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N-METALLO-IMINES: A NEW APPROACH TO α-AMINO ALCOHOLS FROM CYANOHYDRINS.

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Summary: The addition of lithium alkyls to the *in situ* generated o-protected α-hydroxy N-diisobutylaluminium-imines, proceeds in a stereocontrolled manner as indicated by the predominant formation of the *syn* adduct (4) from cyanohydrins (1) in satisfactory yields.

The basic concept of the addition of organometallic reagents to "masked" imine derivatives of ammonia, is now a very well established carbon-carbon bond-forming reaction. This reaction has been extensively used for the synthesis of amines and azetidinones starting from metallo-imines (and sulfenyl-imines) obtained from enolizable and non-enolizable aldehydes[1]. During our study on the synthesis and utilization of metallo-imines in organic synthesis, we have recently demonstrated the synthetic usefulness of aluminium-imines easily obtainable *via* hydroalumination of nitriles[2]. Moreover the possibility of using homochiral silyl-imines in a high stereocontrolled total synthesis of *trans* non-classical β-lactam antibiotics has been recently demonstrated[3]. We wish now to report our recent disclosures on the use of α-hydroxy-aluminium-imines in the synthesis of 2-aminoalcohols which constitute important structural moieties of pharmacologically useful substances, for instance natural and unusual aminoacids[4].

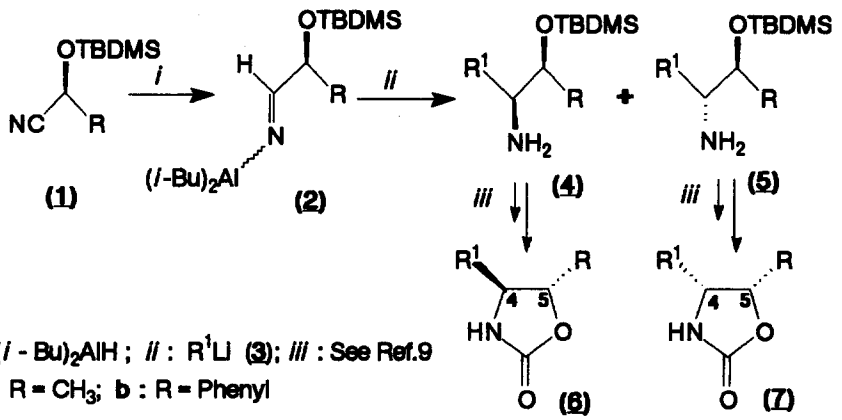
Aluminium-imines, derived from cyanohydrins *via* hydroalumination, appear to exist only in the imino form and show no obvious tendency to tautomerize. More importantly the presence of an α - standing stereocenter bearing an hydroxy functionality addresses the attack of nucleophiles in a stereocontrolled manner so that a privileged diasteroisomer is obtained. A summary of our findings is presented herein.

Imines (2a) and (2b) were easily generated by direct addition of diisobutylaluminium hydride to commercially available mandelonitrile and lactonitrile

protected as *t*-butyldimethylsilyl ether[5]. Addition of lithium alkyls to the reactive aluminium-imines occurred with good stereoselectivity.

In a typical procedure treatment of (1) (1 mmol) under argon atmosphere with diisobutylaluminium hydride[6] (DIBAH) (1.1 mmol), at -78°C using pentane as solvent, affords α-silyloxy-aluminum imine (2) as depicted in the Scheme 1.

Scheme 1



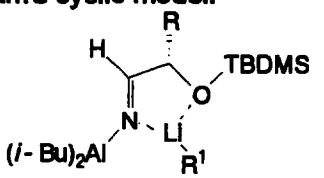
i : (*i* - Bu)$_2$AlH ; *ii* : R^{1}Li (3); *iii* : See Ref.9
a : R = CH_3; **b** : R = Phenyl

After 2-4 hr at -78°C, the organometallic reagent (3) (2.5 mmol) is added to the mixture and the reaction is allowed to reach room temperature while stirring is continued for 12-24 hr. Quenching with a satured NH_4Cl solution, extraction with ethyl acetate and flash chromatography of the crude products on silica gel eluting with ciclohexane-ethyl acetate 7:3, affords compounds[7] (4) and (5) in a region of 45 % yields. The results are shown in Table1. Our stereochemical assignements for the products bearing two contiguous asymmetric centers were based on spectral (^{1}H and ^{13}C NMR) as well as chemical evidence. Moreover the stereochemistry of most adducts was best determined by building up the relative 1,3-oxazolidin-2-one derivatives[8] (6) and (7). A large volume of literature[9] shows that the H_4 - H_5 coupling constant of the *cis* isomer in the cyclic derivatives is larger than that of the *trans* isomer. Confirmation of the assigned structure is then been obtained from the greater shielding of the carbons joined in the cis linkage at ^{13}C NMR spectra.

TABLE 1: 1,2-Amminoalcohols from nitriles

Entry	R	R^1	Ratio 4/5	Yields%
1	Phenyl	Allyl	91/9	43
2	Phenyl	Butyl	91/9	48
3	Phenyl	*sec*-Butyl	67/33	35
4	Phenyl	*ter*-Butyl	11/88	27
5	Phenyl	Pentyl	86/14	40
6	Phenyl	Hexyl	89/11	35
7	Phenyl	Methyl	75/25	29[10]
8	Methyl	Allyl	72/28	47
9	Methyl	Butyl	76/24	57
10	Methyl	*ter*-Butyl	45/55	60

The results in Table 1 illustrate that nearly all type of organometallic reagents may be employed; thus 1°, 2°, and 3° carbons give addition products. Analysis of the diastereomeric ratio clearly shows a predominance of the *syn* isomer compared to the *anti* one. This diastereofacial selectivity can been explained assuming a chelation control in the addition of the nucleophile to imines with the formation of the cyclic intermediate (6) in analogy to what happens in the case of chiral α-carbonyl compounds[11] according the Cram's cyclic model.



(6)

In conclusion we have demonstrated that this new methodology provides an excellent route for obtaining a variety of 2-aminols. The recent availability of homochiral cyanohydrin *via* chemical as well as enzimatic route[12], makes this procedure available for the synthesis of biologically active compounds as statine[13] and biotine[14]. Application of this technology to homochiral compounds of biological interest as well as mechanistic aspects of this reaction are now actively investigated and will be reported in due course.

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4. For alternative synthesis of 1,2 aminols see Ciufolini, M.A.; Spencer, G.O.; *J. Org. Chem.*, **1989**, 4740 and references therein cited.
5. The silyloxy cyanohydrins were prepared from cyanohydrins by treatment with *t*-butyldimethyl silyl chloride in DMF in the presence of imidazole (r.t. 12 hr). The target was isolated by vacuum distillation (80% yield).
6. Addition of *i*-Bu_2AlH was followed by monitoring (GC) the reaction mixture and the resulting aluminium-imines were further processed after complete disappearance of the starting nitrile. In some cases an overreduction has been observed.
7. Yields are reported for isolated chromatographically pure products and have not been optimized. ^1H ,^{13}C NMR, IR and GC/MS spectra were entirely consistent with the assigned structure and satisfactory combustion analyses were obtained.
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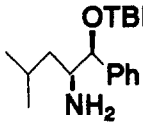
10. A certain amount (22%) of (9) was isolated.This behavior is under investigation.



(9)

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