

N-Metallo Imines: A New Approach to α -Amino Alcohols from Aldehydes.

Gianfranco Cainelli*, Daria Giacomini, Elisabetta Mezzina,
 Mauro Panunzio*, Paola Zarantonello

Dipartimento Chimico "G. Ciamician" Università and C.S.F.M.-C.N.R.
 Via Selmi, 2 I 40126 BOLOGNA Italy

Key Words: α -Hydroxy N trimethylsilylimines; 1,2-Aminols; Diastereoselective Addition to the Azomethine Carbon.

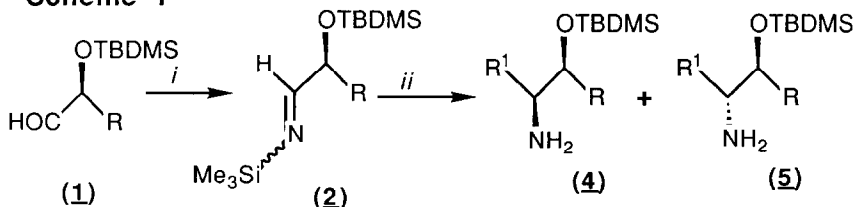
Abstract: The addition of lithium alkyls or Grignard reagents to the *in situ* generated O-protected α -hydroxy-N-trimethylsilylimines proceeds in good yields and highly stereocontrolled manner to produce 1,2-aminols.

Stereocontrolled synthesis of 1,2 aminols continues to be an area of intense activity. The recent discovery of new aminoacids related to statine¹ sustains the interest of synthetic and medicinal chemists. The potential of 1,2 aminols for serving as efficient synthons for a variety of natural products has provided added interest². We wish to report in this letter our recent results on the use of α -hydroxy-N-trimethylsilylimines in the synthesis of 1,2-amino alcohols³.

The synthetic usefulness of N-metallo imines⁴ has been demonstrated by the synthesis of amines⁵, 1,2-diamines⁶, β -lactams⁷, aziridines⁸ and aminols⁹. Moreover the possibility of using homochiral silyl-imines in a highly stereocontrolled total synthesis of *trans* non-classical β -lactam antibiotics¹⁰ has been recently reported.

α -Hydroxy-N-trimethylsilylimines can be easily prepared from the corresponding aldehydes¹¹ *via* addition-elimination reaction with lithium hexamethyldisilylamide (LiHMDS)¹⁰. When these substrates are reacted with lithium alkyls or Grignard reagents, the presence of the α -standing stereocenter bearing an hydroxy functionality addresses the attack of the nucleophile on the strongly electrophilic azomethine carbon in a stereocontrolled manner so that a preferred diastereoisomer is obtained¹² (Scheme 1).

Scheme 1



i : LiHMDS *ii* : R^1Li or R^1MgX (3).

Thus treatment of (**1**) (2 mmol) under argon atmosphere with LiHMDS (2.4 mmol), at -78°C using THF as solvent, afforded the α -silyloxy-N-trimethylsilyl imine (**2**) which gave clean conversion to the desired adducts¹³ (**4**) and/or (**5**), upon treatment with organometallic reagent (**3**) as depicted in the Scheme 1.

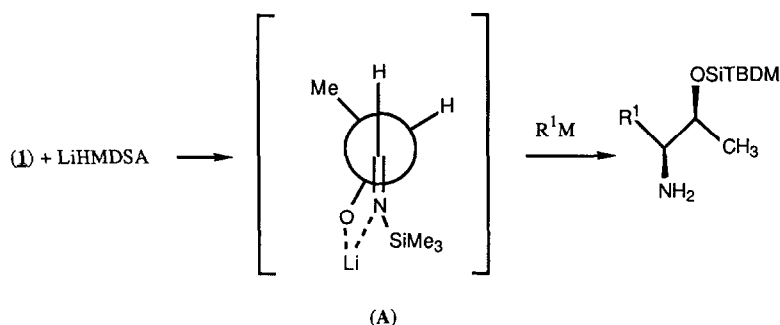
Table I gives the results for a variety of α -silyloxy-N-trimethylsilylimines¹⁴. In general, the reaction proceeds in high yields and high stereochemical control and represents one of the few available methods for efficiently adding an alkyl and particularly an allyl group to the azomethine functionality¹⁵. Since the hydroxyethyl group represents a latent carboxylic unit through its oxidation¹⁶, this methodology provides potentially a useful strategy to prepare α -amino acids.

Sample Experimental Procedure: : To a solution of N-trimethylsilylimine (**2**) (2 mmol) in THF is added a solution of the organometallic reagent (**3**) (2.4 mmol) in THF at -78°C. The reaction mixture is stirred at -78°C for 2 hrs and then is allowed to reach room temperature while stirring is continued for two hours. Quenching with a saturated NH₄Cl solution, extraction with ethyl acetate and flash chromatography of the crude products on silica gel eluting with cyclohexane-ethyl acetate 7:3, affords compounds (**4**) and (**5**). The results are shown in Table1.

Table 1: Aminols from aldehydes

Entry	R	R ¹ M	Yields%	Ratio 4/5
a	Methyl	AllylMgBr	50	25/75
b	Methyl	AllylMgCl	66	4/96
c	Methyl	AllylMgCl/Et ₃ Al	69	5/95
d	Methyl	AllylMgCl/ZnBr ₂	96	9/91
e	Methyl	ButylLi	46	98/2
f	Methyl	<i>sec</i> -ButylLi	39	57/43
g	Methyl	BenzylMgCl	50	100/0
h	Methyl	CyclohexylmethylLi	70	80/20
i	Methyl	CyclopropylLi/BF ₃	33	77/23
10	Phenyl	BenzylMgCl	66	100/0
11	Phenyl	AllylMgCl	65	18/82

Our stereochemical assignments were based on spectral data (¹H and ¹³C NMR). Moreover the stereochemistry of most adducts was best determined by preparing the corresponding 1,3-oxazolidin-2-one derivatives⁹. A large volume of literature¹⁷ shows that the H₄ - H₅ coupling constant of the *cis* isomer in the cyclic derivatives is larger than that of the *trans* isomer. Confirmation of the assigned structure was then obtained from the greater shielding of the carbons involved in the *cis* linkage at ¹³C NMR spectra. Analysis of the diastereomeric ratio clearly shows a predominance of the *syn* isomers compared to the *anti* ones. This diastereofacial selectivity can be explained assuming a chelation control in the addition of the nucleophile to imines with the formation of the cyclic intermediate (**A**) in analogy to what happens in the case of chiral α -carbonyl compounds¹² according to Cram's cyclic model.



Why in the case of allyl magnesium chloride the reaction shows an interesting high anti diastereoselectivity, is currently under investigation.

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aldehydes (Y 88%, $[\alpha]_D^{25} = +5.5$ (neat) used in this work were prepared through reduction of the correspondig esters protected on the hydroxy functionality as *tert*-butyldimethylsilyloxy ether by means of diisobutylaluminum hydride in ether.

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- 13 Yields are reported for isolated chromatographically pure products and have not been optimized. In most cases for an accurate evaluation of the diastereomeric ratio the isomers (**4**) and (**5**) were isolated as mixture and evaluated as such by ^1H and ^{13}C NMR spectroscopy. ^1H NMR, ^{13}C NMR and GC/MS spectra as well as combustion analyses were entirely consistent with the assigned structures. Selected data as follow: (**4a**) ^1H NMR (300 MHz, CDCl_3) 5.74 (m, 1 H); 5.10 (m, 2 H); 3.71 (dq, 1 H $J_1 = 6.20$ Hz, $J_2 = 4.50$ Hz); 2.75 (m, 1 H); 2.40-1.90 (m, 2 H); 1.65 (bs, NH_2); 1.10 (d, 3 H, $J=6.20$); 0.92 (s, 9H); -0.03 (s, 6 H). ^{13}C NMR (300 MHz, CDCl_3) 136.4; 117.0; 71.5; 56.8; 38.7; 25.6; 20.2; 18.0; -4.4; -5.1. (**5a**) ^1H NMR (300 MHz, CDCl_3) 5.74 (m, 1H); 5.10 (m, 2 H); 3.65 (dq, 1 H, $J_1=6.20$ Hz, $J_2=4.20$ Hz); 2.60 (, 1 H); 2.40-1.90 (m, 2 H); 1.65 (bs, NH_2); 1.18 (d, 3 H, $J=6.20$); 0.85 (s, 9 H); 0.04 (s, 6 H). ^{13}C NMR (300 MHz, CDCl_3) 136.3; 116.7; 71.0; 56.3; 37.5; 25.6; 18.0; 17.8; -4.6; -5.1. (**4e**) ^1H NMR (300 MHz, CDCl_3) 3.59 (m, 1 H); 2.45 (m, 1 H); 1.50-1.17 (m, 8 H); 1.12 (d, 3 H, $J=6.2$ Hz); 0.94-0.82 (m, 12 H); 0.05 (s, 6 H). ^{13}C NMR (300 MHz, CDCl_3) 72.0; 57.3; 33.7; 28.5; 25.6; 22.6; 20.2; 17.8; 13.7; -4.5; -5.1. (**5e**) ^1H NMR (300 MHz, CDCl_3) 3.69 (m, 1 H); 2.67 (m, 1 H); 1.50-1.17 (m, 8 H); 1.03 (d, 3H, $J=6.0$ Hz); 0.94-0.82 (m, 12 H); 0.06 (s, 3 H); 0.04 (s, 3H). ^{13}C NMR (300 MHz, CDCl_3) 71.7; 56.8; 32.6; 28.7; 25.6; 22.6; 17.8; 16.8; 13.7; -4.5; -4.8. (**4g**) ^1H NMR (300 MHz, CDCl_3) 7.25 (m, 5 H); 3.75 (dq, 1 H, $J_1=4.20$ Hz, $J_2=6.16$ Hz); 2.91-2.75 (m, 2 H); 2.40 (m, 1 H); 1.4 (bs NH_2) 1.2 (d, 3 H, $J=6.16$ Hz); 0.9 (s, 9 H); 0.1 (s, 6 H). ^{13}C NMR (300 MHz, CDCl_3) 139.9; 129.19; 128.4; 126.07; 71.52; 58.92; 40.64; 25.88; 20.34; 18.06; -4.05; -4.77. (**4i**) ^1H NMR (300 MHz, CDCl_3) 7.4-7.1 (m, 10 H); 4.53 (d, 1H, $J=5.77$ Hz); 3.15 (m, 1H); 2.70 (dd, 1H, $J_1=13.61$ Hz; $J_2= 3.64$ Hz); 2.35 (dd, 1 H, $J_1=13.61$ Hz, $J_2=9.95$ Hz); 2.05 (bs, NH_2); 0.9 (s, 9H); 0.1 (s, 3 H); -0.2 (s, 3 H). ^{13}C NMR (300 MHz, CDCl_3) 142.3; 139.5; 129.0; 126.0; 78.92; 59.67; 39.64; 25.80; 18.1; -4.49; -5.05. (**4m**) ^1H NMR (300 MHz, CDCl_3) 7.28 (m, 5 H); 5.74 (m, 1 H); 5.06 (m, 2 H); 4.41 (d, 1 H, $J=5.7$ Hz); 2.82 (m, 1 H); 2.09 (m, 1 H); 1.87 (m, 1 H); 1.53 (bs, NH_2); 0.86 (s, 9 H); 0.01 (s, 3 H); -0.26 (s, 3 H). ^{13}C NMR (300 MHz, CDCl_3) 142.9; 136.1; 128.2; 127.5; 127.0; 117.2; 78.8; 57.8; 37.8; 25.6; 17.9; -4.8; -5.3. (**5m**) ^1H NMR (300 MHz, CDCl_3) 7.28 (m, 5 H); 5.74 (m, 1 H); 5.06 (m, 2 H); 4.44 (d, 1 H, $J=6.0$ Hz); 2.91, m, 1 H); 2.40 (m, 2 H); 1.25 (bs, NH_2); 0.86 (s, 9 H); 0.00 (s, 3H); -0.24 (s, 3 H). ^{13}C NMR (300 MHz, CDCl_3) 142.2; 136.2; 128.2; 127.5; 127.2; 117.3; 78.7; 57.1; 37.3; 25.7; 17.9; -4.7; -5.2.
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