# Directing effects in the hydroboration of steroidal alkenes

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The balance between steric and electronic effects on the regiochemistry of the hydroboration:oxidation of steroidal alkenes is reviewed.

**Keywords:** hydroboration, steroidal alkenes

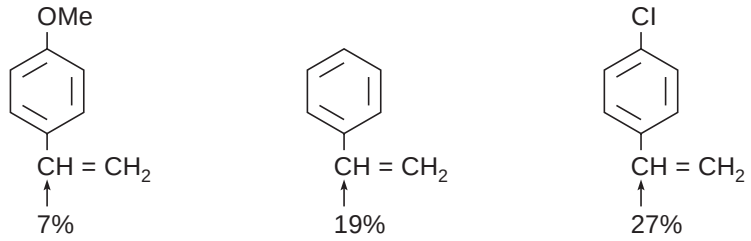
The rapid addition of borane to alkenes to form alkylboranes and the subsequent replacement of the carbon–boron bond by a carbon–oxygen bond by oxidation with alkaline hydrogen peroxide is one of the more widely used reactions in synthetic organic chemistry.[1,2] The addition is concerted and the electron-deficient boron behaves as the electropositive component in the cyclic transition state.[3,4] This leads to *cis* addition with the boron attached to the less highly substituted carbon of an unsymmetrical alkene. The oxidation with alkaline hydrogen peroxide occurs with retention of configuration so that a hydroxyl group replaces the boron atom of the organoborane. The procedure therefore leads to the overall *cis* anti-Markownikoff hydration of a double bond with a regiochemistry that is in contrast to that of acid-catalysed hydration. Both the hydroboration and the subsequent oxidation of the borane are normally free of the carbon skeletal rearrangements that can accompany other hydration procedures.

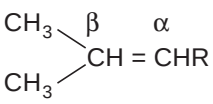
Studies on the hydroboration:oxidation of simple cyclic olefins such as 1-methylcyclopentene, 1-methylcyclohexene, norbornene and α-pinene[5] led to the conclusion that the reaction proceeded preferentially from the less-hindered face of the alkene. These studies were extended to steroidal alkenes[6,7] in which it was shown that hydroboration took place on the less-hindered α-face of the alkene opposite to the 10β-methyl group. Thus cholest-1-ene **1** gave 5α-cholestan-1α-ol **2** (35%) and 5α-cholestan-2α-ol **3** (40%), 5α-cholest-2-ene gave 5α-cholestan-2α-ol (35%) and 5α-cholestan-3α-ol (45%) and 5α-cholest-3-ene gave 5α-cholestan-3α-ol (40%) and 5α-cholestan-4α-ol (45%). Although the addition had been directed to the less-hindered face of the alkene, there was little differentiation between axial and equatorial attack. The trisubstituted alkenes, cholest-4-ene **4** and cholest-5-ene gave the 4α- **5** and 6α-alcohols (60% and 70% respectively). Other investigations on cholesterol have also revealed the formation of small amounts of 5β-cholestan-3β,6β-diol.

Theoretical studies on the hydroboration reaction have led to the suggestion[8,9] that the addition of borane occurs in two steps. There is an initial formation of a π-complex between the alkene and the borane which then gives the four-centred transition state leading to the formation of the alkylborane. A comparison[10] between the α- and β-face selectivity observed in the hydroboration of androst-5-ene and B-norandrost-5-enes did not parallel the differences between the force-field energies calculated for α- and β-cyclobutane models. This suggested that the facial selectivity was not determined by the four-centre transition state, but by the relative ease of formation of the π-complex between the alkene and borane.

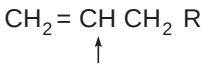
## The directing effects of substituents

The overall hydration of simple 1-alkenes by hydroboration and oxidation with alkaline hydrogen peroxide leads to over 90% of the corresponding primary alcohol.[11] However, in the reaction of styrene with borane, 19% of the borane adds to the benzylic position and this increases to 26–38% for derivatives with electron-withdrawing substituents on the aromatic ring, *i.e.* the regiochemistry of the reaction is sensitive to electronic effects.[11-15] Some directing effects for simple functionalised alkenes are shown in Scheme 1. Vinyl substituents carrying



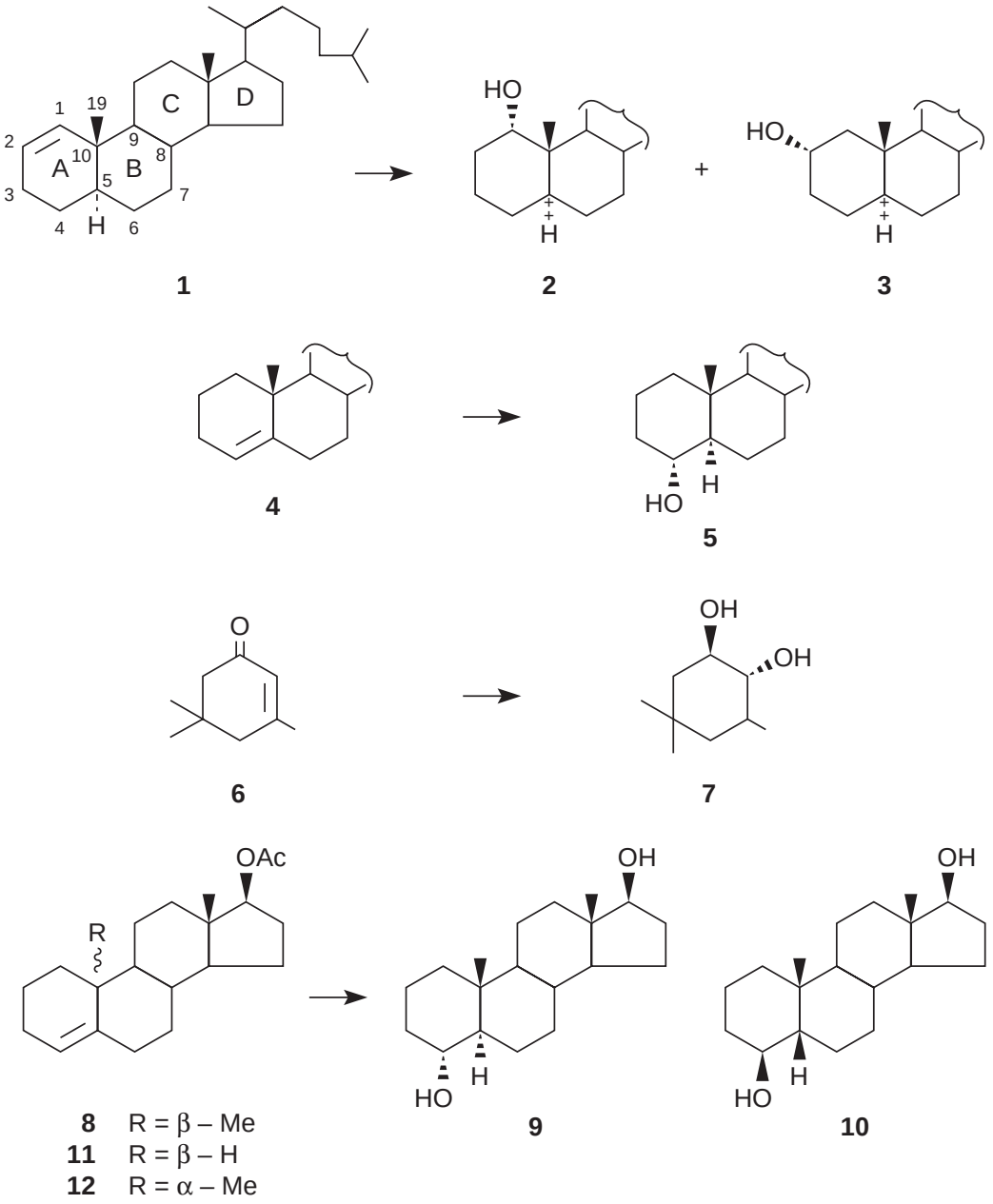

| | α | β |
|---|---|---|
| R = H | 99% | |
| R = Cl | 84% | 7% |
| R = OEt | trace | 88% |
| R = OAc | 95% | trace |




| | |
|---|---|
| R = H | 6% |
| R = Cl | 40% |
| R = OEt | 19% |
| R = OAc | 35% |
| R = OTs | 45% |

**Scheme 1** Directing effects in simple functionalised alkenes.[14,15]

* Correspondence.




substituents with a +M effect such as –OR and –$NR_2$ direct the addition of boron to the β-position whereas –M substituents have a weaker effect, directing the addition to the α-position. Chlorine with a -I effect directs boron predominantly to the α-position. In the hydroboration of allylic derivatives, addition to the β-position relative to the substituent increases with increasing electronegativity. However, functional groups can direct the addition not only by steric and electronic effects but also by the formation of cyclic transition states.

In a study[16,17] of the hydroboration:oxidation of substituted αβ-unsaturated cyclohexenones and cyclohexenols, the products were found to be predominantly diequatorial *trans* 1,2-diols accompanied by minor amounts of the 1,3-diols (*e.g.* **6**→**7**). The allylic hydroxyl group had displayed both a regio- and stereo-chemical directing effect on the reaction, leading to the predominant formation of *trans*-1,2-diols.

## Directing effects in polycyclic systems

*Allylic substituents*

In polycyclic systems exemplified by the steroids, there is a balance between the steric effects exerted by the carbon skeleton and its substituents such as the angular C-10 (β) methyl group,[6,7] and the stereoelectronic effects exerted by vinyl and allylic substituents.

The competing roles of the allylic and vinylic substituents and the C-10(β) methyl group (C-19) have been evaluated for steroidal ring A alkenes.[18] Whereas the hydroboration:oxidation of 17β-acetoxyandrost-4-ene **8** gave predominantly 5α-androstane-4α,17β-diol **9** (81%) and only a relatively small amount of 5β-androstan-4β,17β-diol **10** (17%), the 19-norandrost-4-ene **11** lacking the C-10 methyl group, gave similar amounts of 19-nor-5α-androstane-4α,17β-diol (35%) and 19-nor-5β-androstan-4β,17β-diol (38%). The retro-steroid, 17β-acetoxy-9β,10α-androst-4-ene **12**, in which the C-10 methyl group is now on the α-face, gave mainly 5β,9β, 10α-androstane-4β,17β-diol (77%) and a small amount of 5α,9β,10α-androstan-4α,17β-diol (14%). Comparison of these results emphasises the transannular stereochemical directing effect of the 10-methyl group on the facial selectivity of hydroboration of a 4-ene which was described in the earlier work.[6,7] However, both 17β-acetoxyandrost-4-en-3β-ol **13** and 19-norandrost-4-ene-3β,17β-diol **14**, gave the corresponding 5α-androstane and 19-nor-5α-androstane-3α,4α,17β-triols

whilst 17β-acetoxyandrost-4-en-3α-ol **15** gave entirely products, such as 5β-androstane-3α,4β,17β-triol, arising from β-face attack. This was despite the steric hindrance arising from the C-10β methyl group. Hydroboration of the unsaturated ketone, testosterone **16**, and oxidation of the derived borane gave 5α-androstane-3β,4α,17β-triol.[19] The stereochemistry of the allylic hydroxyl group had determined the facial selectivity of the hydroboration and directed it to the *anti* face.

The hydroboration:oxidation of 6α- and 6β-hydroxyandrost-4-en-17-one **17** and **18** also took place predominantly on the face of the alkene *trans* to the allylic hydroxyl group to give 5β-androstane-4β,6α,17β-triol (58%) and 5α-androstane-4α,6β,17β-triol (66%), with only small amounts of products arising from addition *cis* to the original hydroxyl group.[20] Interestingly 5β-androstane-5β,6α,17β-triol (11.5%) was also isolated from the reaction of the 6α-androst-4-en-17-one. The formation of this product revealed the tendency of the hydroxyl group to direct the addition of the borane to the adjacent carbon atom in opposition to the normal *anti*-Markownikoff regiospecificity of the hydroboration:oxidation. The same effect was observed[21] with a 5α-hydroxyl group that was allylic to an androst-3-ene. The presence of this hydroxyl group increased the proportion of addition of borane to the adjacent C-4 position compared to the unsubstituted steroid. This also led to an increased amount of β-face addition despite the steric hindrance of the C-10β methyl group. In the 19-nor series, lacking this methyl group, only products arising from addition to the β-face *trans* to the 5α-hydroxyl group, were obtained.

Hydroboration:oxidation of 17β-acetoxy-5β-androst-3-ene **19** took place predominantly from the β-face giving, for example **21**, with a relatively small amount of material arising from α-face addition. Although there is a propensity for an allylic hydroxyl group to direct the borane and hence the new hydroxyl group to the *anti* face, hydroboration of 17β-acetoxy-5β-hydroxyandrost-3-ene **20** did not give any 4α,5β-diols. Instead there was a substantial amount of a hydrogenolysis product, 5α-androstane-4α,17β-diol **9** (41%). This had arisen by elimination of the 5β-hydroxyl group and rehydroboration of the resultant 4-ene. Deuteriation studies showed that this reaction might involve a 4α-borane-5β-borinate *trans* diaxial elimination. A similar elimination has been observed in the hydroboration of 3-methyl-3-hydroxy-$\Delta^4$-steroids.[23] Hydroboration followed by elimination with acetic anhydride has been used with testosterone acetate as a means of preparing 5α-androst-3-en-17β-ol.[24,25]

A comparison between the hydroboration:oxidation of $\Delta^2$-steroidal 1α-allylic and 5α-homoallylic alcohols has shown[26] that whereas both alcohols have a stereochemical directing effect, only the allylic alcohol modified the regiospecificity, producing a substantially greater amount of 1,2- as opposed to 1,3-diols.

The hydroboration:oxidation of 3α-,3β-,6α- and 6β-methoxy-androst-4-enes has been shown[27] to proceed predominantly *trans* to the methoxy group and in the case of the 6-methoxy compounds some Markownikoff hydration occurs to form the tertiary C-5 alcohols. Thus 6α-methoxyandrost-4-en-17-one gave 5β,17β-dihydroxy-6α-methoxyandrostane (16%) as well as 4β,17β-dihydroxy-6α-methoxy-5β-androstane (38%) and 4α,17β-dihydroxy-6α-methoxy-5α-androstane (21%). The methyl ethers thus parallel the corresponding alcohols. A possible explanation for these results is that there is a repulsive interaction between the lone pairs on the oxygen and the alkene π-system which increases the electron-density on the opposite face of the alkene favouring *trans* face addition.

*Vinylic substituents*

The directing effect of the halogen of a vinyl halide has been shown[28] to enhance the extent of addition of the borane to the carbon atom bearing the halogen. Hydroboration of 1-chloro-3-methylpropene proceeded more slowly than with the unsubstituted alkene to give a C-1 borane. Oxidation with alkaline hydrogen peroxide gave the aldehyde, 2-methyl-propanal.[15] In other situations the reaction was accompanied[29,30] by an α-group transfer involving migration of the halogen to the boron. For example hydroboration of β-bromostyrene and oxidation with alkaline hydrogen peroxide, gave 2-phenyl-ethanol.

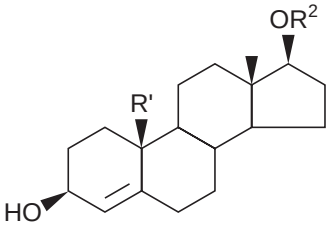
The stereochemistry of hydroboration of 2- and 3-methylene-5α-androstanes, *e.g.* **22**, to form the 2- and 3-hydroxymethyl steroids, *e.g.* **25**, has been rationalised[31] in terms of the initial formation of a π-complex between the alkene and the borane. The preferential *exo*-face selectivity may be determined not only by easier steric access but also by a hyperconjugative interaction between the alkene and the adjacent axial C-H bonds which enhances the electron-density on one face of the alkene. Hydroboration of the corresponding 2- and 3-dibromo and dichloromethylene-5α-androstanes, *e.g.* **23**, gave[32] the same 2β- and 3α- and 3β-hydroxymethyl-5α-androstanes that were obtained from the unsubstituted alkenes. It is possible that the halogen may be removed by an α-transfer mechanism. Since dibromomethylene and dichloromethylene derivatives can be readily obtained from the corresponding ketones under mild conditions,[33] this preparation of hydroxymethyl compounds may offer some advantages over the classical Wittig and hydroboration sequence. Vinyl halides can also be prepared from ketones with reagents such as phosphorus oxychloride. The hydroboration:oxidation of the resultant alkene can lead to the introduction of oxygen at the position adjacent to the original ketone. Thus it has been possible to prepare steroidal 16α-alcohols and ketones from 17-ketones.[34]

When the 2-,3- and 17-methoxymethylene-5α-androstanes (*e.g.* **24**) were subjected[35] to the hydroboration:oxidation sequence, the products were again the 2-, 3- and 17-hydroxymethyl steroids possessing the same stereochemistry as obtained from the alkenes. This may be rationalised in terms of the addition of the borane to the β-position relative to the methoxyl group. This is followed by elimination of the methoxyl group and further rehydroboration of the resultant alkene.

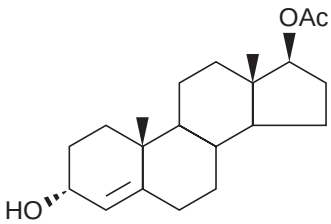
*Dienes*

Hydroboration of buta-1,3-diene and oxidation of the borane by alkaline hydrogen peroxide has been shown[36,37] to produce 1,3- and 1,4-butanediols in a 3:7 ratio. The directing influence of one alkene on the reactions of the other was offset by the introduction of alkyl substituents and 2,3-dimethyl-1, 3-butadiene was converted almost exclusively into the 1, 4-diol. These results were interpreted in terms of boracycle formation. In the steroid series hydroboration of cholesta-3, 5- and 4,6-diene and oxidation of the boranes was reported[38] to give entirely a 1,3-diol, cholestan-4α,6α-diol (**26**→**27**).

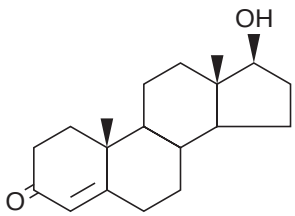
Hydroboration:oxidation of 17β-hydroxy-3-methylene-androst-4-ene gave[39] 3β-hydroxymethyl-5α-androstan-4α,17β-diol. Androsta-3,5-diene-17-one afforded the 4α,6α-diol and also some 3β,6β- and 4β,6α-diols whilst 17β-acetoxyandrosta-4,6-diene gave the 4α,6α-, 4β,6β- and 4β,7β-diols. The products were mainly 1,3-diols suggesting that the borane formed on one double bond may be directing a significant proportion of the second borane to the β-carbon. Hydroboration of 17β-acetoxy-3-chloroandrosta-3,5-diene proceeded slowly and gave mainly the 3α,6β-dihydroxy product.[32] The formation of this 1,4-diol may be rationalized by the chlorine directing the addition of the borane to the C-3β position and then inversion of configuration taking place on the α-transfer.



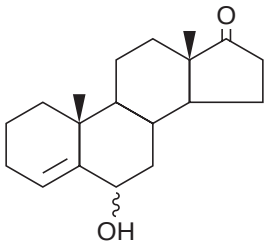

**13** R' = Me, $R^2$ = Ac
**14** R' = $R^2$ = H



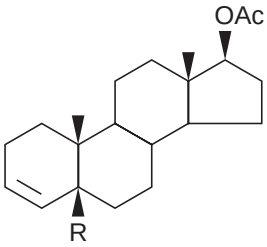

**15**



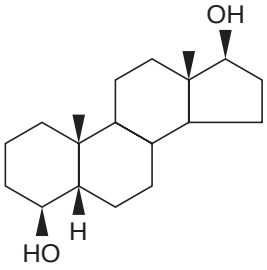

**16**



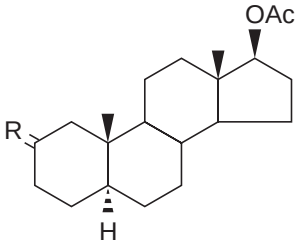

**17** α = OH, β – H
**18** β – OH, α – H



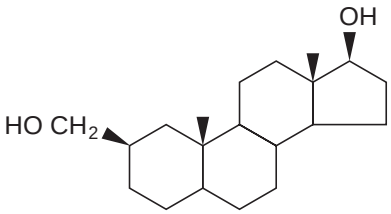

**19** R = H
**20** R = OH



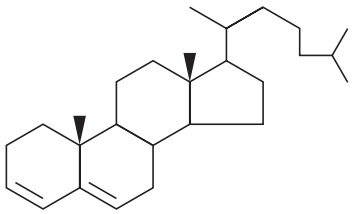

**21**



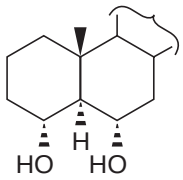

**22** R = = $CH_2$
**23** R = = C $Cl_2$
**24** R = = CH OMe




**25**



**26**




**27**

## Conclusion

In conclusion these results show that there is a subtle interplay between steric and stereo-electronic effects in the hydroboration:oxidation sequence in cyclic systems. Consequently the stereochemical outcome of such a synthetic step should not always be assumed but may need careful confirmation.

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