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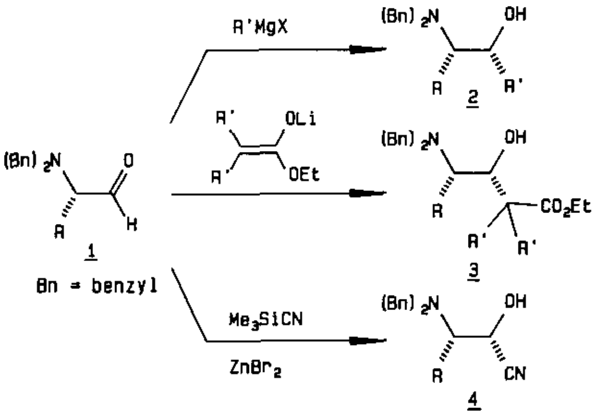
STEREOSELECTIVE ADDITION OF LITHIATED HETEROCYCLES TO CHIRAL α-AMINO ALDEHYDES

M.T. Reetz*, W. Reif, and X. Holdgrün

Fachbereich Chemie der Universität, Hans-Meerwein-Strasse, 3550 Marburg, FRG

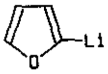
Abstract–Lithiated heterocycles 5-9 add diastereoselectively to optically active α-N,N-dibenzylamino aldehydes 1 with 80-95% nonchelation control.

The chiral pool of α-amino acids has been exploited extensively by organic chemists¹⁾. One area of interest is the preparation and use of optically active N-protected α-amino aldehydes. Grignard and aldol additions provide a large number of β-amino alcohols, some of which are biologically active²⁾. The t-butoxycarbonyl protective group (BOC) has been used most often. However, the vast majority of nucleophilic additions show low degrees of diastereoselectivity²⁾. Another problem is the ease of enantiomerization of some BOC-protected α-amino aldehydes²,³⁾. The 9-phenyl-9-fluorenyl protective group imparts configurational stability onto the aldehydes, but Grignard and aldol additions provide mixtures of diastereomers³⁾. We have previously shown that N,N-dibenzyl protected aldehydes 1, prepared from amino acids, are configurationally stable at room temperature and react with RMgX, RLi, Li-enolates and $Me_3SiCN/ZnBr_2$ to provide the nonchelation controlled adducts with 90-99% diastereoselectivity⁴⁾. Deprotection using Pd-black/HCO_2H affords the debenzylated free amines in good yield⁴⁾. Certain highly Lewis acidic reagents provide the chelation controlled adducts with 80-95% diastereoselectivity⁴⁾.



Dedicated to Sir Derek Barton on the occasion of his 70th birthday.

In view of the potential biological properties of β-amino alcohols containing heterocyclic residues, we undertook a study directed toward the stereoselective addition of lithiated heterocycles (Het-Li) 5-9 to the α-amino aldehydes 1. In the following we report on our preliminary results.



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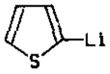

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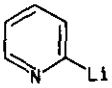

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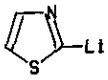

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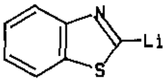

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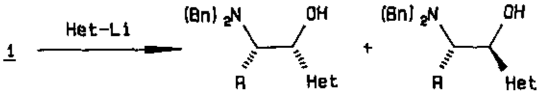

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Table 1. Diastereoselective Additions of Lithiated Heterocycles to α-Amino Aldehydes 1

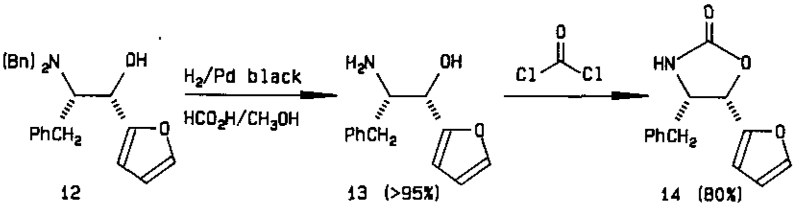
R in 1	Het-Li[a]	Solvent	Temp./Time (°C/h)	% Conversion (% isolated)	10:11[b]
$PhCH_2$	5	THF	-78/4	90 (76)	83:17
$tC_4H_9(Me)_2SiOCH_2$	5	THF	-78/2	87 (66)	81:19
CH_3	6	Et_2O	-78/4	>95 (49)	87:13
$PhCH_2$	6	Et_2O	-78/4	>95 (91)	89:11
$(CH_3)_2CH$	6	Et_2O	-78/4	>95 (85)	>95:<5
$(CH_3)_2CHCH_2$	6	Et_2O	-76/4	>95 (74)	81:19
$tC_4H_9iOCH_2$	6	Et_2O	-78/2	80 (59)	76:24
$PhCH_2$	7	THF	-78/4	>95 (86)	88:12
$tC_4H_9(Me)_2SiOCH_2$	7	Et_2O	-78/4	80 (53)	91: 9
$PhCH_2$	8	Et_2O	-78/3	>95 (79)	91: 9
$tC_4H_9(Me)_2SiOCH_2$	8	Et_2O	-78/3	86 (67)	91: 9
$tC_4H_9(Me)_2SiOCH_2$	9	Et_2O	-78/4.5	- (61)	86:14

a) Reagents 5, 6, 8 and 9 were prepared by lithiation of the neutral heterocycles using n-butyllithium, 7 by halogen/metal exchange of the bromide. In all cases 1.5 equivalents of Het-Li were used.

b) Determined by ^1H or ^{13}C-nmr spectroscopy (300 MHz instrument) of the crude product.

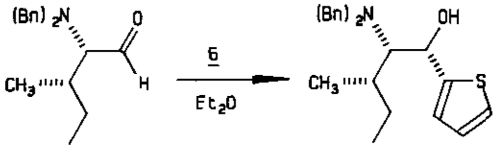
Table 1 shows that in all cases the nonchelation controlled adducts 10 are formed preferentially, the diastereomeric ratios being in the range of 80:20 to 95: 5. Thus, the degree of 1,2-asymmetric induction is a little lower than in the case of alkyllithium additions4). It should be noted that the aldehyde 1 with R=$tC_4H_9(Me)_2SiOCH_2$ is derived from serine and leads to highly functionalized adducts5).

The configurational assignments were made by analogy to previous reactions of RLi with the aldehydes4), i.e., nonchelation control was assumed. This was put on a firm basis by quantitative debenzylation of the furanyl adduct of phenylalaninal (1, R=$PhCH_2$) followed by formation of the oxazolidinone 14. The vicinal H,H coupling constant of 8.1 Hz is in line with a cis arrangement of 14 6), as are nOe studies. Control experiments4) show that no racemization of 1 occurs during reaction, irrespective of the nature of the organometallics (Li, Mg, Zn; see below).



12 13 (>95%) 14 (80%)

The aldehyde 15 derived from isoleucine reacts with 6 quantitatively to deliver a single diastereomer 16 having three chiral centers:



15 16 (93%)

Nonchelation control is in line with the Felkin-Anh model4). Although we have not completed a systematic study of the effect of trans-metalating to magnesium, cerium, manganese, zinc or titanium reagents7), initial experiments were performed with $MgCl_2$ and $ZnCl_2$ 8) as additives. Upon treating 5 in THF with these salts and then adding 1 (R=$tC_4H_9(Me)_2SiOCH_2$) at 0°C (in case of $MgCl_2$: 24 h; in case of $ZnCl_2$: 24 h warming to +22°C), nonchelation control increased significantly

(10/11 ratios of 89:11 and >95:<5, respectively). However, the rates of addition turned out to be much lower, reducing the %-conversion to the adducts (54% and 31%, respectively). In the case of the reaction of 8 with 1 (R=$PhCH_2$), addition of $ZnCl_2$ or $MgCl_2$ had no beneficial effects. It remains to be seen if further optimization using these and other metals is possible and whether reversal of diastereoselectivity can be achieved. Nevertheless, the present methodology represents a useful diastereoselective entry into optically active heterocyclic compounds of the type 10, 13 and 14. Since a host of other lithiated heterocycles and heteroatom substituted aromatics are readily available, our approach is likely to be quite general for the synthesis of potentially biologically active β-amino alcohols containing heterocyclic moieties. The basicity of the amino group is sufficiently low to allow slightly acidic conditions during workup[9].

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9) Typical Procedure: A solution of 1 mmol of 1 in 1 ml of diethyl ether was added slowly to a solution of 1.5 mmol of Het-Li in 10 ml of diethyl ether at -78°C. The resulting solution was stirred for 4 h. The reaction mixture was quenched with 5 ml of a saturated solution of ammonium chloride and extracted several times with diethyl ether. The organic phase was dried over $MgSO_4$ and concentrated. The crude product was purified by column chromatography (silica gel; petroleum ether:diethyl ether; 10:1). In the synthesis of 1 from the primary alcohol[4], the usual Swern conditions were applied (A.J. Mancuso, S.L. Huang, and D. Swern, J.Org.Chem., 1978, **43**, 2480); in the workup 1% HCl was used.

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