Asymmetric Induction in the Ene Reaction of Chloral with (1*S*,5*S*)-(−)-β-pinene; Control of Stereoselectivity by the Choice of Lewis Acid Catalyst

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Summary The thermal ene addition of chloral to (−)-*β*-pinene affords a 17:83 mixture of the two diastereoisomers (**1**) and (**2**), the ratio of which is altered appreciably if a Lewis acid is employed to enhance the rate of the ene addition; with ferric chloride the 97:3 ratio of (**1**):(**2**) indicates that the reaction has become almost completely stereoselective, and the results can be rationalised by a simple steric model.

THE thermal ene addition of *β*-pinene to maleic anhydride, methyl fumarate, methyl maleate,[1] and methyl pyruvate,[2] or of cyclopentene, or *cis* or *trans*-but-2-ene, to maleic anhydride[3] affords mixtures of stereoisomers because of competing *endo* and *exo* addition. The Lewis acid-catalysed ene reaction between pent-1-ene and (−)-menthyl glyoxylate has been found to occur with low to moderate amounts of asymmetric induction.[4] Our results, presented here, on the reaction of (−)-*β*-pinene with chloral reveal that the ratio of diastereoisomers can be altered by the appropriate choice of reaction conditions. They represent the first example of virtually quantitative asymmetric induction in an ene reaction in which the hydrogen transfer occurs from a non-chiral carbon atom.

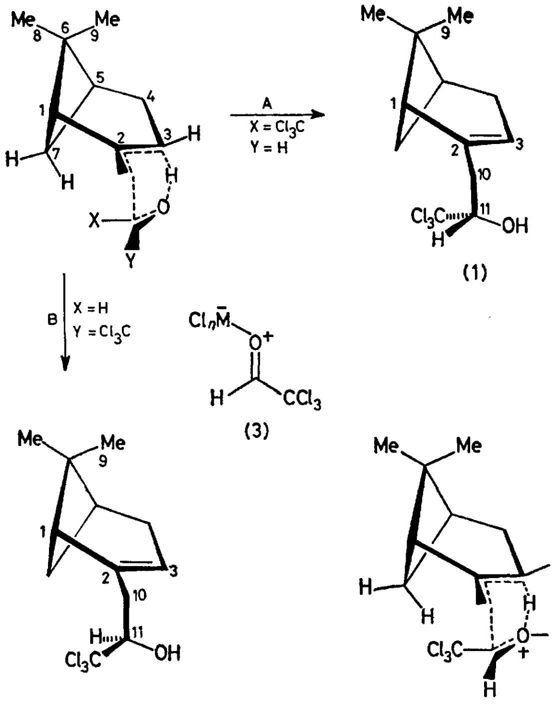
The thermal reaction of (1*S*,5*S*)-(−)-*β*-pinene, $[\alpha]^{24}_{D}$ −23·2° ($CHCl_3$, *c* 0·48), with chloral afforded an ene adduct, $[\alpha]^{24}_{D}$ −4·6° ($CHCl_3$, *c* 0·537), which was initially thought, because of the previous results referred to above, to comprise a 1:1 mixture of the diastereoisomers (**1**) and (**2**). The 100 MHz ^1H n.m.r. spectrum of the product did not exhibit the expected duplication of some of the resonances, at least not until the H–O–C–H coupling was removed by exchange with D_2O. Under these conditions, the complex multiplet for the hydrogen atom attached to C-11 was simplified to an overlapping pair of doublet of doublets (centred on τ 6·00 and 6·05) of unequal intensity. The use of $Eu(fod)_3$ increased the chemical shift difference and, at suitable concentrations of the shift reagent, various other resonances of the two components become resolved including those for the *syn* (*i.e.* C-9) methyl groups (originally superimposed at τ 9·12). Peak area integrations thus gave an estimate for the (**1**):(**2**) ratio. Likewise, area integration of the resolved signals in the ^{13}C n.m.r. spectrum provided a separate estimate for the proportions of the two diastereoisomers. The mean values for these two sets of results are given in the Table.

TABLE. Ratios of diastereoisomers formed in the ene addition of chloral to (−)-*β*-pinene

	Ratio (**1**):(**2**)		
Catalyst[a]	^1H n.m.r.	^{13}C n.m.r.	$[\alpha]^{24}_{D}$[d] (°)
—[b]	17:83	18:82	−4·6 (*c* 0·537)
BCl_3[c]	*ca.* 50:50	—	—
2% $AlCl_3$	76:24	77:23	−35·1 (*c* 0·538)
10% $AlCl_3$	75:25	76:24	—
2% $SnCl_4$	90:10	92:8	−42·8 (*c* 0·489)
2% $FeCl_3$	97:3	96:4	−45·9 (*c* 0·486)

[a] Reactions conducted in dry CCl_4 solution at room temperature. [b] 95 °C, neat. [c] An inefficient catalyst; appreciable by-product formation resulted from the necessarily prolonged period of reaction, and clear cut integration of the n.m.r. signals was not possible. [d] Rotenone employed as the calibration standard for all optical rotation measurements. (**1**), $[\alpha]^{24}_{D}$ − 47·8; (**2**), $[\alpha]^{24}_{D}$ + 4·5° by extrapolation.

The ene reaction is greatly accelerated in the presence of a Lewis acid catalyst (see preceding communication). Reactions were performed using a range of catalysts, and the (**1**):(**2**) ratios estimated by the procedures outlined above; these ratios were predicted and found to be dependent upon the catalyst employed (see Table). The most important and interesting feature of these results is the complete inversion of the (**1**):(**2**) ratio as compared with the thermal reaction. In particular, in the case of the sterically bulky catalysts $SnCl_4$ and $FeCl_3$ reaction is seen to proceed in a direction that almost entirely favours the formation of one of the diastereoisomers, that is of (**1**). In the isolation of the ene adducts from the reaction mixture it is clear, because of a lack of change in the (**1**) : (**2**) ratios, that neither distillation nor chromatography on silica effected the fractionation of (**1**) and (**2**), nor were these compounds found to be equilibrated under the conditions of the reaction, or even upon prolonged contact with the Lewis acid. Their ratio therefore reflects the difference in energy between the two topologically distinct stereochemical arrangements of the reaction centres at the transition states of the kinetically controlled ene reactions.



(1)

(2)

(3)

(4)

These results can be accommodated by a simple steric model for the transition states.[5] It is well established that β-pinene reacts in ene reactions by selective transfer of one of the diastereotopic allylic hydrogens, namely the *endo* hydrogen atom.[6] The two groups (Cl_3C and H) attached to the prochiral centre in chloral are of widely different steric bulk (*cf.* methyl pyruvate[2]). Hence, non-bonded repulsions should be minimised if chloral approaches the olefin from the methylene bridge side with the Cl_3C group orientated away from the hydrocarbon skeleton (path B), resulting in an *R* configuration at the new asymmetric centre of the adduct (**2**). Hence (**2**) should be the predominant isomer in the thermally initiated reaction. In the catalysed reactions, however, it is clear, because very appreciable rate enhancements are observed, that the enophile is a chloral–Lewis acid complex. The most likely site for co-ordination is that which places the MCl_n unit *anti* to the bulky Cl_3C group, as indicated by structure (**3**), thereby changing the preferred geometry of interaction of the ene and enophile in the transition state. For the range of catalysts studied (BCl_3, $AlCl_3$, $SnCl_4$, and $FeCl_3$) it was expected that there would be a progressive change in favour of the geometrical approach indicated by (**4**) because of an increase in the effective bulk of the Lewis acid, and should result in the growing dominance of isomer (**1**) of *S*-configuration at C-11. The results show the expected trend in (**1**):(**2**) ratios, but the absolute configurations of the two isomeric products have yet to be assigned unequivocally.

The 97 : 3 mixture of isomeric alcohols from the $FeCl_3$-catalysed ene reaction was converted into a mixture of the *p*-bromobenzoate esters which, unfortunately, could not be induced to crystallise. Hence, attempts to define absolute configuration on the basis of heavy atom anomalous dispersion results from an *X*-ray structure analysis were abandoned. Instead, configuration was fixed relative to the known absolute configuration of the pinene skeleton (*i.e.* 1*S*,5*S*) by employing the crystalline tosylate ester.

The tosylate derivative (see preceding communication) of the minor alcohol isomer was readily removed by fractional crystallisation to constant m.p. 79—79·5 °C, to afford pure (**1**)-tosylate, $[\alpha]_D^{23}$ − 69° ($CHCl_3$, *c* 0·173). *X*-ray diffraction data[7] for an orthorhombic crystal (space group $P2_12_12_1$) was refined to *R* 0·0447, without recourse to weighting analysis, for 1547 independent reflections. The structure thus obtained showed that C-11 had the *S*-configuration, thereby validating the above stereochemical assignments.

The precise electronic mechanism whereby Lewis acids are able to catalyse ene reactions must be considered to remain unresolved until the results of appropriate mechanistic studies are available. However, the above results do highlight the steric requirements of the metal halide unit, and suggest possible choices of reaction partners that could lead to highly stereoselective ene additions. The synthesis of optically active molecules by extensions of the above procedures is currently under investigation. In principle, if the part of the molecule derived from the enophile can be detached, without loss of chirality, the ene component can be recycled thereby taking on the role of a 'chemical template.'

Added in proof. Adduct (**1**) is produced with 100% stereoselectivity in the $TiCl_4$-catalysed reaction (2 mol %); $[\alpha]_D^{24}$ −48·2° (*c* 0·052). Diastereoisometric impurity (**2**) could not be detected in the ${}^1H$ n.m.r. spectra with Eu(fod)$_3$ as 'shift' reagent.

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