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The Stereoselective Crotylboration of Alpha-Oxocarboxylic Acids

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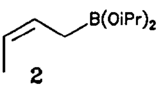
Abstract: Crotylboronates react with alpha-oxocarboxylic acids in a highly stereocontrolled manner. The reaction presumably proceeds through a bicyclic transition state. The alpha-carboxylic substituent exerts a remarkable effect on the rate, regio- and stereoselectivities of the reaction; homoallylic alpha-hydroxycarboxylic acids are formed with regio- and stereoselectivities approach 100%.

Acyclic stereocontrol is one of the most important concerns in organic synthetic chemistry[1]. Extensive studies have resulted in a number of methods for stereoregulated syntheses of conformationally non-rigid complex molecules such as macrolides and polyether antibiotics[2]. Aldol condensation[3] and aldol-like carbon-carbon coupling reactions[4] have played fundamental roles in the synthesis of natural products of propiogenic/acetogenic biosynthetic origins[5]. Over the past few years, the reaction of allyl- and crotylmetal reagents with carbonyl compounds have proven to be important in acyclic diastereoselective syntheses[6]; allyl- and crotylboron reagents are particularly attractive for the synthesis of polyketide natural products. In recent years several chiral allylboron reagents have been developed which provide enantio- and diastereoselectivities, approaching 100% in reaction with aldehydes[7] to form secondary alcohols; however, the diastereoselective synthesis of tertiary alcohols from ketones are not as common[8].

In a previous study[9], we found that an alpha-hydroxyl sate exerts a remarkable effect on the rate and diastereoselectivity of the reaction of allyl- and crotylboranes with ketones. Homoallylic alcohols were produced with diastereoselectivity approaching 100%. We now wish to report that (E)-crotylboronate 1 and (Z)-crotylboronate 2 react with the alpha oxocarboxylic acid 3 to yield the tertiary homoallylic, alpha-hydroxycarboxylic acids 4 and 5, respectively.

1



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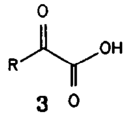

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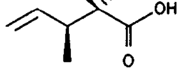

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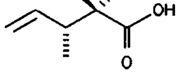

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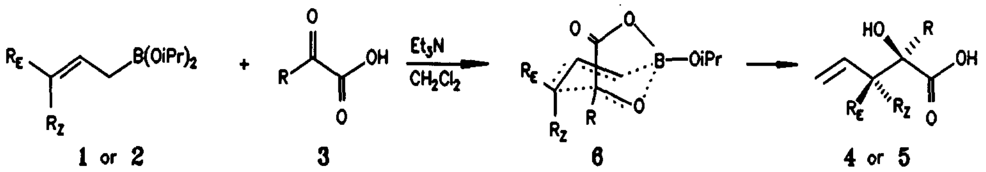
The resultant tertiary homoallylic, alpha-hydroxycarboxylic acids 4 and 5 are synthetically important intermediates constituting the framework of natural macolides, such as the pyrrolizidine macrolide alkaloids[10]. Thus, both the syn and anti isomers of pyrrolizidines can be easily constructed using an appropriate derivative of 4 or 5.

The excellent selectivities suggest that the reaction proceeds through a bicyclic transition state such as 6 (Scheme 1) to yield products with regio- and stereoselectivities approaching 100%. A possible mechanism for the triethylamine initiated allylboration involves the formation of an alpha-oxocarboxylic triethylammonium salt, followed by a ligand exchange[11], to form a mixed boronate which then reacts via transition state 6.

Scheme 1. Proposed Transition State of Crotylboration of Oxocarboxylic Acids

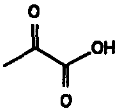
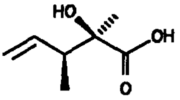
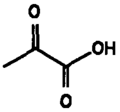
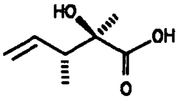
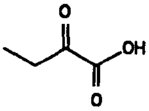
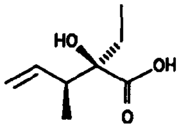
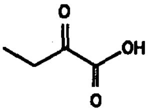
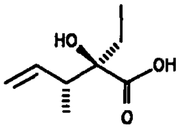
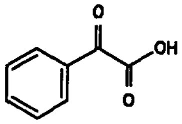
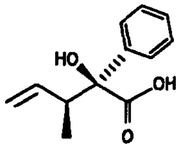
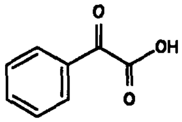
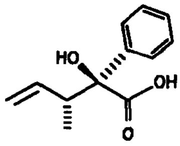


As summarized in Table 1, treatment of an alpha-oxocarboxylic acid with triethylamine (1.0 equivalent, -10 °C for 5 minutes), followed by the addition of one equivalent of the crotylboronate (at -10 °C), and then warming the reaction mixture to room temperature, produced tertiary homoallylic alpha-hydroxycarboxylic acids in high yields and with excellent regio- and diastereoselectivities.

The crotylboronates were obtained using the recently modified Schloesser procedure[14] employing the potassium salt of either trans-or cis-2-butene in a reaction with triisopropylborate followed by acid hydrolysis and reesterification; the products were purified by vacuum distillation. Preliminary solvent investigations revealed that the reactions are faster in methylene dichloride than in THF which is consistent with recent observations[9]. These studies also revealed that the isopropyl boronates react faster than pinacol boronates.

In summary, alpha-carboxylic substituents exert a remarkable effect on the rate, regio- and diastereoselectivies of crotylboration reactions. The bicyclic transition state produce regio- and diastereoselectivities approaching 100%.

Table 1. Crotylboration of Alpha-Oxocarboxylic Acids.

Oxocarboxylic Acid	Allylborate	Product [b]	Yield % [a]	Syn/Anti [d]
	1	 [c]	95·0	99/1
	2	 [c]	96·1	1/99
	1		93·0	99/1
	2		92·3	1/99
	1		96·5	99/1
	2		95·6	1/99

(a) Isolated yields (b) Structures were determined by NMR analyses and confirmed by elemental analyses· (c) Structures were confirmed by comparison to literature values·[12] All other structures were deduced by NMR evaluation of literature reports[8,12,13] (d) Maximum syn/anti; ratio based on purity of starting crotylborate agents which were 99%·

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