Tetrahedron Letters, Vol. 33, No. 50, pp. 7783-7786, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

Reversal of Diastereoselectivity in the Addition of C-Nucleophiles to *N* -Trimethylsilyl Imines *via* Grignard Derived Organo Copper-Boron Trifluoride Reagents.

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

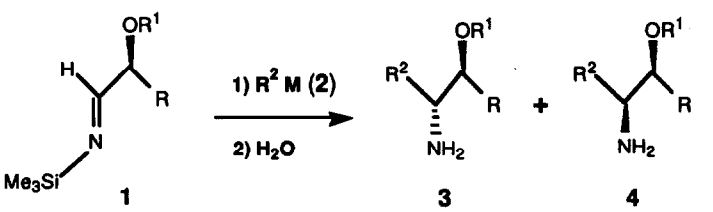
Dipartimento di Chimica "G. Ciamician" Università and C.S.F.M.-C.N.R.
Via Selmi, 2 - 40126 Bologna Italy.

Abstract: The N-trimethylsilyl imines of O-protected α-hydroxy aldehydes react with RCuMgXI BF_3 to give β-amino alcohols with high *anti* diastereoselectivity.

Recently we have reported that *N* -trimethylsilyl imines of O-protected α-hydroxy aldehydes, when reacted with ester enolates, are excellent substrates for the preparation of β-lactam derivatives with very high diastereoselectivity. Using this methodology enantiomerically pure β-lactam antibiotics (+) PS-5[1a], (+) PS-6[1b] and Aztreonam[1c] have been prepared. In a further development, we have found that the reactions of *N* -trimethylsilyl[2a] or *N* -diisobutylaluminium imines[2b] of O-protected α-hydroxy aldehydes with lithium alkyls or Grignard reagents furnish the corresponding *syn* β-amino alcohols with good diastereoselectivity. This *syn* diastereoselection might be explained in terms of a chelation controlled mechanism[3]. More difficult is to achieve a fairly good *anti* diastereoselectivity which would presume a non chelated transition state. In fact very few examples have been reported on the nucleophilic addition to α-hydroxy imines to give β-aminoalcohols with *anti* diastereoselection[4]. Therefore a systematic study towards this aim was started and the preliminary results are reported in this Letter.

Various organometallic reagents, additives, and solvents were investigated in the reaction shown in Scheme 1.

Scheme 1



1 3 4

3a, 4a : R = Me, R^1=TBDMS, R^2= Bu; **3b, 4b:** R = Me, R^1=^{t}Bu, R^2= Bu; **3c, 4c:** R = Me, R^1=Trityl, R^2= Bu; **3d, 4d:** R = Me, R^1=TBDMS, R^2= Allyl; **3e, 4e:** R = Me, R^1=TBDMS, R^2= Cyclopropyl; **3f, 4f:** R = Me, R^1=TBDMS, R^2= Cyclohexylmethyl; **3g, 4g:** R = Ph, R^1=TBDMS, R^2= Bu; **3h, 4h:** R = Ph, R^1=^{t}Bu; R^2= Bu; **3i, 4i:** R = Ph, R^1=^{t}Bu; R^2= Me; **3j, 4j:** R = Ph, R^1=TBDMS, R^2= Allyl.

Among other organometallic reagents, we focused our attention on the organocopper derivatives[5] and, as model imine, we used the *N* - trimethylsilyl imine obtained from O-*tert* -butyldimethylsilyl protected lactic aldehyde[1b].

Experimental procedure : A solution of *N* - trimethylsilyl imine (**1**) (2 mmol) in THF (5 ml) is added at -78°C to a solution of the organometallic species (**2**) (4 mmol). The resulting solution is kept at -78°C for 2 hrs and then allowed to reach room temperature (8 hrs). Quenching with a buffer solution of NH_4OH /NH_4Cl, extraction with methylene chloride and flash chromatography of the crude product on silica gel eluting with $CHCl_3$:CH_3OH:NH_4OH = 25:1:0.1 affords the compounds (**3a**) and (**4a**) in the yields and ratio reported in Table 1.

Table 1. Aminols (**3a**) and (**4a**) from lactic imine (**1a**).

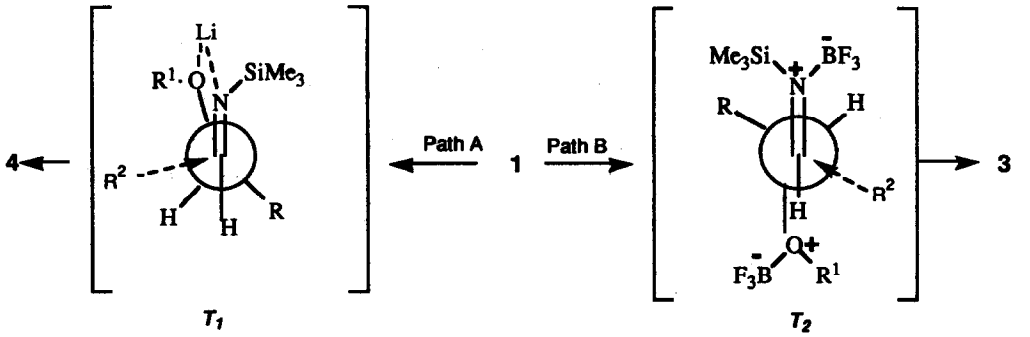
Exp	Organometallic (2)	Solvent[6]	Yield[7]	*anti* (3a) / *syn* (4a)[8]
1	BuMgBr	THF	0	---
2	BuLi	THF	46	2/98
3	$Bu_2CuMgBr$ MgBrI	THF	Traces	---
4	BuCuMgBrI BF_3	THF/DMS	54	>99/1
5	BuCuMgBrI BF_3	Ether/DMS	17	90/10
6	BuCuLiI BF_3	THF/DMS	28	43/57
7	Bu(CN)CuMgBr BF_3	THF	15	79/21
8	Bu(CN)CuMgBr BF_3 2LiCl	THF	37	>99/1
9	Bu(CN)Cu MgBr BF_3 2LiCl	Ether	48	86/14

The success of the reaction is strictly correlated to the nature of the organometallic species involved. Insofar Grignard reagents and $Bu_2CuMgBrI$ give rise only to traces of the addition products (see experiments 1 and 3), the sole effective reagents able to give the addition product with high *anti* diastereoselectivity[8] being the BuCuMgBrI BF_3 reagent[9] (Exp 4).

A remarkable metal tuning has been observed. In fact if the copper reagent is generated from lithium alkyl a very moderate degree of the *anti*- selectivity is achieved (exp 6), whereas a far superior or exclusive *anti* diastereoselectivity is obtained when Grignard derived copper reagents are used (exp 4). Although the precise mechanism of the present reaction is still an open question, the stereoselection might be explained in terms of chelation-controlled and open-chain models. When lithium alkyls are used a Cram cyclic model may be invoked to explain the very high *syn* stereoselection observed (Chelation control, *Path A*, $\mathbf{T_1}$ of Scheme 2). In contrast, when copper boron trifluoride reagents are used a Cornforth' s dipolar model[10] (*Path B*, $\mathbf{T_2}$ of Scheme 2) could explain the *anti* diastereoselection observed. In fact the BF_3 being incapable of chelation, could cause double complexation (of both nitrogen and oxygen atoms) which results in the formation of an adduct with rigid antiperiplanar conformation due to electrostatic repulsion. The complexation of the azomethinic group with BF_3 enhances its electrophilicity thus explaining its increased reactivity in comparison with $Bu_2CuMgBr$ reagent (exp 3 *vs* exp 4).

More difficult appears to explain the above mentioned metal tuning effect in the organocopper reagents. In an oversimplification, one can assume a stronger chelating effect of the lithium cation (exp 6)*versus* the magnesium cation so that a competition between Path *A* and Path *B* is observed. A similar trend was found, for instance, in the addition reaction of phenyl lithium and phenyl magnesium bromide to the *N*-phenyl imine of glyceraldeyde acetonide[11].

Scheme 2



In order to demonstrate the usefulness of the present method to obtain *anti* 1,2-amino alcohols, the synthesis of selected amino alcohols was performed, the results being reported in Table 2.

Table 2. 1, 2-Aminols from silylimines (See Scheme 1)[12]

Exp	R	R^1	R^2M	Product(s)	Yield[6]	*anti/syn* [7]
1	Me	TBDMS	ButylCu MgBrI BF_3	**3a+ 4a**	54	>99/1
2	Me	^{t}But	ButylCu MgBrI BF_3	**3b+ 4b**	40	>99/1
3	Me	Tr	ButylCu MgBrI BF_3	**3c + 4c**	86	92/8
4	Me	TBDMS	AllylCu LiI BF_3	**3d + 4d**	54	91/9
5	Me	TBDMS	AllylCu MgClI BF_3	**3d+ 4d**	63	>99/1
6	Me	TBDMS	CyclopropylCu LiI BF_3	**3e+ 4e**	51	10/90
7	Me	TBDMS	CyclopropylCu MgBrI BF_3	**3e +4e**	40	95/5
8	Me	TBDMS	CyclohexylCH_2Cu MgBrI BF_3	**3f + 4f**	70	>99/1
9	Ph	TBDMS	ButylCu MgBrI BF_3	**3g +4g**	24	>99/1
10	Ph	^{t}But	ButylCu MgBrI BF_3	**3h + 4h**	37	97/3
11	Ph	^{t}But	MethylCu MgBrI BF_3	**3i + 4i**	30	>99/1
12	Ph	TBDMS	AllylCu MgClI BF_3	**3l+ 4l**	67	81/19

The relative stereochemistry of the purified products was proved on the basis of the 300 MHz ^1H and 75 MHz ^{13}C spectra as well as by spectroscopic evidence from their derivatives. To this aim each product was converted into the corresponding oxazolidin-2-one *via t* -Boc protection of the amine group, removal of the O-protective group, and ultimately ring closure in basic medium to the oxazolidin-2-one ring[2a, 2b].

In conclusion we are in a position to prepare either *syn* or *anti* aminoalcohols simply by changing the organometallic species involved.

Acknowledgement: Financial support was provided by MURST (Fondi 40 e 60%).

References and Notes.

1 a) Cainelli, G.; Panunzio, M.; Giacomini, D.; Martelli, G.; Spunta, G. *J. Am. Chem. Soc.*, **1988**, *110*, 6879. (b) Andreoli, A.; Cainelli, G.; Panunzio, M.; Bandini, E.; Martelli, G.; Spunta, G. *J. Org. Chem.* **1991**, *56*, 5984. (c) Andreoli, A.; Billi, L.; Cainelli, G.; Panunzio, M.; Bandini, E.; Martelli, G.; Spunta G. *Tetrahedron* **1991**, *47*, 9061.

2 (a) Cainelli, G.; Giacomini, D.; Panunzio, M.; Zarantonello, P. *Tetrahedron Lett.*, **1991**, 33, 2967. (b) Cainelli,G.; Mezzina, E.; Panunzio, M. *ibid* **1990**, *32*, 3481. For recent syntheses of optically active β-amino alcohols see: (c) Reetz, T.M. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1531. (d) Yamamoto, Y.; Sato, H.; Yamada, J. *Synlet*, **1991**, 339. (e) Jackson, W.R.; Jacobs, A.H.; Jayatilake, S.G.; Matthews, B.R.; Watson K.G. *Aust. J. Chem.* **1990**, *43*, 2045. (f) Brussee, J.; van Bentherm, A.T.M.R. *Tetrahedron Assym.* **1990**, *1*, 163. (g) Kruse, C.G.; and Van Der Gen, A. *Tetrahedron*, **1990**. (h) Poll, R.; Peterson, MA.M. *Tetrahedron Lett.* **1990**, *31*, 4985. (i) Brussee, J.; Dofferhoff, F.; Kruse, C.G.; and Van Der Gen, A. *Tetrahedron*, **1990**, *46*, 1653. (j) Mikami, K.; Kaneko, M.; Loh, T.-P.; Terada, M.; Nakai, T. *Tetrahedron Lett.* **1990**, *31*, 3909. (k) Reetz, M.T.; Drewes, M.W.; Schimitz, A. *Angew. Chem. Int. Ed. Engl.*, **1987**, *26*, 1141.

3 For leading references of chelation controlled reactions see: (a) Chen, X.; Hortelano, R.E.; Eliel, L.E.; Frye, S. *J. Am. Chem. Soc.* **1992**, *114*, 1778. (b) Reetz, M.T.; *Angew. Chem. Int. Ed. Engl.*, **1984**, *23*, 1035. For a structural investigation of Li-O-N chelation see: Arnett, E.M.; Nichols, M.A.; McPhail, A.T. *J. Am. Chem. Soc.* **1990**, *112*, 7059. See also references 2.

4 (a) Yamamoto, Y.; Komatsu, T.; Maruyama, K. *J. Chem. Soc. Chem. Commun.*, **1985**, 814. For other examples of *anti* diastereoselectivity in the addition of nucleophiles to C=N bond see (b) Matsumoto, T.; Kobayashi, Y; Takemoto, Y.k; Ito,Y.; Kamijo, T.; Harada,H.; and Terashima, S.; *Tetrahedron Lett.*, 1990, **31**, 4175. (c) Ukaji, Y.; Watai, T.; Sumi, T. Fujisawa, T.; *Chem. Lett.*, **1991**, 1555. (d) Fronza, G.; Fuganti, C.; Grasselli, P.; Fantoni, G. *Tetrahedron Lett.*, **1981**, 5073. (e) Fuganti, C.; Grasselli, P.; Fantoni, G. *J. Org. Chem.*, **1983**, *48*, 909. (f) A reversal diastereoselectivity upon the addition of CuI to α-alkoxy hhydrazones is reported: Claremon, A.D.; Lumma, K.P.; Philips, T.B. *J. Am. Chem. Soc.* **1986**, *108*, 8265.

5 Lipshutz, B.H.; Sengupta, S. *Org. React.* **1992**, *41*, 135.

6 In the preparation of the copper reagents, where indicated, a 8:2 mixture of THF/DMS (dimethylsulfide) was used: Bertz, H.S.; Dabbagh, G. *Tetrahedron*, **1989**, *45*, 425.

7 The yields haven't been optimized and have been determined, after flash chromatography, on the diastereomeric mixture without separation of the two diastereoisomers. All the compounds reported exhibited the expected spectral data (i.r., ^1H and ^{13}C NMR, mass spectra, combustion analysis).

8 The *anti/syn* ratio was determined on the crude mixture of aminols by integration of the relative signals at ^1H 300 MHz NMR. The relative configuration was determined by conversion of the amino alcohols after chromatographic purification, to oxazolidin-2-ones.

9 To avoid side reaction resulting from the presence of Cu(II) compounds, CuI was purified through its complex with dimethylsulfide: House, O.H.; Chu, C-Y.; Wilkins, M.J.; Umen, J.M. *J. Org. Chem.* **1975**, *40*, 1460.

10 Cornforth, J.W.; Cornforth, R.H.; Methew, K.K. *J. Chem. Soc.*, **1959**, 112.

11 Yoshimura, J.; Ohgo, Y.; Sato, T. *J. Am. Chem. Soc.* **1964**, *86*, 3858.

12 The experimental procedure was that above described. A mixture of THHF/DMS 8/2 was used in all cases described. Silylimines (1) were prepared acoording the procedure reported in Ref. 2b.

(Received in UK 22 September 1992)