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CHIRAL α-METHOXY-E-CROTYLBORONATES, REAGENTS FOR STEREOSELECTIVE C-C-BOND FORMATION UNDER REAGENT CONTROL OF DIASTEREOSELECTIVITY

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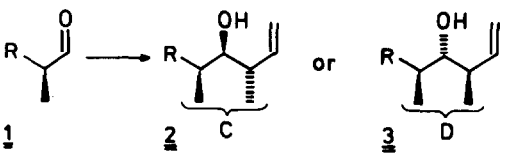
Abstract: Treatment of the previously described α-chloro-E-crotylboronate with lithium-methoxide in THF furnished the title compound 6 of 88 - 94 % e.e. On addition to achiral aldehydes complete transfer of chirality was realized, resulting in the β-methyl-homoallyl alcohols 7 with a Z-configuration of the enol-ether double bond. On reaction of 6 with chiral aldehydes excellent (matched pair) to good (mismatched pair) selectivities in favor of the stereotriades C or D respectively were realized.

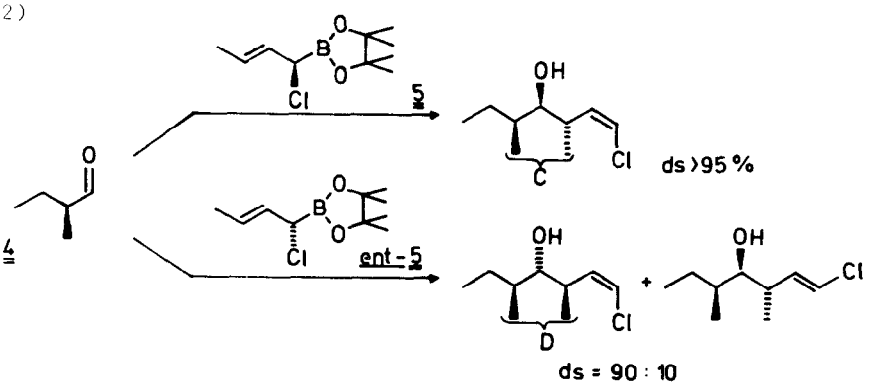
The elaboration of an α-methyl-branched chiral aldehyde 1 to give selectively either homoallyl alcohol 2 or 3 corresponding to the stereotriades C or D [1] constitutes a potentially important step in the synthesis of polyketide derived natural products.

Scheme (1)



Of the two stereoisomers, one (the Cram product 2) will be favored by the asymmetric induction caused by the chirality of 1. Selectivity in favor of this product can be enhanced by applying the principle of double stereodifferentiation using chiral reagents (matched pair [2]). The generation of the other stereoisomer 3 in this reaction is possible only by making recourse to reagent control of diastereoselectivity [2]. This requires chiral reagents which themselves have such a high level of asymmetric induction that they can override the asymmetric induction originating from the chirality of the aldehyde. The feasibility of this strategy [3] has been demonstrated in the reaction of the aldehyde 4 with both enantiomers of the α-chloro-E-crotylboronate 5 [4].

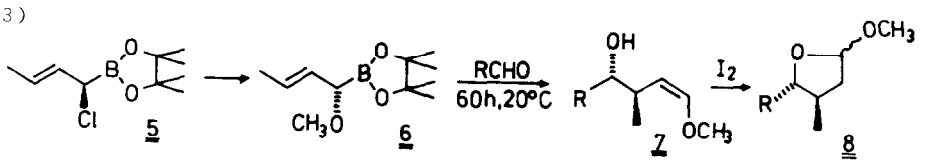
Scheme (2)



Yet the asymmetric induction of this reagent of ca. 97 : 3 (corresponding to $\Delta\Delta G^{\neq}$ = 2 kcal of the competing transition states) is not enough to effectively override the asymmetric induction of such chiral aldehydes which exert a Cram/anti-Cram selectivity of ≥ 90 : 10. Having encountered such a case in an ongoing synthetic project requiring the generation of the stereotriade D by reagent control of diastereoselectivity we set out to develop other chiral α-substituted E-crotylboronates capable of higher asymmetric induction than 5.

Earlier investigations [5] on α-substituted allylboronates suggested that alkoxy-substituents could lead to a significant improvement. We therefore generated the α-methoxy-E-crotylboronates 6 by nucleophilic substitution of the chlorine atom in 5 with methoxide. Utilizing a suspension of lithium methoxide in THF we were able to obtain the α-methoxy-E-crotylboronates 6 in 80 - 90 % yield. The latter added cleanly to aldehydes generating the anti-methoxy-homoallyl alcohols 7 having a Z-configuration of the new double bond [5].

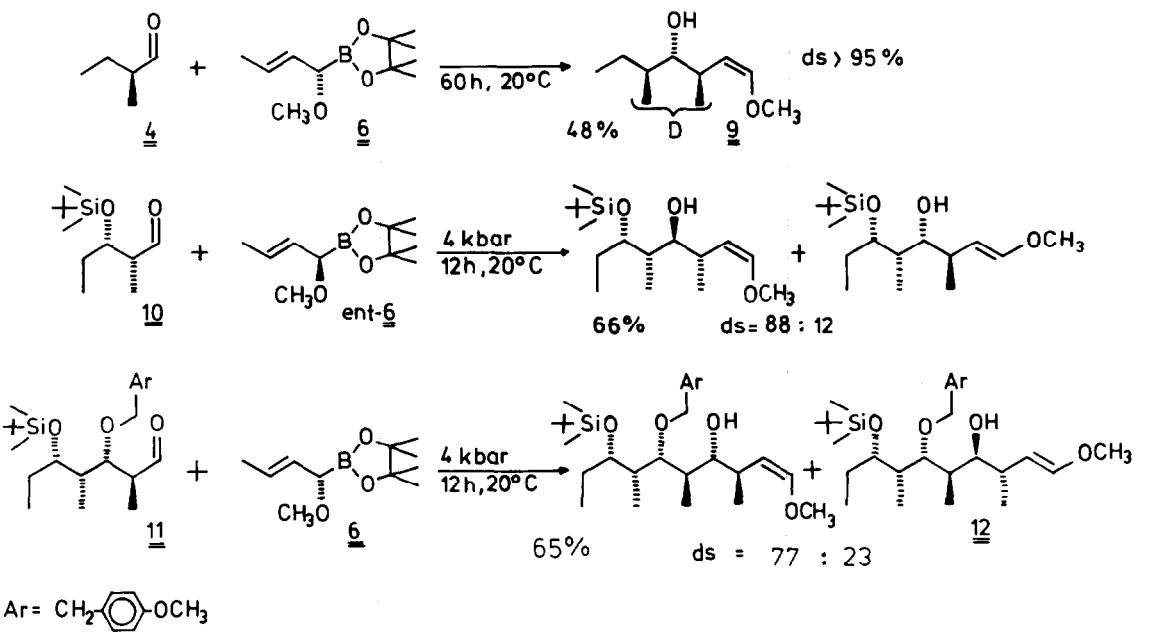
Scheme (3)



R = Me	64 %	ee:	94 %
= Et	81		90
= nHex	87		88
= iPr	82		90
= Ph	65		90

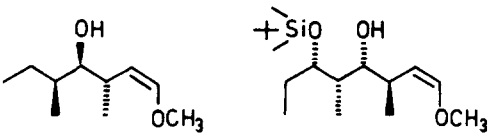
The fact that no product with an E-double bond could be detected by ^{1}H- or ^{13}C-NMR spectroscopy testifies an asymmetric induction by 6 of >95 : <5. The enantiomeric purity of the homoallyl alcohols 7 was determined by derivatisation with S-(-)-1-phenyl-ethyl isocyanate and GC-analysis on a capillary column. This revealed that in the conversion of 5 to 7 via 6 some racemisation had occured. This probably happened during the substitution step, since the chloride liberated can racemise the substrate 5 via a S_N2-displacement [6]. Fortunately the extent of the racemisation remained so small that it was no obstacle in evaluating the ability of the new reagent 6 to control the diastereoselectivity on addition to chiral aldehydes. The following transformations were realized, and constitute each a mismatched pair.

Scheme (4)



Since the starting materials, the α-methoxy-crotylboronates were not enantiomerically pure (containing 4 - 6 % of the respective enantiomer) the products likewise were contaminated by a small amount of another stereoisomer being the product of a matched pair e.g. 13 and 14. These stereoisomers have been prepared for comparison in a diastereoselectivity of >> 95 % by reaction of the aldehyde 4 with ent-6 and the aldehyde 10 with 6.

Scheme (5)



13 **14**

In all the examples of scheme (4) the diastereoselectivity under reagent control was substantially higher than that achieved with the α-chloro-E-crotylboronates 5. Notably, the yields turned out to be lower. This is a consequence of the fact that a reaction under reagent control of diastereoselectivity (mismatched pair) has to pass over a transition state, which is higher in energy than that of a matched pair. The stronger the asymmetric induction from the aldehyde, that has to be overcome, the slower becomes the reaction. In order to offset this drawback two of the reactions were carried out under 4 kbar pressure. It is likely that even then more extended reaction times, than the ones used, could give somewhat higher yields. However, the compulsory slowness of the desired reaction favors all kinds of side reaction eventually decreasing the yield of the main product.

The resulting homoallyl alcohols 7 are quite sensitive towards traces of acids which cause cyclisation to the lactol ethers 8. This process could be effected cleanly by treating the enol ethers 7 with a crystal of iodine, the cyclisation being presumably triggered by traces of HI.

All in all, we have developed a route to both enantiomers of the α-methoxy-E-crotylboronates 6. These reagents exert a higher asymmetric induction on addition to aldehydes than their chloro-precursors 5. The superior control of diastereoselectivity by the reagent 6 has hence been utilized to effectively generate the stereotriade D on addition to representative α-methyl-branched aldehydes.

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References

1) R.W. Hoffmann, Angew. Chem. 99, 503 (1987); Angew. Chem., Int. Ed. Engl. 26, 489 (1987).
2) S. Masamune, W. Choy, J.S. Petersen and L.R. Sita, Angew. Chem. 97, 1 (1985); Angew. Chem., Int. Ed. Engl. 24, 1 (1985).
3) cf. also: R.P. Short and S. Masamune, Tetrahedron Lett. 28, 2841 (1987); W.R. Roush and R. Halterman, J.Am.Chem.Soc. 108, 294 (1986); W.R. Roush, M.A. Adam, A.E. Walts and D.J. Harris, ibid 108, 3422 (1986); W.R. Roush and A.D. Palkowitz, ibid 109, 953 (1987); W.R. Roush, A.D. Palkowitz and M.A.J. Palmer, J.Org.Chem. 52, 317 (1987); H.C. Brown and K.S. Bhat, J.Am.Chem.Soc. 108, 5919 (1986).
4) R.W. Hoffmann and S. Dresely, Angew. Chem. 98, 186 (1986); Angew. Chem., Int. Ed. Engl. 25, 189 (1986).
5) P.G.M. Wuts and S.S. Bigelow, J.Org.Chem. 47, 2498 (1982); E. Moret and M. Schlosser, Tetrahedron Lett. 25, 4491 (1984); R.W. Hoffmann and B. Landmann, Chem. Ber. 119, 1039 (1986).
6) D.S. Matteson and E. Erdik, Organometallics 2, 1083 (1983).

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