9** of known (2*S*) configuration.[3a]



9 ee = 70%

ent.8* $[\alpha]_D^{20}$ = -65 (C=0.5, $CHCl_3$)

The high stereoselectivity of the addition of organometallics to the dibenzylamino compound **3** can be well rationalized by the preliminary formation of the corresponding iminium ion [5] followed by an approach of the nucleophile from the less hindered face of the more stable conformation of this iminium ion, as dictated by $A_{1,3}$ strain.[6]



For the additions to the monobenzylamino compound **2** we can only postulate that, contrary to our expectations,[7] a transition state entailing a chelation of the bridge oxygen and the imino nitrogen to the magnesium seems not involved.

Although further mechanistic studies are warranted, easy access to amino diols of structural variety and of well defined stereochemistry is provided. A simple retro Diels-Alder reaction afforded with excellent yields (Table 2) unsaturated amino alcohols which could be obtained in either enantiomerically pure form starting from homochiral lactols **1**.

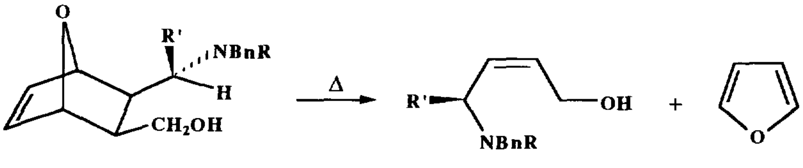


Table 2 : Thermolysis conditions of **4** and **6**

Substrate	R	R'	Thermolysis conditions(b)	T°C	Time (h)	Yield (%)(a)
4a	H	nButyl	Neat	160	6	74
4b	H	Vinyl	Neat	160	6	80
6a	Bn	nButyl	Xylenes solution	145	8	85
6b	Bn	Vinyl	Xylenes solution	145	2.5	95
6c	Bn	Methyl	Xylenes solution	145	4	85
6d	Bn	Phenyl	Xylenes solution	145	3	92

(a) Yield of pure isolated compounds.

(b) The thermolysis could be also carried under microwave irradiation in 10 minutes [8] with yields superior to 90%.

Further experiments to precise the mechanism of organometallics additions to the compound **2** and applications to the synthesis of various homochiral aminoalcohols and aminoacids are currently under investigation.

References and Notes

1. For recent reviews see: a) Johansson, A. *Contemporary Organic Synthesis* **1995**, *2*, 393-407. b) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207-2293. c) Volkmann, R.A. in *Comprehensive Organic Synthesis,* S.L. Schreiber, Ed.; Pergamon Press, Oxford, **1991**, Vol. 1, p. 355-396. d) Kleinmann, E.F.; Volkmann, R.A. in *Comprehensive Organic Synthesis*, C.H. Heatchock Ed.; Pergamon Press, Oxford, **1991**, Vol. 2, p. 975-1006.
2. To our knowledge only two studies dealing with the reaction of organometallic reagents with similar hemiaminals (derived from sugars) have been recently reported : a) Nagai, M.; Gaudino, J.J.; Wilcox, C.S. *Synthesis* **1992**, 163-168. b) Cipolla, L.; Lay, L.; Nicotra, F.; Pangrazio, L.; Panza, L. *Tetrahedron* **1995**, 51, 4679-4690.
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5. a) Ref. 2a. b) Berrien, J.F.; Royer, J.; Husson, H.P. *J. Org. Chem.* **1994,** *59*, 3769-3774.
6. Hoffmann, R.W. *Chem. Rev.* **1989,** *89*, 1841-1860.
7. Chelated transition states have been often postulated to explain the sense of stereoselective additions of organometallics reagents to alkoxy imines. See for example : a) Lay, L.; Nicotra, F.; Paganini, A.; Pangrazio, C.; Panza, L. *Tetrahedron Lett.* **1993**, *34*, 4555-4558. b) Higashiyama, K.; Inoue, H.; Takahashi, H. *Tetrahedron* **1994**, *50*, 1083-1092. c) Veith, U.; Leurs, S.; Jäger, V. J. *Chem. Soc. Chem. Commun.* **1996**, 329-330.
8. Microwave irradiations have been made in collaboration with Dr A. Loupy.

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