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Stereoselective Synthesis of *anti*-1,3-Diols *via* Allylboration

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Abstract: Allylboration of β-hydroxy aldehydes and ketones with allylboronic acid at room temperature produces the corresponding *anti*-1,3-diols as the major products.

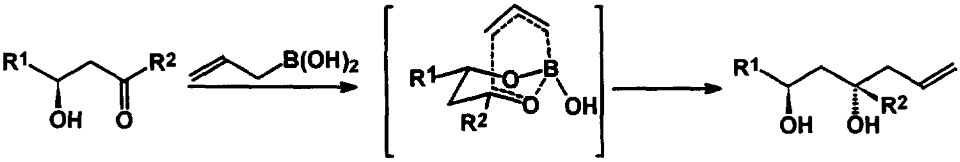
The 1,3-diol subunit is commonly found in many natural products and has often served as a focal point for the development of new synthetic methodology. Syntheses of stereochemically defined 1,3-diols generally involve directed reductions of β-hydroxy ketones, nucleophilic opening of chiral epoxides and related methods.[1] Interestingly, the starting materials in these syntheses are often prepared from homoallylic alcohols, and the allylboration of aldehydes is widely regarded as the method of choice for the synthesis of chiral homoallylic alcohols.[2]

Most successful methods for acyclic stereochemical induction employ the concept of chelation control.[3] The high levels of stereospecificity observed in additions of organometallic reagents to chiral α-alkoxy ketones are thought to involve well defined 5-membered chelates as intermediates.[4] For example allylations of α-hydroxy ketones with allylsilane[5] and allylstannane[6] produce *syn*-1,2-diols as the major products which is consistent with an intramolecular allylation involving chelation control.

A remarkable effect on the rate and diastereoselectivity of allyl- and crotylborations with α-hydroxy ketones[7] and α-oxocarboxylic acids[8] has been reported. The α-alkoxy ketones are known to give stereocontrolled products via chelation control, however the chelation control effect diminishes for β-alkoxy ketones.[9] Here we wish to report the preliminary results of a study involving the allylboration of β-hydroxy aldehydes and ketones with allylboronic acid.

The β-hydroxy aldehydes were prepared in two steps: allylation of aldehydes and ketones with allylmagnesium bromide followed by sodium periodate oxidation of homoallylic alcohols in the presence of a catalytic amount of osmium tetroxide.[10] β-Hydroxy ketones were prepared either by the reductive hydrolysis of Δ^2-isoxazolines[16] or via crossed aldol reactions.

In this study allylboronic acid was selected as the allylborating reagent because it is easily prepared and is more reactive than acyclic allylboronates.[11] Allylboration of freshly prepared β-hydroxy aldehydes [12] (entry1-7) in dichloromethane at room temperature furnished *anti*-1,3-diols as the major products, Table 1. The diastereoselectivity of the reaction is comparable to the selectivity observed in the allylzirconation of β-hydroxy aldehydes.[13] The stereochemistry of the 1,3-diols was determined by converting them to the corresponding acetonides and analyzing their ^{13}C NMR chemical shifts. It is known that the *syn*-1,3-diol acetonides display acetal methyl resonances at 19 and 30 ppm and the acetal carbon resonates at 98.5 ppm, while the methyl resonances of the *anti*-1,3-diol acetonides are at 25 ppm and the acetal carbon resonates at 100.5 ppm.[14] When allylboration was carried out at -78 °C, *syn* and *anti* diols were obtained in 1:1 ratio. At -78 °C, allylboration through the non chelation pathway may be competing with the chelation of allylboronic acid and the substrate.

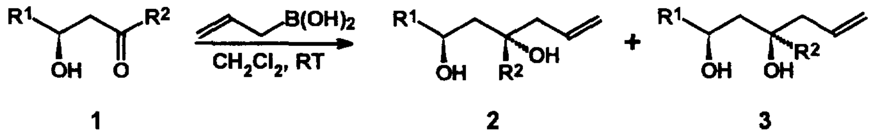


Allylboration of β-hydroxy ketones with allylboronic acid in dichloromethane at room temperature produced 1,3-diols in high yield and with excellent diastereoselectivity (entries 8-14). We have tentatively assigned the *anti* stereochemistry to the major diastereomer based on COSY, HETCOR and ROESY NMR experiments.[15] Further studies are underway to confirm these stereochemical assignments.

In a typical procedure, allylboronic acid (2.25 mmol, 1.0 M in dichloromethane) was added to the β-hydroxy carbonyl compound (2.0 mmol) in dichloromethane (20 mL) over a period of 15 minutes at room temperature and the mixture stirred at room temperature for 2-5 h to ensure completion of the reaction (thin layer chromatography). Dichloromethane was removed under reduced pressure, the residue dissolved in ether (25 mL) and oxidized with NaOH(1N) /H_2O_2(30%). The aqueous layer was saturated with solid NaCl and then extracted with ethyl acetate (15 mL X 3). The combined organic extracts were dried (Na_2SO_4), the solvent removed using a rotary evaporator and the product purified by column chromatography (EtOAc:Hexane, 1:5 v/v). The diols were converted to the corresponding acetonides and the diastereoselectivity determined by NMR.[14]

The allylboration of β-hydroxy carbonyl compounds has been investigated. The *anti* diols are obtained in good to excellent yields.

Table 1: Allylboration of β-Hydroxy aldehydes and ketones.



Entry	R^1	R^2	Yield(%)^{a,b} (2+3)	Diastereoselectivity (2:3)^{c}
1	C_6H_5	H	85	72 : 28^{d,17}
2	$C_6H_5CH_2$	H	83	73 : 27
3	c-C_6H_{11}	H	85	67 : 33
4	n-C_4H_9	H	84	68 : 32
5	n-$C_{11}H_{23}$	H	88	65 : 35
6	$C_6H_5(CH_3)CH$	H	90	60 : 40
7	t-C_4H_9	H	86	70 : 30
8	C_6H_5	CH_3	88	89 : 11
9	C_6H_5	C_2H_5	84	90 : 10
10	C_6H_5	C_6H_5	93	86 : 14
11	n-C_4H_9	CH_3	87	88 : 12
12	$C_6H_5CH_2$	C_6H_5	93	92 : 8
13	i-C_3H_7	C_6H_5	89	92 : 8
14	c-C_6H_{11}	C_6H_5	90	91 : 9

a) All the starting materials used were racemic.

b) Isolated yield of the diastereomeric mixture which gave satisfactory analytical and spectral data.

c) Determined by NMR analysis of their acetonides. For ketones the assignments were based on chemical shifts of acetonide carbons as well as 2D NMR studies.

d) Diisopropyl allyboronate also gave the same selectivity.

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