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Diastereo- and enantio-selective crotylation of α-ketoesters using crotyl boronic acid ester complexes

Yanping Chen,[a] Laxman Eltepu[a] and Paul Wentworth, Jr.[a,b,*]

[a]*Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, USA*
[b]*Oxford Glycobiology Institute, Department of Biochemistry, University of Oxford, South Parks Road, Oxford OX1 3QU, UK*

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Abstract—A diastereo- and enantio-selective crotylation of ethyl pyruvate has been achieved using a chiral boronic acid auxiliary-based approach. This reaction creates two contiguous stereogenic centers, one of which is a quaternary carbon with complete diastereoselectivity and with enantioselectivities up to 7:1 (73% ee).
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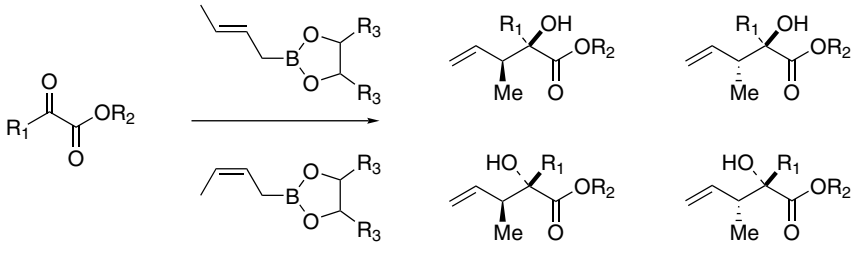
Despite the ubiquitous methodologies available for efficient enantioselective addition of alkyl groups to aldehydes, yielding stereochemically-defined secondary alcohols,[1] the corresponding asymmetric addition of alkyl groups to ketones, to yield homochiral tertiary alcohols has been much less investigated.

Asymmetric allylation and crotylation of aldehydes is one of the most extensively studied processes for the carbon–carbon bond formation, driven in part by the versatility of homoallylic alcohols as synthetic intermediates.[2,3] We are particularly interested in expanding this methodology to ketones, specifically in the context of asymmetric crotylation of α-ketoesters such as pyruvate. Such a stereoselective reaction would be of tremendous utility, because it leads to the generation of chirally-defined α-hydroxy-esters, which are versatile synthetic precursors.[4] This reaction is particular challenging because it involves the simultaneous control of two contiguous stereogenic centers one of which is a quaternary carbon.

Crotyl dialkylboranes and crotyl boronic acid esters have both been useful in the asymmetric crotylation of aldehydes leading to adducts with high diastereo- and enantioselective control. By analogy, the crotylation of pyruvates with crotyl dialkylboranes, such as crotyl-9-BBN, was investigated and resulted in good to excellent diastereoselectivities.[5] However, an investigation of the utility of crotyl boronic acid esters to the crotylation of α-ketoesters has not yet been investigated (Scheme 1).[6] Crotyl boronic acid esters are attractive as auxiliary intermediates because of the wide variety and availability of chirally-defined 1,2-diols.[7] Thus, by modulation of the crotylation reagent, it is theoretically possible for the four possible crotylation products to be obtained. Herein we report the diastereospecific and



Scheme 1. Strategy for asymmetric crotylation of α-ketoesters utilizing crotyl boronic acid esters.

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* Corresponding author. Tel.: +1 858 784 2576; fax: +1 858 784 2590; e-mail: paulw@scripps.edu

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highly enantioselective crotylation of ethyl pyruvate **7** with chirally-defined crotyl boronic acid esters.

The (*E*)- and (*Z*)-crotylboronate diethanolamine complexes (**1** and **2**) were prepared according to Roush's procedure, starting from (*E*)- or (*Z*)-butene, respectively, (Scheme 2).[8] These crotylboronate diethanolamine complexes are stable crystalline compounds and were sufficiently stable that they could be stored at 4 °C for more than three months without any detectable decomposition. Additional chiral crotylboronate complexes (**3**–**6**) were prepared in high-yield (>85% yield) by transesterification that involved shaking a mixture of the respective chiral 1,2-diol and crotyl diethylanolamine complex (**1** or **2**) in diethyl ether with an aqueous solution of sodium chloride.

With the chiral crotylborates **3**–**6** in hand, the crotylation of ethyl pyruvate **7** was investigated (Scheme 3). Crotylation of **7** with borate **3** in toluene at −78 °C gave the crotylation products **8** and **9** as an enantiomeric pair[9] in good yield (84%) and with high diastereoselectivity (>98% de, determined by NMR), but with only a 7% ee (the ratio of **8** to **9** was determined by chiral GC[10]) (Scheme 3).

More favorably however, the asymmetric crotylation of ethyl pyruvate with (*R*,*R*)-diisopropyl tartrate derived boronate (**4**) had a much-improved enantioselectivity (73% ee) again with the same high diastereoselectivity (>98% de). An investigation of the effect of solvent on the crotylation of **7** with boronate **4** revealed that the highest enantioselectivity was achieved in toluene at −78 °C (Table 1). Changing to the more sterically hindered borate **6** resulted in a complete loss of reaction.

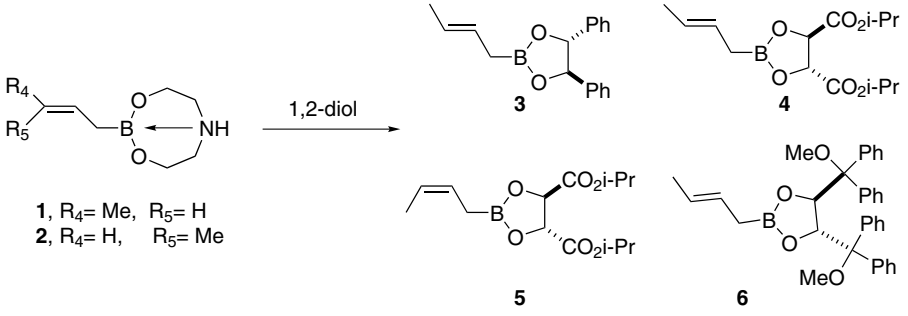
The reaction between **7** and chiral borate **5** gave the α-hydroxyesters **10** and **11** as a pair of enantiomers in high diastereoselectivity.[11] The enantiomeric ratio of **10** and **11** had to be measured via a Mosher's ester method because **10** and **11** could not be separated by GC. Thus, the mixture of **10** and **11**, generated from the asymmetric crotylation reaction, was reduced by $LiAlH_4$ and then treated with *S*-(+)-Mosher chloride (Scheme 4). The enantiomeric excess was then easily measured by proton NMR (Table 1).

The relative configuration of each crotylation product was established by NMR analysis in a two-step process. Primarily, the mixture of esters **8** and **9** was saponified (NaOH aq/EtOH) and the resulting α-ketoacids were converted into their corresponding diastereomeric iodolactones **14** and **15** (I_2/acetonitrile). NOE experiments

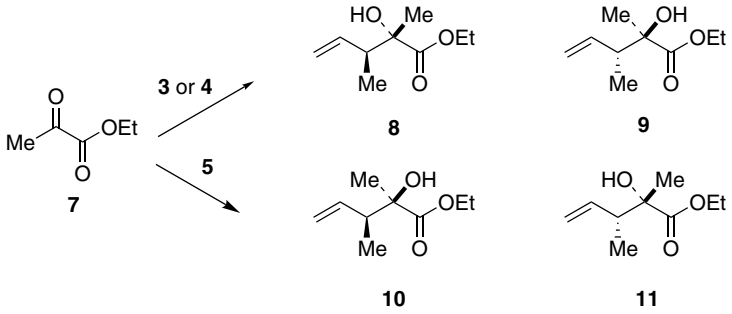
Table 1. Reaction of chiral boronates with ethyl pyruvate

Entry	Chiral borate/solvent	Product **8**:**9**[a]/% ee	Product **10**:**11**[b]/% ee	Yield/%
1	**3**/toluene	53:47/6	NA	86
2	**4**/toluene	7:1/73	NA	84
3	**4**/THF	3.2:1/53	NA	82
4	**4**/Et_2O	5:1/62	NA	80
5	**4**/CH_2Cl_2	2:1/33	NA	83
6	**5**/toluene	NA	5.4:1/69	87

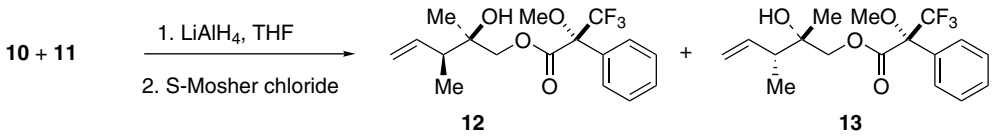
[a] Determined by chiral GC.
[b] Determined by the Mosher's ester method outlined in Scheme 4.



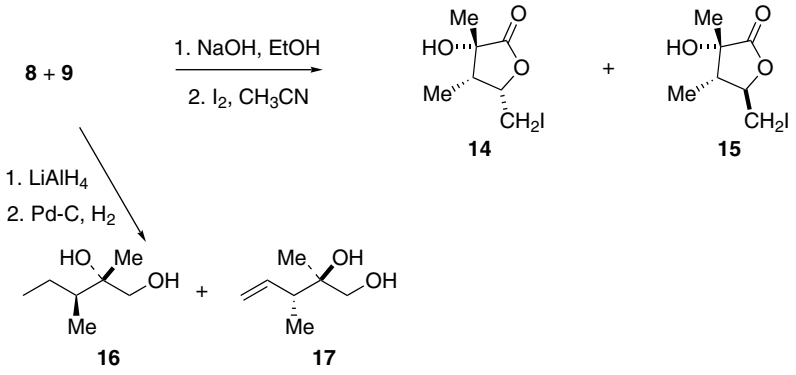
Scheme 2. Preparation of homochiral boronic acid esters **3**–**6**.



Scheme 3. Crotylation of ethyl pyruvate **7** with chiral borates **3**–**5**.



Scheme 4. Mosher's esters **12** and **13** were formed to elucidate the enantiomeric excess of **10** and **11**.



Scheme 5. Determination of relative and absolute stereochemistry of the α-hydroxy acids **8** and **9** formed in the asymmetric crotylation reaction.

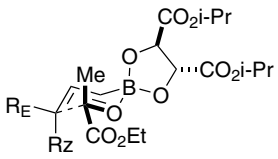


Figure 1. Hypothesized transition-state for crotylation of **7** by crotylboronate ester **4**.

revealed that the methyl groups are *anti* with respect to the faces of the five-membered lactone ring, as shown in compound **14** and **15** (Scheme 4). To elucidate the absolute configuration of the enantiomers, esters **8** and **9** were reduced by $LiALH_4$ to afford the corresponding 1,2-diols, which were hydrogenated to yield **16** and **17** as a mixture of diols. Comparison of the optical rotation of this mixture with the known optical rotation of compound **16**,[12] revealed that the major enantiomer formed during this asymmetric crotylation reaction with **4** corresponds to the (*S*,*S*)-absolute stereochemistry (Scheme 5).

In conclusion, we have established that chiral boronates can react with ethyl pyruvate to yield crotylation products in a diastereospecific manner. By far the best enantioselectivity (up to 73% ee) was achieved with chiral diisopropyl tartrate-derived boronates. Thus, by starting with (*E*) or (*Z*)-butene and D or L-diisopropyl tartrate, the four possible crotylation products with two contiguous stereogenic centers can be generated. The major enantiomer formed in this asymmetric crotylation is consistent with the transition-state model shown (Fig. 1).

1. General procedure

A solution of crotylboronate (1.3 mmol) in dry toluene (3 mL) under argon was treated with powdered 4 Å molecular sieves (60 mg) and then cooled to −78 °C. A solution of ethyl pyruvate (0.11 mL,1 mmol) in dry toluene (1 mL) was then added dropwise over 30 min. The reaction mixture was stirred for 6 h at −78 °C and then allowed to warmed to room temperature. The crude material was purified by silica gel chromatography (10–20% diethyl ether in hexanes) to give the crotylation product in analytically pure form.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.09.082.

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9. Spectral data for compound **8**+**9**: ^{1}H NMR 500 MHz (δ, ppm, $CDCl_3$): 5.71–5.78 (m, 1H), 4.98–5.03 (m, 2H), 4.17–4.22 (m, 2H), 2.43–2.49 (m, 1H), 1.36 (s, 3H), 1.26–1.29 (t, J = 7.0 Hz, 3H), 1.05–1.06 (d, J = 6.9 Hz); ^{13}C NMR 125 MHz (δ, ppm, $CDCl_3$): 176.8, 139.2, 115.9, 61.7, 46.1, 23.5, 14.2, 13.5.
10. Chiral column: Cyclosil B 112–6632; length: 30 m, ID: 0.25 mm, film, 0.25 μm. t_R of Compound **8**: 32.66 min; t_R of compound **9**: 31.24.
11. Spectra data for compound **10**+**11**: ^{1}H NMR 500 MHz (δ, ppm, $CDCl_3$): 5.72–5.79 (m, 1H), 5.04–5.09 (m, 2H), 4.19–4.25 (m, 2H), 3.04 (br s, 1H), 2.40–2.46 (m, 1H), 1.32 (s, 3H), 1.27–1.29 (t, J = 7.0 Hz, 3H), 0.92–0.94 (d, J = 7.0 Hz); ^{13}C NMR 125 MHz (δ, ppm, $CDCl_3$): 176.9, 138.4, 116.6, 61.8, 46.2, 24.2, 15.1, 14.1.
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