Acyclic Stereocontrol Based on Nonchelation-controlled Ene Reactions with α-Haloaldehydes

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Aluminium(III)-promoted ene reactions with α-haloaldehydes are shown to exhibit a high *anti*-diastereofacial (non-chelation) selection or *syn*-diastereoselection to afford an efficient method for preparing stereochemically-defined β-haloalcohols including the 22*R*-hydroxy side chain unit in steroids.

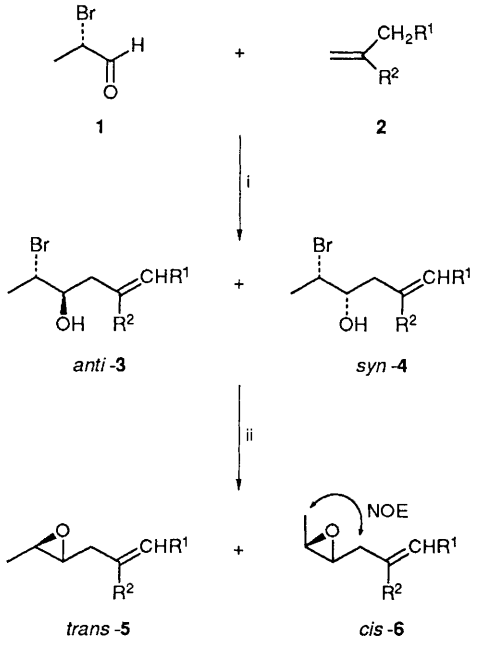
The ene reaction involving carbonyl compounds, aldehydes in particular, as enophiles (carbonyl–ene reaction) has currently emerged as a new tool for acyclic stereoselection.[1] However, the types of aldehyde enophile explored thus far have been limited.[2] Herein we report a new type of Lewis acid-promoted ene reaction using α-bromo- or α-chloro-aldehydes as enophiles (haloaldehyde–ene reaction) which proceeds at relatively low temperatures under effective nonchelation control with high *syn*-diastereoselectivity.

The reactions of α-bromopropanal **1** and isobutene **2a** (2 equiv.) at −78 °C in dichloromethane (Scheme 1) were found to give the ene products **3a** and **4a** in good yields, using organoaluminium reagents (1 equiv.) as the Lewis acid (Table 1). The *anti* (nonchelation) stereoisomer **3a** was obtained as the major product, the ratio depending on the nature of the Lewis acid employed. Of special value is the Me_2AlCl-promoted reaction which provides **3a** in relatively high selectivity. The structural assignment of the ene products **3** and **4** was based on conversion to the epoxides **5** and **6**; the epoxide **6** derived from the minor ene product **4** showed a relatively strong NOE between the methylene and methyl protons. The *anti*-diastereofacial selectivity thus observed is reasonably explained in terms of Felkin–Anh's or Cram's dipolar model.[3] Thus, this new type of ene reaction is proved to proceed under effective nonchelation control.

Table 1 Haloaldehyde–ene reactions[a]

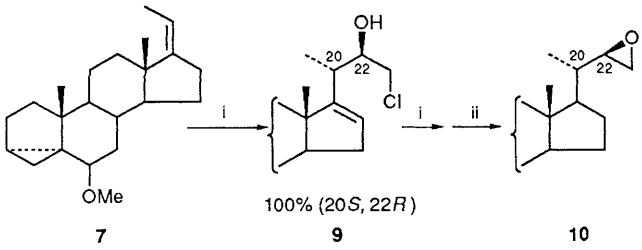
Alkene	AlL_n	**3** : **4**[b]	Total yield (%)[c]
2a	Me_2AlCl	79 : 21	90
2a	$ArOAlMeCl$[d]	72 : 28	82
2a	$(ArO)_2AlCl$[d]	68 : 32	80
2b	Me_2AlCl	75 : 25	87
2c	Me_2AlCl	79 : 21	87

[a] All reactions were carried out on a 1 mmol scale under argon. [b] The isomer ratio was determined by ^{13}C NMR and HPLC analyses. [c] Yield of isolated product after silica gel chromatography. [d] Ar = 2,4,6-$Me_3C_6H_2$.



a; R^1 = H, R^2 = Me
b; R^1, R^2 = –[CH_2]$_5$–
c; R^1 = H, R^2 = Ph

Scheme 1 *Reagents and conditions*: i, AlL_n, CH_2Cl_2, −78 °C; ii, NaH, dimethylformamide



Scheme 2 *Reagents and conditions*: i, $ClCH_2CHO$ **8**, Me_2AlCl, CH_2Cl_2, −78 °C; ii, NaH; iii, H_2, PtO_2

Next, we examined the simple diastereoselection of the haloaldehyde–ene reaction in the context of steroid side chain synthesis.[4] Thus, the reaction of the easily available steroidal alkene **7**[5] and chloroacetaldehyde **8** (1 equiv. each) with Me_2AlCl was found to show an extremely high level of simple *syn*-diastereoselection. The 20*S*,22*R*-*syn* product **9** was obtained as a single stereoisomer in 73% yield. The stereochemistry was assigned on the basis of the ^{13}C and ^{1}H NMR analyses,[6] after conversion to the steroidal epoxide **10**, a key intermediate of 22*R*-α-hydroxylated steroid side chains.[6]

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