PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY A MATHEMATICAL, PHYSICAL & ENGINEERING SCIENCES

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Stereoselective reactions of chiral α-amino aldehydes

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Optically active α-amino acids can be converted into the corresponding doubly protected *N*,*N*-dibenzyl α-amino aldehydes. These react diastereoselectively with Grignard reagents, lithium enolates and Me_3SiCN/ZnX_2 to provide the non-chelation-controlled adducts. Molecular modelling explains some of the results. The sense of stereoselectivity can be reversed if Lewis acidic chelating reagents are used. Undesired racemization does not occur.

Introduction

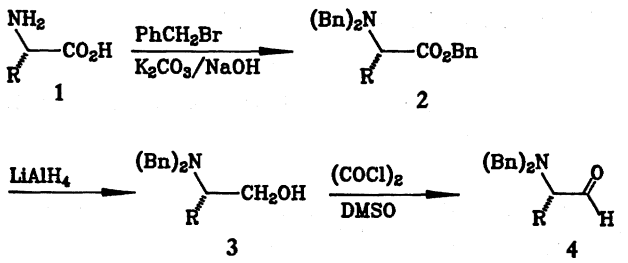
The chiral pool of natural L-α-amino acids provides a convenient source of optically active compounds that have been utilized by organic chemists for various purposes (Martens 1984; Coppola & Schuster 1987). One possibility is to convert them into the corresponding *N*-protected α-amino aldehydes, because these are potentially useful building blocks in such C–C bond-forming reactions as Grignard and aldol additions. The problem is to find ways to control diastereofacial selectivity that allow the formation of either of the two possible diastereomers on an optional basis. Although several successful examples of stereoselective additions to certain protected α-amino aldehydes have been reported (Coppola & Schuster 1987; Danishefsky *et al.* 1982; Woo 1985), the vast majority of reported examples involve the formation of mixtures of diastereomers. Generally, the protective group BOC (*t*-butoxycarbonyl) has been used, but this causes another problem, namely the difficulty in handling the aldehyde due to the relative ease of enantiomerization. Although the 9-phenyl-9-fluorenyl protective group leads to fairly stable aldehydes, Grignard and aldol additions afford mixtures of diastereomers (Lubell & Rapoport 1987).

This paper outlines a general solution to both problems, making β-amino alcohols with two stereocentres available in all four possible stereoisomeric forms. This is of synthetic interest because such compounds occur widely in Nature, e.g. as components in certain amino sugars (Kennedy & White 1983), in biologically active peptides such as antihypertensive renin inhibitors (Rich 1985), and in glycosphingolipids (Hakomori 1986). Synthetic analogues are also of interest in pharmaceutical chemistry.

Results

Our approach to the above problem involves the synthesis of doubly protected α-amino aldehydes followed by the addition of suitable organometallic reagents (Reetz *et al.* 1987). Upon reacting natural L-amino acids **1** with benzyl bromide in the presence of K_2CO_3/NaOH, the *N*,*N*-dibenzylamino benzyl esters **2** are formed (67–73%) (scheme 1). Lithium aluminium hydride reduction leads to the over 99% optically active alcohols **3** (69–75%), which in turn

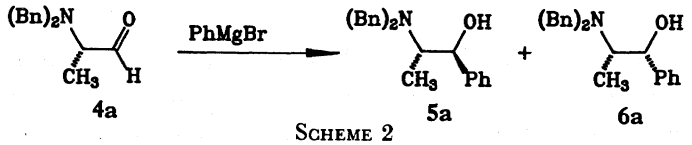
are readily converted into the desired aldehydes **4** by Swern oxidation (88–92%). Compounds **4** are configurationally stable at room temperature. The enantiomers are accessible by using the mirror images of **1**.



SCHEME 1

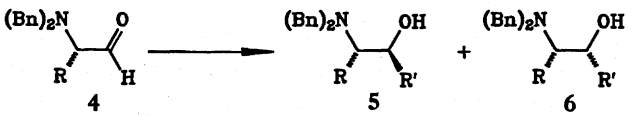
Because of the presence of the α-amino group, **4** can undergo either chelation-controlled or non-chelation-controlled Grignard-type additions. For the extensively studied analogous α-alkoxy aldehydes, reagents of the type RLi or RMgX lead to mixtures, whereas Lewis acidic compounds $RTiCl_3$ preferentially afford chelation controlled products (Reetz 1984). Alternatively, a Lewis acid such as $TiCl_4$, $SnCl_4$ or $MgCl_2$ may be used to first form octahedral chelates, followed by chelation controlled additions of dialkylzinc, enol- and allylsilanes or cyanotrimethylsilane. The more difficult problem of non-chelation control has been solved to a limited extent by using less Lewis acidic titanium reagents such as $RTi(OiPr)_3$ (Reetz 1984). In this case the absence of intermediate chelation means more degrees of freedom, resulting in a lower stereoselectivity.

Because of the above reasons, it was expected that RLi and RMgX should add to the amino aldehydes **4** either stereorandomly or perhaps with a moderate degree of chelation control. Surprisingly, this turned out not to be so (Reetz *et al.* 1987). Rather, 97% non-chelation control was observed upon adding PhMgBr to the aldehyde **4a** derived from alanine (85% yield) (scheme 2). The configurational assignment was made by debenzylating the product **6a** with Pd-black/HCO_2H to provide the known norephedrine.



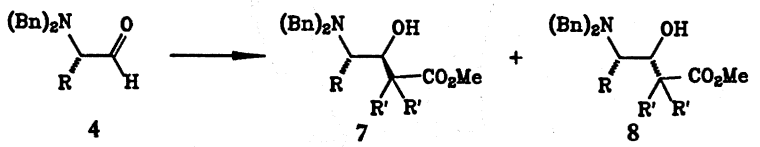
SCHEME 2

This pronounced degree of diastereoselectivity in favour of non-chelation control is general. Thus, a variety of Grignard and alkyllithium reagents behave in the same manner. This also applies to aldehydes **4b–d** (R = $PhCH_2$, $(CH_3)_2CHCH_2$, $(CH_3)_2CH$). Organotitanium reagents (Reetz 1986) having alkoxy or amino ligands are even more selective, although they are generally not needed. These and other reactions of **4** occur without any racemization (scheme 3).



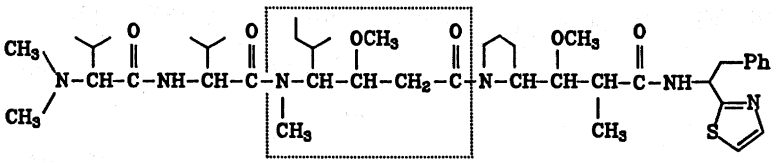
SCHEME 3

Similarly, lithium enolates derived from acetic acid ester or isobutyric acid ester add with over 90% non-chelation control (80–85% yields) (scheme 4).



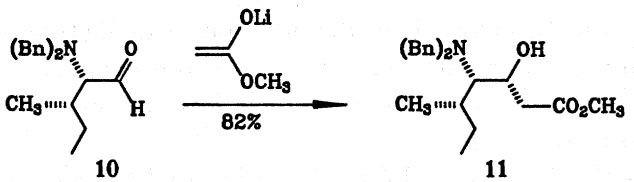
SCHEME 4

In this connection it is of interest to note that dolastatin-10 (formula **9**), the most powerful antineoplastic compound known to date (Pettit *et al.* 1987), contains the structural unit of an *O*-methylated β-amino alcohol which can be thought of retrosynthetically as the product of an aldol reaction of the appropriate aldehyde (cf. box in **9**).



9

Because the structural unit contains three chiral centres, four diastereomeric forms, each as an enantiomeric pair, are possible. Although the absolute and relative configuration is currently not known, we have prepared one of the eight stereoisomers in the form of the *N*,*N*-dibenzyl derivative **11** by performing a non-chelation-controlled aldol addition (over 97% stereoselective) to the aldehyde **10** derived from L-isoleucine (scheme 5).

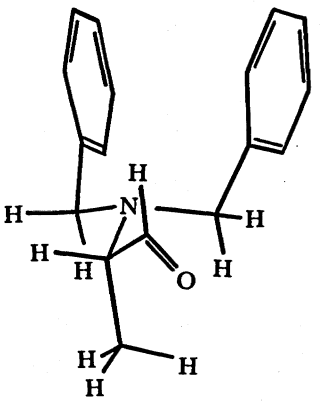


SCHEME 5

These remarkably stereoselective reactions can be explained on the basis of the Felkin–Anh model, but the source of diastereoselectivity in favour of non-chelation control may also be related to a ground state property. Indeed, molecular modelling of **4a** shows that the most stable conformer (cf. **12**) has one π-face exposed, leading to the non-chelation-controlled adducts.

On the basis of the above, non-organometallic reagents should show the same sense of diastereofacial selectivity. Sulphur yields such as $Me_2S{=}CH_2$ do in fact afford epoxides of the type **15** (86–90% stereoselectivity), which are also accessible via an organometallic route (**13**:**14** = 6:94) (scheme 6).

It turns out that chelation-controlled Grignard and aldol additions are more difficult to perform. By using the methodology developed for α-alkoxy aldehydes, aldehydes **4** were



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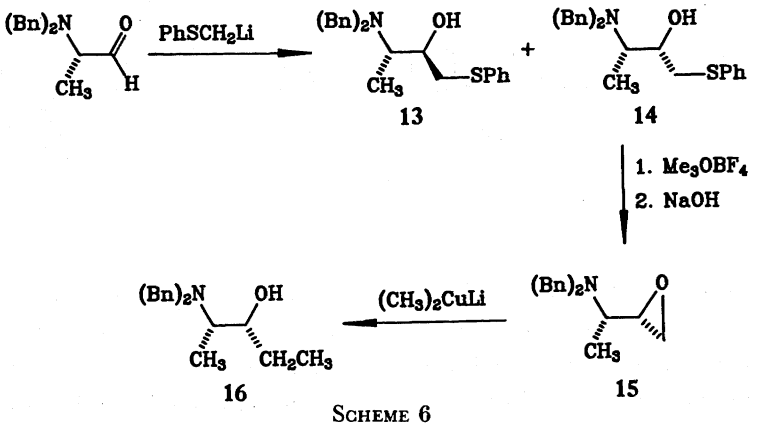


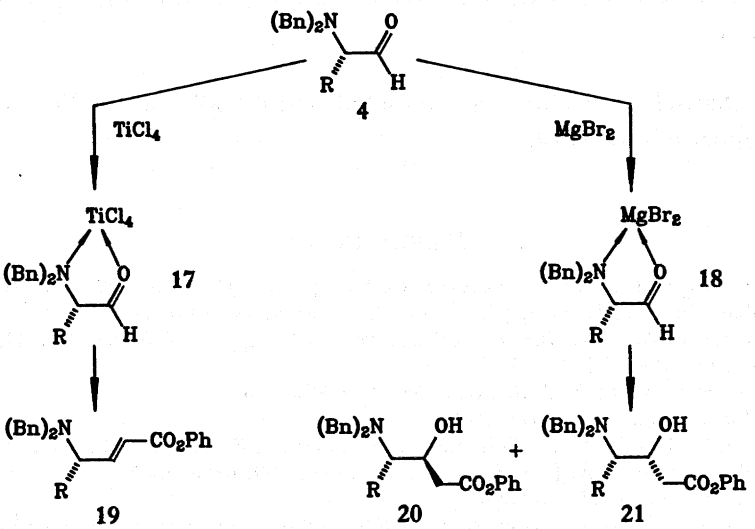
SCHEME 6

treated with $TiCl_4$ or $SnCl_4$, followed by the addition of dialkylzinc or allylsilanes (Reetz *et al.* 1987). Chelation control was achieved in all cases, but the degree of diastereoselectivity is not always above 90%. An alternative method involves smaller protective groups in combination with cuprates.

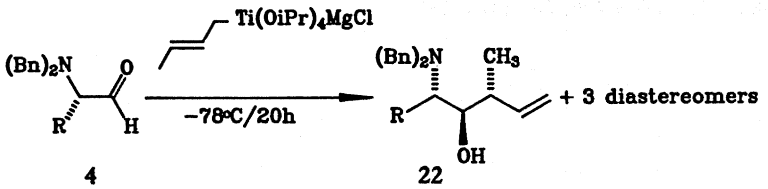
For aldol additions, $TiCl_4$ causes aldol condensation to **19**. Such compounds can also be prepared by Horner–Emmons olefination and are useful building blocks in other reactions (scheme 7). Chelation-controlled aldol additions are not possible even if MgX_2 (X = Cl, Br) is used in combination with 1-phenoxy-1-trimethylsiloxyethylene (**20** + **21** = 5%). Cyanohydrin formation with Me_3SiCN occurs with non-chelation control in the presence of BF_3 or ZnI_2 and with chelation control in the presence of MgX_2.

Prochiral nucleophiles can be made to react so that primarily one of the four possible diastereomers is formed. An example is the addition of crotyltitanium ate complexes (Reetz 1986), leading to **22** having two new stereocentres (scheme 8). As expected, diastereofacial selectivity is non-chelation controlled, whereas simple diastereoselectivity is *anti* (Masamune nomenclature).

Finally, α-amino acids having additional (protected) functional groups are attractive starting materials. For example, the aldehyde **23** made from serine shows the same reactivity patterns as **4**. The absolute and relative configuration of the non-chelation-controlled adducts

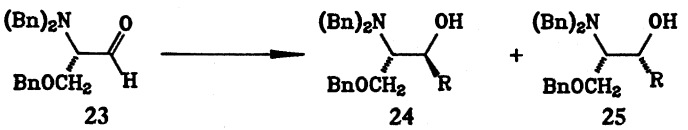


SCHEME 7



R = CH_3	90	:	10
R = $PhCH_2$	94	:	6
R = Me_2CHCH_2	96	:	4
R = Me_2CH	99	:	1

SCHEME 8



CH_3MgI	5	:	95
$TiCl_4/(CH_3)_2Zn$	>95	:	<5
EtMgBr	<5	:	>95
PhMgBr	<5	:	>95
$C_{15}H_{31}MgBr$	<5	:	>95

SCHEME 9

25 correspond to the D-erythro configuration of naturally occurring sphingoide bases (e.g. R = n–$C_{15}H_{31}$) (scheme 9).

CONCLUSIONS

Our method for the control of stereoselectivity in nucleophilic additions to chiral α-amino aldehydes is based on the combination of two protective groups at nitrogen and the correct organometallic reagent. The absence of racemization is another important feature. The results

have opened up new avenues for the effective exploitation of the chiral pool of α-amino acids in organic synthesis.

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