Cram-selective Addition of α-Allyl Sulphinyl Anion to Chiral Aldehydes: Synthesis of (*E*)-1,4-Dihydroxyalk-2-enes

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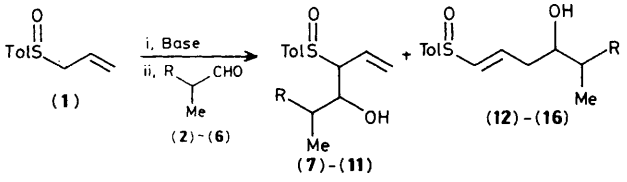
The stereoselective introduction of an allylic alcohol function into chiral aldehydes is readily achieved by sequential condensation of aldehydes with an allylic sulphinyl anion and thiophile-promoted desulphurization of the resulting α-substituted allylic sulphoxides.

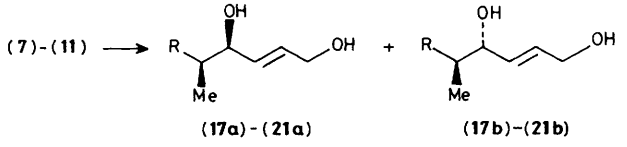
A number of highly stereoselective and useful transformations of allylic alcohols and their derivatives have become available in recent years,[1—3] and so the stereocontrolled insertion of such a moiety into organic substrates is of importance in organic synthesis. As demonstrated by the elegant work of Evans[4] and Hoffmann,[5] allylic sulphoxides can provide an easy route to allylic alcohols taking advantage of the facility of the allylic sulphoxide–sulphenate [2,3] sigmatropic rearrangement.[6,7] We report here that this approach can be exploited to introduce a $-CH{=}CHCH_2OH$ group into chiral aldehydes with fair to excellent degrees of stereoselection. Treatment of racemic allyl *p*-tolyl sulphoxide (**1**) with 1.1 mol. equiv. of lithium di-isopropylamide (LDA) in tetrahydrofuran (THF) at −78 °C, followed by addition of 4.4 mol. equiv. of hexamethylphosphorous triamide (HMPA) and of 3.0 mol. equiv. of the chiral aldehydes (**2**)—(**6**) at −78 °C (condensation time 2 min) gave a mixture of readily separable α-[compounds (**7**)—(**11**)] and γ- [(**12**)—(**16**)] adducts, the α-products always being largely predominant.[8] Exposure of (**7**)—(**11**) to an excess of a thiophile (trimethyl phosphite or diethylamine in MeOH)[4] resulted in quenching of the allylic sulphoxide–sulphenate equilibrium and afforded diastereoisomeric mixtures of the diols (**17a,b**)—(**21a,b**) (Method A).

Higher chemical yields were obtained when the latter reaction was performed directly on the crude α–γ-adduct mixtures (Method B),† the stereochemical result being unchanged (Scheme 1). Overall yields, and regioisomeric, and diastereoisomeric ratios are collected in Table 1.

The reported data deserve a few comments. The α:γ regioisomer ratios are markedly higher than those obtained in the reaction of the anion of (**1**) (generated by LDA in THF) with *aromatic* aldehydes at −10 °C.[9] We believe that our synthetically useful regiocontrol is the result of the combination of various factors. Indeed, in preliminary experiments we observed that the α:γ ratios were greatly improved by carrying out the condensation in the presence of increasing amounts of HMPA; for instance with 2-phenylpropanal (**5**), the ratios of (**10**) to (**15**) were 1:1, 1.4:1, and 9:1 with 0.0, 1.1, and 4.4 mol. equiv. of HMPA, respectively. Furthermore, the use of a lower (−78 *vs.* −10 °C) reaction temperature and of a three-fold excess of an *aliphatic* aldehyde minimizes retro-aldol type processes observed[9] only for α- and not for γ-adducts.‡§

The diastereoisomeric diols (**17a,b**)—(**21a,b**) are obtained exclusively in the (*E*) form ($J_{HC=CH}$ 15—16 Hz), as expected on the basis of a variety of previous observations for related allylic sulphoxide-mediated syntheses of allylic alcohols.[4,5] More interesting, in our opinion, are the diastereoisomeric ratios in which the diols (**17a,b**)—(**21a,b**) are produced. These range from about 2:1 in the case of (**17a,b**) (R = Et) up to 28:1 for (**20a,b**) (R = Ph), as determined by 300 MHz ^{1}H n.m.r. spectroscopy. The stereochemical assignments for (**17a,b**)—(**21a,b**) rest on the reasonable assumption that *syn*[12] diols are expected to predominate over their *anti*[12] counterparts on the basis of Cram's rule,[13] that in its more recent





(**2**), (**7**), (**12**), (**17a,b**), R = Et
(**3**), (**8**), (**13**), (**18a,b**), R = Pr^i
(**4**), (**9**), (**14**), (**19a,b**), R = Cyclohexyl
(**5**), (**10**), (**15**), (**20a,b**), R = Ph
(**6**), (**11**), (**16**), (**21a,b**), R = 6-Methoxy-2-naphthyl

Scheme 1. Only one enantiomer of racemic (**17**)—(**21**) is indicated for simplicity. Tol = *p*-MeC_6H_4.

Table 1. Synthesis of diols (*E*)-(**17a,b**)—(**21a,b**) from (**1**).

Product	Method	α:γ ratio[a]	Yield (%)[b]	**a**/**b** ratio[c]
(**17a,b**)	A	6.1:1	40	2.1:1
(**17a,b**)	B	—	65	2.2:1
(**18a,b**)	A	10:1	40	5.1:1
(**19a,b**)	A	5.6:1	57	6.4:1
(**19a,b**)	B	—	61	6.4:1
(**20a,b**)	A	9:1	67	28:1
(**21a,b**)	A	9:1	40	10:1

[a] Determined by isolation of α- and γ-adducts by flash chromatography (SiO_2, Et_2O); α-adducts always showed higher R_f values than their γ-counterparts.[9] [b] Overall yields of diols (**17a,b**)—(**21a,b**) from (**1**); isolated by flash chromatography (SiO_2, Et_2O). All new compounds gave satisfactory analytical and spectral data. [c] Determined by 300 MHz ^{1}H n.m.r. spectroscopy (see text).

† Unfortunately it was not possible to extend method B to diols (**18**), (**20**), and (**21**) which could not be obtained free from the corresponding γ-adduct (**13**), (**15**), and (**16**). Recovery of unchanged aldehydes (both methods) and (**1**) (method A) is generally possible.

‡ We note that under conditions very similar to those employed in this work allyl *p*-tolyl sulphoxide anion gave exclusively γ-adducts in Michael addition to cyclopentenones.[10,11]

§ In a control experiment it was shown that under our conditions condensation of (**1**) with benzaldehyde and isobutyraldehyde gave the corresponding adducts in α:γ ratios of 1.3:1 and 2:1, respectively.

version[14] explains the increase of stereoselection observed with increase of the steric requirements of the R residue, the large (L) group of the Felkin–Anh[14] model. This model can also provide a rationale for the definitely higher levels of stereoselection obtained, at least in the case of compounds (**18**)—(**21**), with respect to those generally observed for alkyl- or allyl-lithium additions to similar chiral aldehydes.[15,16] One can envisage that a very sterically demanding and electron rich α-allyl sulphinyl anion would attack the carbonyl carbon in such a way that unfavourable steric and electronic interactions with both the L (R) and M (medium; methyl) groups would be minimized.

The following ^{1}H n.m.r. observations should provide further support to the proposed attribution of configuration for (**17a,b**)—(**21a,b**): (i) the smaller values of C*H*OH–C*H*Me coupling constants (*J* 5.1—6.0 Hz) found for the predominant products with respect to the minor ones (*J* 6.6—7 Hz);[17] (ii) all the major isomers (and thus all the minor ones) should feature the same relative configuration since they display a common trend in the chemical shift values of some diagnostic signals. Thus the *Me*–CH doublet always resonates at lower field in the major (*syn*) and at higher field in the minor (*anti*) products. A similar trend has been reported for several related *syn*- and *anti*-diastereoisomeric substrates;[17,18] (iii) additional evidence for the stereochemical assignment was achieved in the case of compound (**17a,b**) from two-dimensional nuclear Overhauser effects using variable mixing times (0.1—0.4 s).[19]

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