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Metallo-imines: useful reagents in organic synthesis

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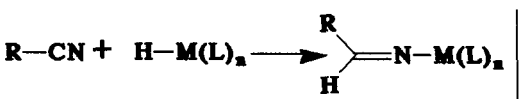
Abstract : The preparation of aluminum, silicon and tin imines from nitriles, aldehydes and ketones, enolizable as well as nonenolizable ones, is reported. The reactivity of these relatively new organometallic compounds has also been explored.

INTRODUCTION

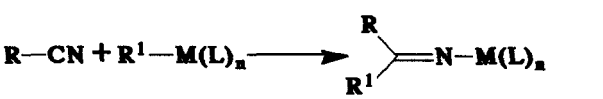
N-metalloimines constitute a relatively unexplored family of organometallic compounds which has found few synthetic applications.
Generally speaking, they are monomeric compounds which are stable under anhydrous conditions. Since the metal-nitrogen bond is easily hydrolysed, the N-metalloimines may be considered a protected, stabilized form of the corresponding elusive imines of ammonia, which are known to be very unstable readily trimerizing to triazines. Although some metalloimines, e.g., the silylimines of certain aldehydes, can be isolated in a pure form by distillation under reduced pressure, for synthetic purposes it is in general more convenient to prepare them *in situ* just before the use. In this case it is possible to ascertain their structure by a combined use of I.R., N.M.R. and mass spectroscopic techniques. The present progress report summarizes our recent efforts directed toward the synthesis of aluminum, tin and silicon imines starting from easily available materials, and the study of the reactivity of these reagents with different nucleophiles with a special attention to the stereochemical outcome.

PREPARATION OF N-METALLO IMINES

There are four main methods for the preparation of N-metalloimines:
1. Addition of an organometallic reagent or a metallo hydride to a nitrile[1]

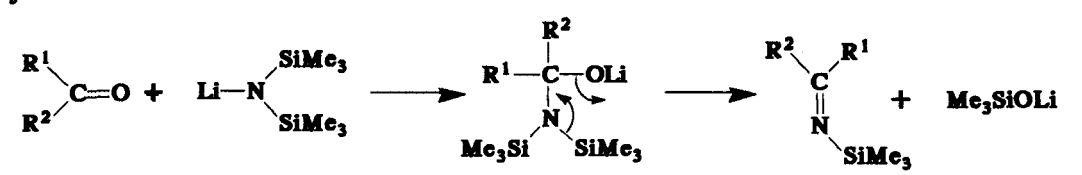


R = Alkyl or Aryl; M = Al, B.



R = Alkyl or Aryl; R^1 = Alkyl or Aryl; M = Li, Mg

2. Reaction of the hexamethyldisilylamide of group I metals (Li, Na, K) with an aldehyde or a nonenolizable ketones.
Silyl imines have been prepared, for the first time, by Rochow[2] starting from aromatic aldehydes and nonenolizable ketones by treatment of the carbonyl compounds with one equivalent of lithium hexamethyldisilylamide in tetrahydrofuran.
The reaction proceeds by an addition-elimination sequence probably involving a four centers cyclic transition state.



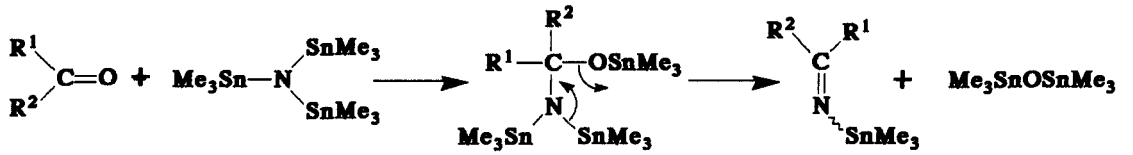
R^1 = Alkyl, Aryl; R^2 = H, Alkyl, Aryl.

The reaction represents the heteroatom variant of the general carbonyl olefination given by any geminal dimetallic compound possessing at least one carbon metal bond capable to add to a carbonyl group[3].

Ketones, bearing an hydrogen atom in α position to the carbonyl group, fail to produce the silylimines since in this case the strongly basic organometallic reagent attacks an α-hydrogen affording the corresponding lithium enolate. Enolizable aldehydes were supposed to behave in the same way[2b]. This notwithstanding we have found that the preparation of such metallo-imines is easier than one might expect[2c] (vide infra).

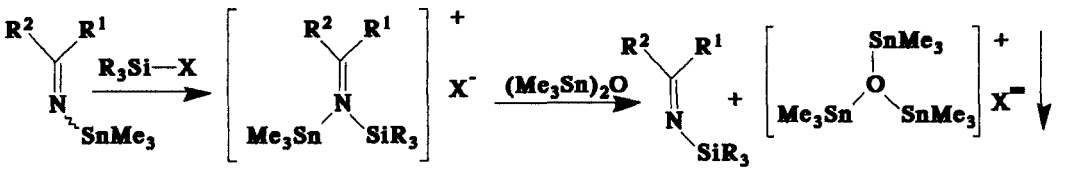
3. Reaction of carbonyl compounds with tris(trimethylstannyl)amine[4].

This new method has been developed in our laboratories and allows the preparation, in good yield and under very mild conditions, of stannyl imines from enolizable and non enolizable aldehydes and ketones. The reaction involves an addition-elimination reaction of the type discussed for the Rochow's procedure. The organometallic reagent is, in this case, the tris(trimethylstannyl)amine[5] easily prepared from trimethyl tin chloride and lithium amide.



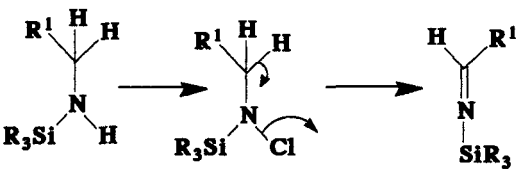
R^1 = Ph, R^2 =H; R^1 = Fu, R^2 =H; R^1 = Me, R^2= Ph; R^1 = C_7H_{15}, R^2 =H; R^1= R^2 = -$(CH_2)_5$-

Since the tris(trimethylstannyl)amine does not show strong basic properties, the α-deprotonation is completely suppressed thus allowing a facile preparation of stannylimines even in the case of enolizable ketones and aldehydes. An interesting features of the stannylimines is the possibility to undergo a transmetallation reaction with trialkylsilylchloride (e.g. chloro *ter*-butyl dimethyl silane) to give the corresponding N-silylimine and tris(trimethyltin) onium chloride, which spontaneously precipitates from the solution. Removal of this precipitate by filtration allows the preparation of almost pure solution of silylimines.

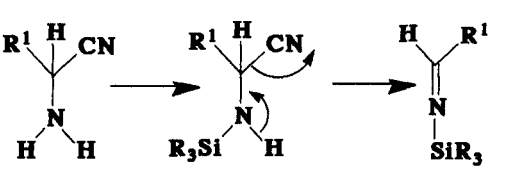


R^1 = Ph, R^2 = H; R^1 = Fu, R^2 = H; R^1 = Me, R^2 = Ph; R^1 = C_7H_{15}, R^2 = H.

4. Finally, N-trimethylsilylimines can be prepared by base-induced elimination of vicinal substituents from N-silyl amines[6].



R^1 = Ph, 2-Fu, COOEt, -CH=CH_2



R^1 = H, Me, Et, n-Pr

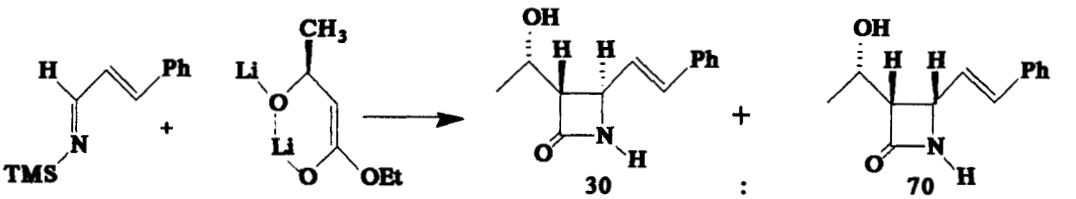
REACTIVITY OF N-METALLO IMINES

A. Synthesis of β-lactam

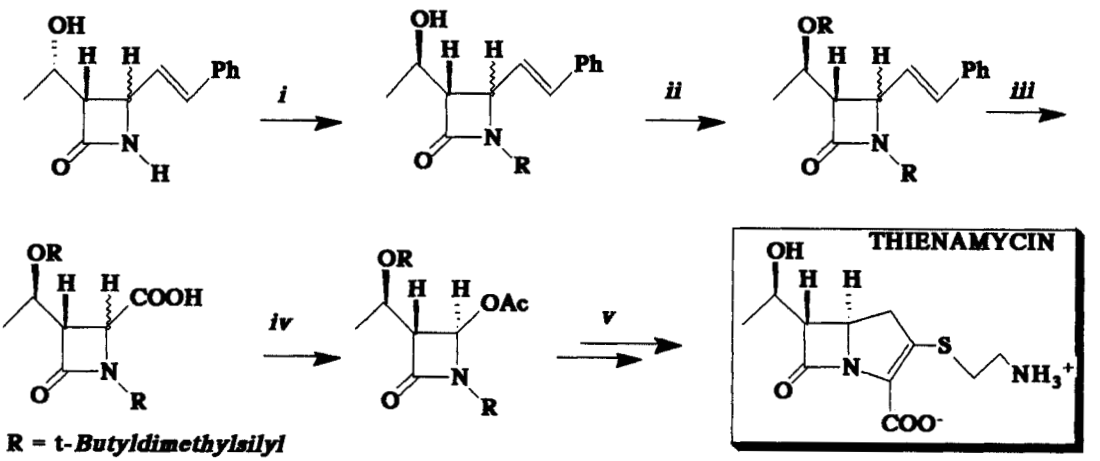
The first application of trimethylsilylimines in our laboratories[7] is concerned with the preparation of a chiral key intermediate in the synthesis of thienamycin and related carbapenems and penems.

The trimethylsilylcinnamylidenimine, prepared from cinnamyc aldehyde and LiHMDSA was reacted with the lithium enolate of (S)-3-hydroxy ethyl butyrate, to give rise to a 70/30 mixture of two diastereomeric β-lactams. By this way the original stereocenter in the

nucleophilic partner has been utilized to induce in a 1,2 lk manner with very high diastereoselectivity (96/4) the new chirality at the adjacent C_3 stereocenter of the forming azetidinone. A lower diastereoselectivity is observed for the C_4 stereocenter. The high induction on the C_3 carbon atom may be explained by assuming a cyclic form of the enolate as result of the coordinating effect of one of the lithium cations so that a preferred attack of the electrophilic imine from the less hindered face of the diastereotopic plane takes place.



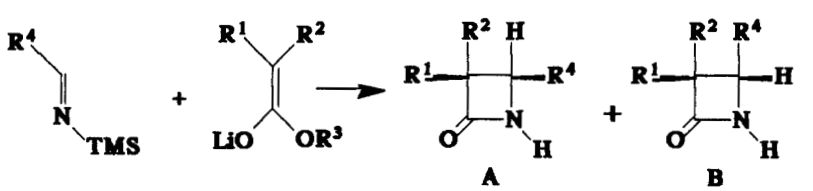
The elaboration of the mixture of the cis and trans stereoisomers includes the inversion of the configuration of the hydroxy functionality in the side chain *via* Mitsunobo procedure, the oxidative cleavage of the stiryl group followed by the radical decarboxylation of the mixture of carboxylic acids obtained by means of lead tetracetate to give the corresponding 4-acetoxy derivative as a single trans isomer.

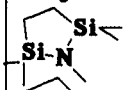
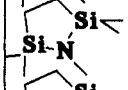
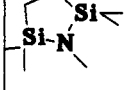


R = t-*Butyldimethylsilyl*

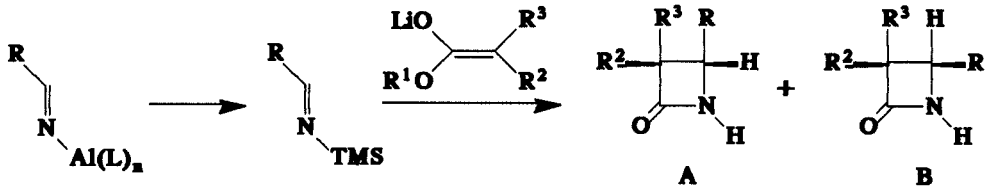
i: DEAD, TPP,HCOOH and then NaOH; ii: TBDMSCl, Imidazole; iii: O_3 , Jones; iv: Pb(OAc)4; v: Ref. 8

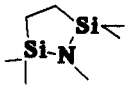
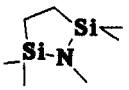
This synthetic strategy allowed us to introduce the natural configuration on the C-3 and C-4 stereocenters of the azetidinone using as chiral auxiliary the nucleophylic partner of the cycloaddition reaction. However, there are some β-lactam antibiotics bearing no asymmetric center in the C-3 side chain[9]. For the enantiospecific synthesis of these compounds the asymmetry has been incorporated in the electrophilic component of the cycloaddition reaction starting from a chiral metallo imine. The choice of this alternative relates to our results on the possibility of building up the azetidinone ring using enolizable metallo-imines[1,2]. As a matter of fact we have recently demonstrated that enolizable silylimines, despite the presence of an acidic hydrogen in alfa position to the iminic carbon, can be used as electrophilic partner in the enolate-imine cycloaddition reaction.



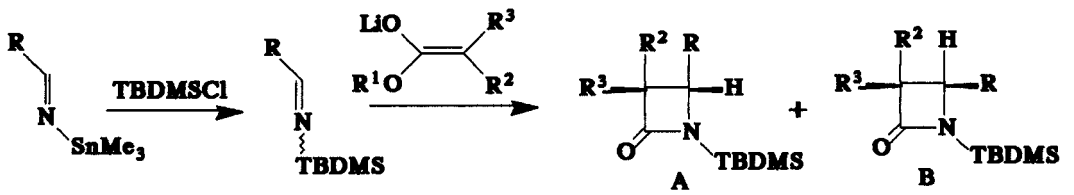
R^1	R^2	R^4	Y%	A	:	B
CH_3	CH_3	i-C_3H_7	60			
CH_3	CH_3	C_2H_5	40			
	H	CH_3	40	90		10
	H	C_2H_5	58	90		10
	H	i-C_3H_7	30	8		92
$Ph(CH_2)_2N$	H	CH_3	38	95		5
C_2H_5	H	C_2H_5	44	92		8

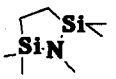
A high cis-stereoselectivity is observed, except in the case of silylimines with branched side chain where the reverse trans-stereoselectivity takes place. An interesting application of this methodology is given by the use of the enolate of STABASE-glycin ethyl ester[10] as nucleophilic partner. This substrate allows the introduction of an amino group in position 3 of the β-lactam ring and is therefore particularly useful for the synthesis of monobactams[11].
An interesting alternative to this methodology for preparing 4-alkylsubstituted azetidinones starting from nitriles is represented by the use of aluminum imines as intermediates[1]. These imines can be obtained from nitriles by addition of different aluminum hydrides (DIBAH, Red Al, Lithium triethoxy aluminum hydride, Lithium diisobutyl butyl aluminum hydride). Since the aluminum imines or the corresponding ate complexes upon reaction with ester enolates gave azetidinones in pour yields, they have been converted to silylimines by transmetallation with trimethylchlorosilane[1]. The resulting silylimines, when reacted *in situ* with ester enolates, afforded the expected β-lactams (A) and (B) in yield ranging from 40 to 70 %.



R	R^2	R^3	Y%	A	:	B
2-Furyl	CH_3	CH_3	60			
2-Furyl	H	Et	56	70		30
2-Furyl	H		40	95		5
p-MeOPh	H	Et	68	90		10
2-Thienyl	H	Et	50	75		25
2-Thienyl	H		38	90		10
n-C_3H_7	H	Et	40	75		25

Taking advantage of the easy metal-metal exchange shown by stannyl imines, we prepared by transmetallation with ter-butyldimethylsilyl chloride, the corresponding silylaldimines whose metal-nitrogen bond, because its resistance to hydrolitic conditions, survives in the cycloaddition product.

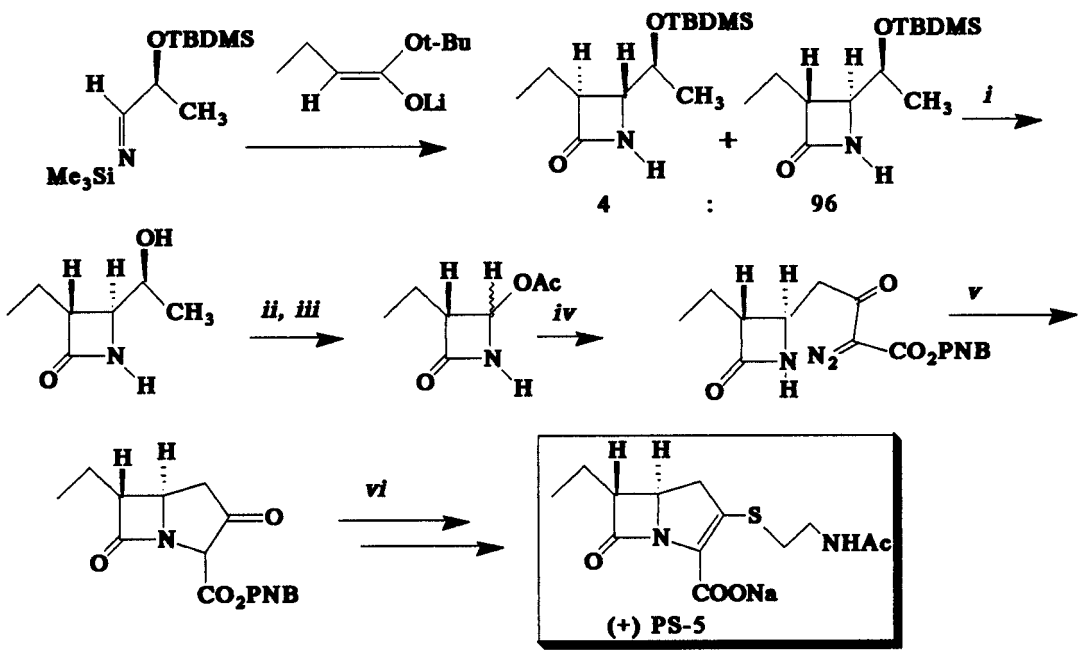


R	R^2	R^3	Y%	A :	B
2-Furyl	CH_3	CH_3	60		
2-Furyl	C_2H_5	H	56	80	20
Cinnamyl	CH_3	CH_3	45		
Phenyl	C_2H_5	H	38	75	25
2-Furyl		H	20	n.d.	

The synthesis of azetidinones starting from chiral N-metallo imines, bearing in α-position an oxygen atom, provides a convenient method for the diastereo- and enantioselective synthesis of β-lactam derivatives.

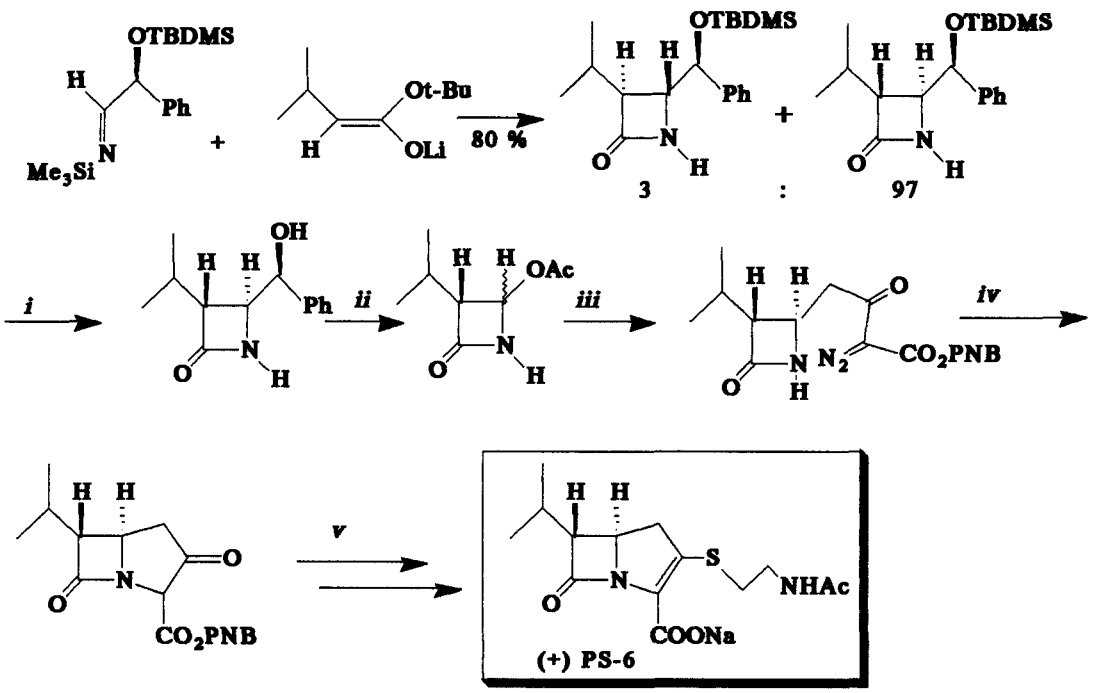
The usefulness of this approach is illustrated by the synthesis of the carbapenems (+)-PS-5[12] and (+)-PS-6[13] and the monobactam Aztreonam[13] reported below.

The synthesis of the antibiotic (+)-PS-5 was achieved by treatment of the N-trimethylsilylimine of (S)-lactic aldehyde and the lithium enolate of ter-butyl butanoate. The reaction affords in a yield up to 62% a 96:4 mixture of the trans azetidinone with the natural configuration at the C-3 and C-4 stereocenters, together with the other trans diastereoisomer. The synthetic plane was completed, after deprotection of the hydroxyl group, via sequential Jones and Bayer-Villinger oxidation. The acetoxy derivative, thus obtained, was converted to the natural carbapenem following the well established Merck procedure[8].



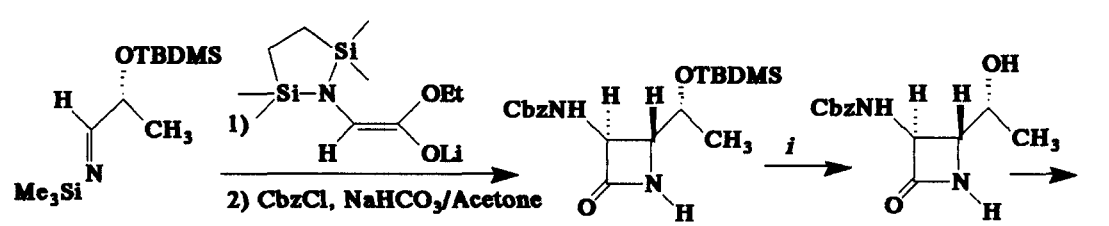
i: HF; CH_3CN; ii: Et_2O, H_2CrO_4; iii: MCPBA, EtOAc; iv:  *$ZnCl_2$; v: $Rd(OAc)_4$; vi: Ref. 8*

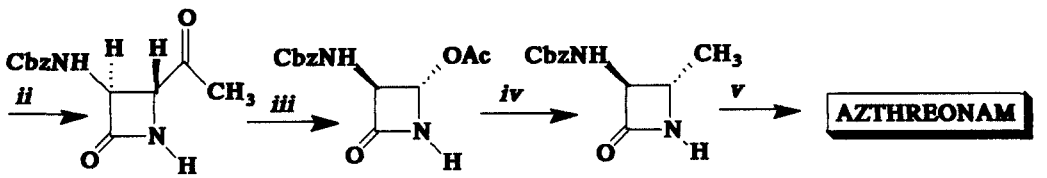
A higher yielding and shorter procedure was developed for the synthesis of (+)-PS-6. In this case the N-silylimine of the (S)-mandelic aldehyde was used. Cycloaddition of this substrate with the lithium enolate of ter-butylisovalerate affords the expected azetidinone in 80% chemical yield and 97/3 diastereoselectivity. The more abundant isomer presenting the natural configuration was desilylated and treated with lead tetracetate, in boiling benzene, to give in one step, through a radical fragmentation reaction, the acetoxy derivative in a 1/1 3(R),4(R) and 3(R),4(S) diastereomeric mixture. Displacement of the acetoxy group with the silylenolether of the p-nitrobenzylester of diazoacetoacetic acid in the presence of zinc chloride afforded the C-4 alkylated product as single trans isomer. This intermediate was further elaborated to the final enantiomerically pure (+)-PS-6 following the previously reported procedure.



Finally, in the synthesis of Azthreonam, in order to introduce the required amino group at the C-3 position of the azetidinone ring, the lithium enolate of the STABASE-glycin ethyl ester was used as nucleophilic component, while the silylimine of the R-lactic aldehyde was necessary to achieve the natural 3S,4R configuration.

The cycloaddition affords in 80% yield exclusively the 3S,4R diastereoisomer which was isolated as carbobenzoxy derivative. Transformation of the C-4 side chain, following the procedure reported for the synthesis of (+)-PS-5, gives, in good overall yield, the 4-acetoxy derivative as trans isomer. The C-4 methyl group of Aztreonam has been then introduced *via* displacement of the acetoxy group by dimethyl lithium cianocuprate.



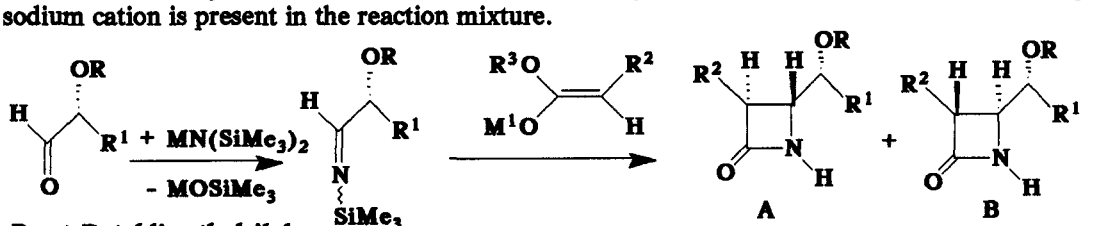


i: 5% HF in CH_3CN_{aq}; ii: Jones; iii: MCPBA; iv: $(CH_3)_2CuCNLi$; v: Ref.11

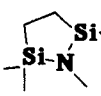
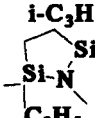
Following this procedure we prepared, starting from the (S)-lactic aldehyde, a variety of new homochiral 3-amino-4-substituted azetidinones, whose alternative preparation in optically active form, may be a difficult task.

R = Ph	68%
R = 2-Fu	25%
R = Allyl	40%
R = But	57%

Concerning the stereochemistry of the cycloaddition using silylimines of α-hydroxy aldehydes, it is worth mentioning that only trans azetidinones have been obtained. The stereochemical outcome of this reaction is strongly affected by the nature of the cations present in the reaction mixture. The highest diastereoselectivity is observed when lithium enolates and silylimines prepared with LiHMDSA are used. In contrast, when NaHMDSA is used either for the preparation of the enolates or as source of the iminic nitrogen, the diastereoselectivity drops dramatically. The almost complete lk-induction of the stereocenter present in the side chain of the imine upon the C-4 stereocenter of the β-lactam observed in the case of the lithium-lithium couple, may be explained by assuming a coplanarity of the nitrogen and the oxygen atoms of the imine due to the chelation of a lithium cation so that a preferred attack by the nucleophile from the less hindered face of the diastereotopic plane takes place. This mechanistic hypothesis is substantiated by the much lower diastereoselectivity observed when the less coordinating sodium cation is present in the reaction mixture.



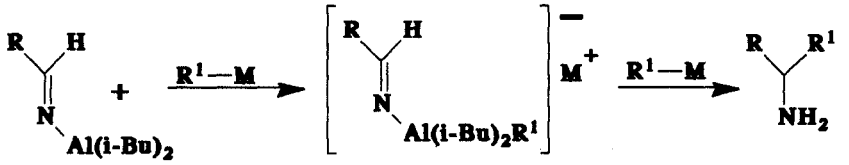
R = *t-Butyldimethylsilyl*

M	M^1	R^1	R^2	R^3	Y%	A:B
Li	Li	CH_3		C_2H_5	76	98:2
Li	Li	CH_3	C_2H_5	t-C_4H_9	60	97:3
Li	Li	Ph	C_2H_5	t-C_4H_9	70	97:3
Li	Li	Ph	i-C_3H_7	t-C_4H_9	80	98:2
Li	Na	CH_3		C_2H_5	50	60:40
Li	Na	CH_3	C_2H_5	t-C_4H_9		
Na	Li	CH_3		C_2H_5	73	55:45
Na	Li	CH_3	C_2H_5	t-C_4H_9	38	70:30
Na	Na	CH_3		C_2H_5	33	50:50

B. Synthesis of primary amines

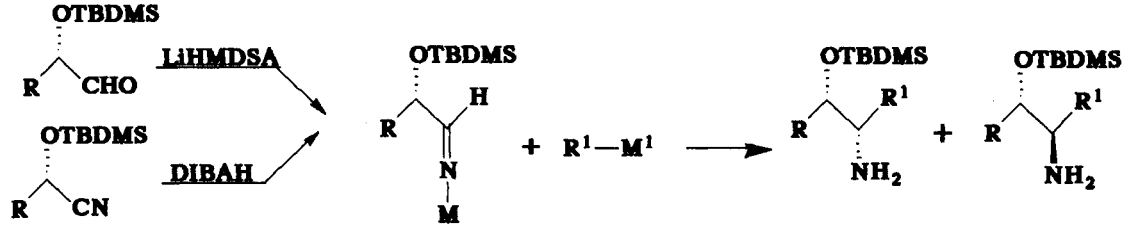
Metallo-imines may add other kinds of nucleophile than esterenolates.

Recently we have developed a method to obtain primary amines from nitriles via the corresponding aluminum imines[14]. In fact, the addition of DIBAH to a nitrile, followed by treatment of the intermediate aluminum imine with two equivalents of a lithium alkyl or a Grignard reagent, affords the corresponding primary amines in good yields.



R	R^1	M	Y%
Ph	Allyl	MgCl	98
2-Furyl	n-Butyl	Li	72
Ph	Benzyl	MgCl	46
n-Butyl	Allyl	MgCl	50
2-Furyl	Allyl	MgCl	70
2-Thienyl	n-Butyl	Li	96
2-Thienyl	Allyl	MgCl	98
n-Octyl	Allyl	MgCl	96

The usefulness of the reaction is demonstrated by the variety of the starting nitriles and the organometallic reagents that may be used, the yield ranging from 46 to 98 %.
An interesting extension of this methodology cames out from the addition of DIBAH to α-silyloxynitriles. The resulting aluminum imines represent a good starting material for the diastereo- and enantioselective synthesis of various aminoalcohols of biological interest. Preliminary experiments show that butyllithium adds to the aluminum imine of mandelic aldehyde to give a mixture of syn-anti diastereisomers in a 91:9 ratio and 48% yield. Similar results can be obtained starting from the corresponding silylimines, arising from aldehydes as previously described.



These results can be a good starting point to develop a general strategy for the diastereo- and enantio selective synthesis of chiral amino alcohols.

REFERENCES AND NOTES

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