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Stereocontrol in allylboration reactions

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Abstract: Crotyl-boronates add to aldehydes with high simple diastereoselection, such that E-crotyl-boronates give anti-homoallyl alcohols, and Z-crotyl-boronates their syn-counterparts. This reaction has been extended to stereoselective ring closure reactions by intramolecular allylboration. Moreover, by using suitably substituted crotyl boronates homoallyl alcohols having quarternary stereogenic carbon centers have been obtained with good diastereoselection. The development of chiral crotyl boronate reagents, having an additional stereogenic center α to the boron atom, allowed reactions with aldehydes to be accomplished with full transfer of chirality; i.e. control of the absolute configuration of the products.

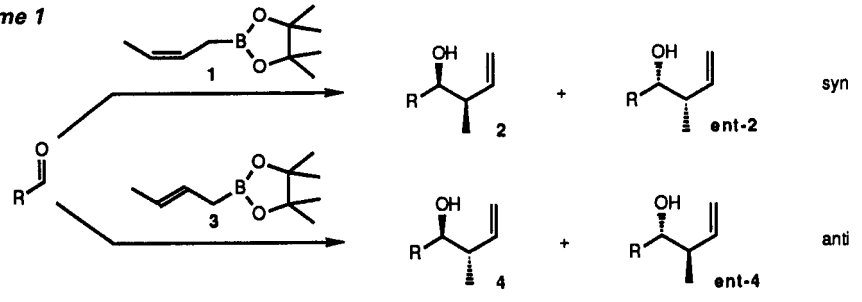
INTRODUCTION

The ideal synthesis for complicated molecules would be one, in which all stereogenic centers and all functionality are generated directly in the C-C-bond forming reactions, which create the molecular skeleton (ref. 1). Hence, a lot of effort has been devoted to reactions, in which two prochiral carbon atoms are joined to form two new stereogenic centers. Typical examples are the Diels-Alder-addition, the Claisen- or Cope-rearrangement and the aldol-addition, reactions which provide excellent control of relative and nowadays also of absolute configuration of the stereocenters formed.

CONTROL OF RELATIVE CONFIGURATION

We have been concerned with another C-C-bond forming reaction, the addition of crotyl metal compounds - in particular that of crotyl-boronates **1**, **3** - to aldehydes. This reaction could claim similar importance if both the relative configuration (syn/anti) and the absolute configuration of the newly formed stereocenters in the alcohols **2** and **4** can be controlled.

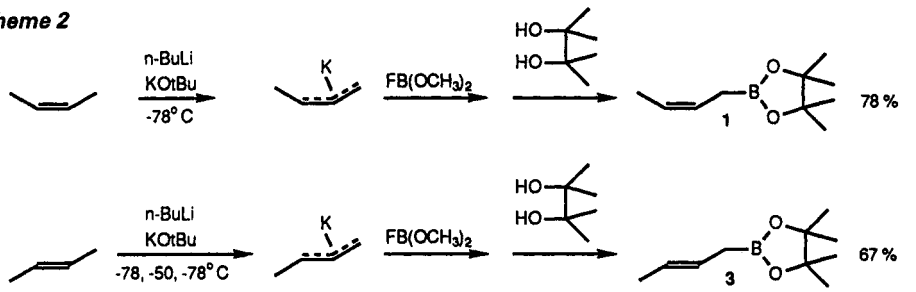
Scheme 1



We found that the geometry of the double bond in the crotylboronate **1** or **3** is cleanly (ds >95%) translated into the relative configuration of the resulting homoallyl alcohols such that the Z-crotyl-boronate **1** leads to the syn-alcohol **2**, and that the E-crotylboronate **3** generates the anti-homoallyl alcohol **4** (ref. 2). The reagents **1** and **3** are prepared from Z- and E-butene respectively, utilizing the stereoselective generation of Z- and E-crotyl-

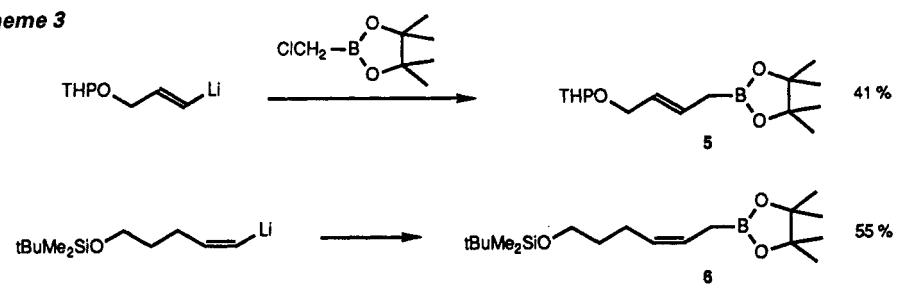
potassium discovered by Schlosser (ref. 3). The reaction conditions were optimized by Roush (ref. 4) and Brown (ref. 5), such that the crotyl-boronates **1**, **3** can now be made routinely. Nevertheless the reaction does not lend itself easily to scale up, nor is it applicable in general for the generation of substituted derivatives of **1** or **3**.

Scheme 2



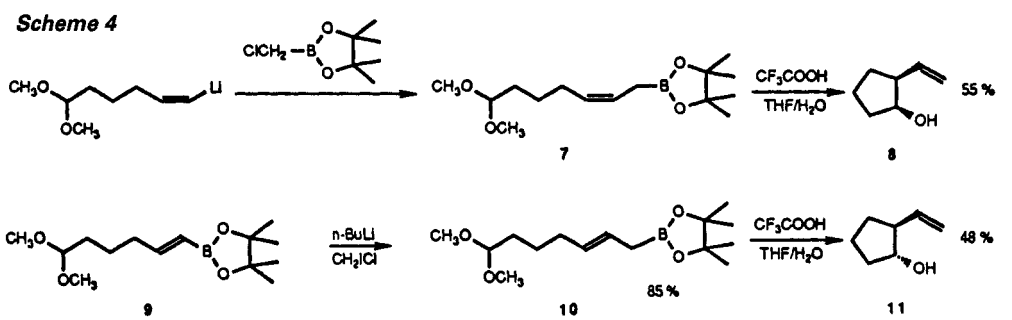
Substituted crotyl-boronates such as **5** or **6** can be obtained in stereo-defined form from vinyllithium-reagents by homologation (ref. 6 & 7) using a procedure originally introduced by Matteson (ref. 8).

Scheme 3



The allyl-boronates **5** and **6** added likewise to aldehydes with high simple diastereoselection. We used this sequence as a starting point to test the diastereoselectivity of intramolecular allyl-boronate/aldehyde-additions (ref. 9). Thus, selective hydrolysis of the acetal function in **7** initiated the cyclisation to the vinylcyclopentanol **8**, which was obtained as a single cis-diastereomer.

Scheme 4

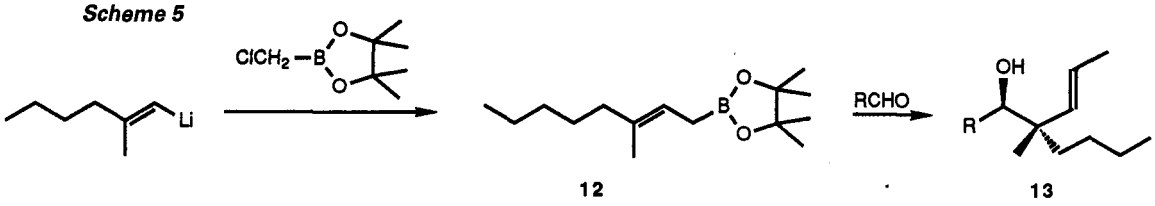


The isomeric E-allyl-boronate **10** was obtained by homologation of the vinylboronate **9**. This time, cyclization led exclusively to the trans-isomer **11** of the vinylcyclopentanol.

As another extension of the crotyl-boronate/aldehyde-addition we investigated (ref. 10) the generation of quarternary carbon stereogenic centers. Again the requisite crotyl-boronates were prepared by homologation of stereodefined vinyllithium reagents.

Thus, the E-isomer of the heptenyl-boronates **12** led with good diastereoselectivity to the anti-homoallyl alcohol **13**. The isomeric Z-heptenyl-boronate **14** led predominantely to the syn-homoallyl alcohols **15**. The

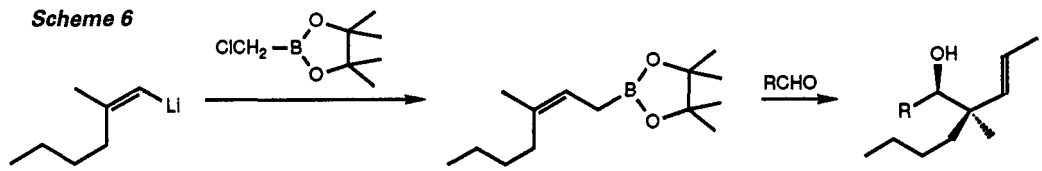
Scheme 5



12 **13**

R	=	CH_3-	83 %	ds	=	95 %
	=	CH_3-CH_2-	70 %		=	95 %
	=	CH_3-CH_2-CH_2-	76 %		=	96 %
	=	$(CH_3)_2$-CH-	81 %		=	99 %
	=	C_6H_5-	71 %		=	99 %

Scheme 6



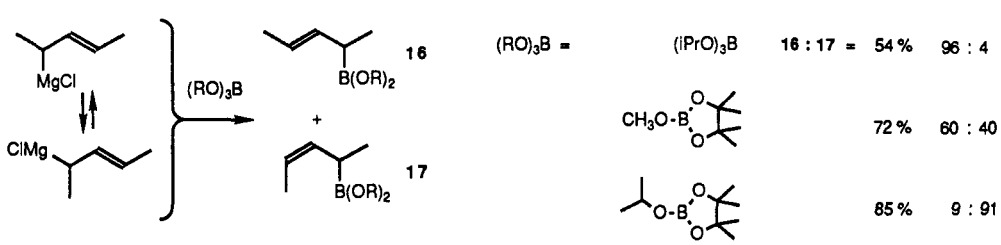
14 **15**

R	=	CH_3-	83 %	ds	=	88 %
	=	CH_3-CH_2-	62 %		=	90 %
	=	CH_3-CH_2-CH_2-	79 %		=	90 %
	=	$(CH_3)_2$-CH-	87 %		=	92 %
	=	C_6H_5-	69 %		=	93 %

sterically demanding Z-substituent in the allylboronate caused a decreased simple diastereoselection, as has been noted before (ref. 7 & 11). This effect was most pronounced on additon to small unhindered aldehydes.

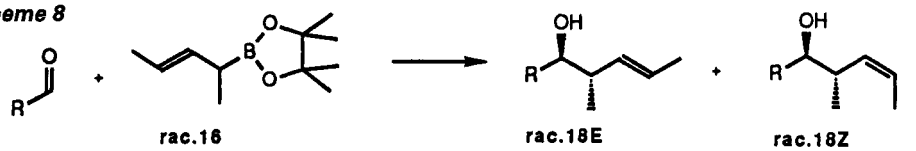
Coming back to the simple E- and Z-crotyl-boronates **1** and **3**: In order to obtain them on a larger scale it would be desireable to generate them in a simple operation, e.g. from crotyl-Grignard reagents. Our attempts to borylate crotyl-Grignard reagents with various borate esters gave at best E/Z-selectivities in the range of 8:2. However, we discovered that attractive E/Z-selectivities could be reached when borylating the related pentenyl-Grignard reagents:

Scheme 7



Thus, depending on the borate ester, one could direct the reaction to either the E- or the Z-pentenyl-boronate **16** or **17**. Each of these reagents added to aldehydes with high simple diastereoselectivity. For instance, **16** led to the anti-homoallyl alcohols **18**. The fact, that **18** comprises an E/Z-mixture is of no consequence, if the double bond is to be hydrogenated or to be cleaved later on.

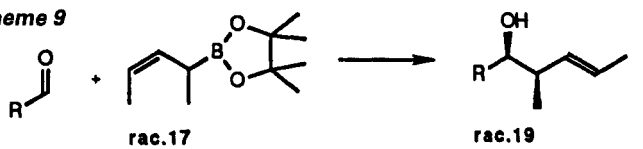
Scheme 8



R =			
	CH_3-CH_2	81 %	35:65
	$(CH_3)_2$-CH	90 %	25:75
	CH_3-CH=CH-CH_2	90 %	23:77
	C_6H_5	92 %	20:80

The Z-pentenyl-boronate **17** gave rise solely to the syn-homoallyl alcohol **19** having an E-double bond.

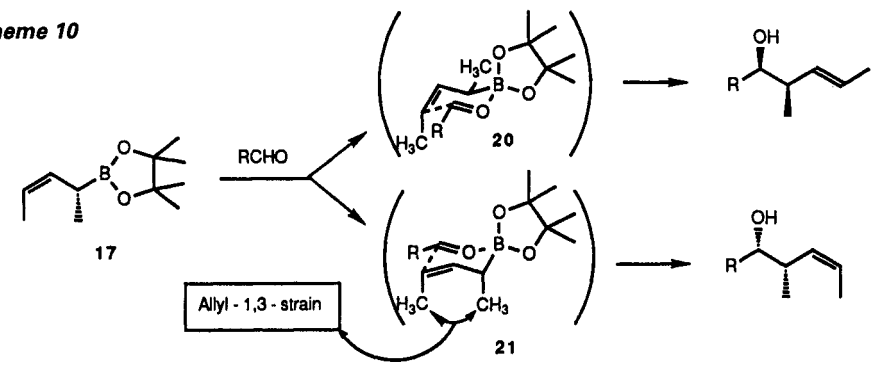
Scheme 9



R =		
	CH_3-CH_2	92 %
	$(CH_3)_2$-CH	90 %
	CH_3-CH=CH-CH_2	90 %
	C_6H_5	95 %

This points out that the the reaction is proceeding via a single transition state **20**, in which the methyl group α to the boron occupies an equatorial position. The corresponding transition state **21** with an axial methyl group is not utilized due to destabilizing allyl-1,3-strain (ref. 12). This demonstrates that the reaction could proceed under complete transfer of chirality, if the boronate **17** were optically pure. This would open a way to control the absolute configuration of the stereocenters formed.

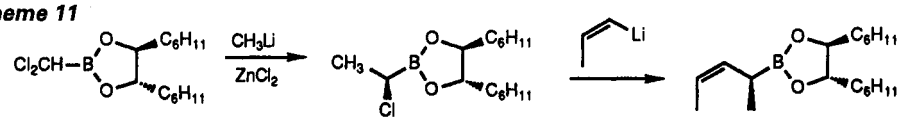
Scheme 10



CONTROL OF ABSOLUTE CONFIGURATION

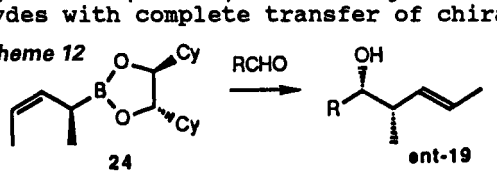
In order to obtain the reagent **17** enantiomerically pure we utilized a reaction sequence introduced by Matteson (ref. 13) for the generation of α-substituted alkylboronates. In our case we used dicyclohexyl-ethanediol as a chiral auxiliary, which is available in both antipodal forms.

Scheme 11



In the reaction of the dichloromethane-boronate **22** with methyllithium a new and decisive stereocenter is created by asymmetric induction from the chiral auxiliary. High (>99%) asymmetric induction is realized if the displacement of one of the diastereotopic chlorine atoms is effected in the presence of $ZnCl_2$. The subsequent conversion of the α-chloroethyl-boronate **23** into **24** is a substitution following a well established inversion of configuration (ref. 8). The reagent **24** or its enantiomer added cleanly to aldehydes with complete transfer of chirality (ref. 14).

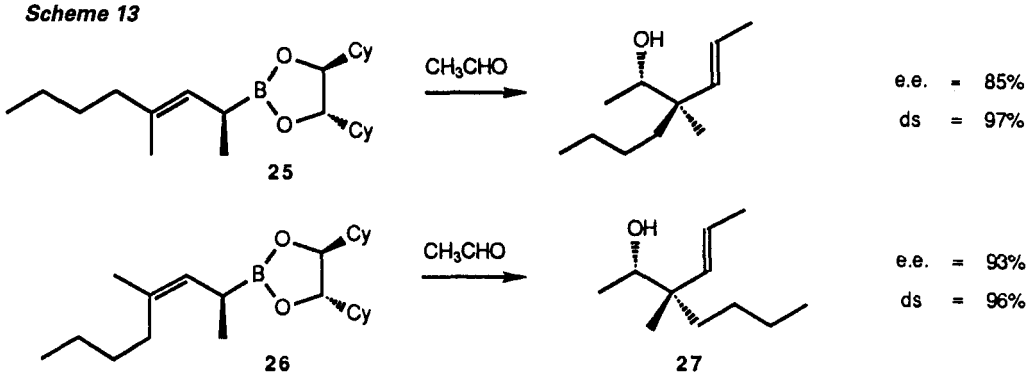
Scheme 12



R =			
	C_6H_5-	71 %	99.5 % e.e.
	= CH_2=C(CH_3)-	74 %	98.5 % e.e.

Similarly, the chiral α-chloroethyl-boronates **23** could be reacted with the vinyllithium compounds already mentioned in schemes 5 and 6. This opened an access to the chiral reagents **25** and **26**, which allowed the generation of quarternary carbon centers, e.g. in the homoallyl alcohols **27** with good levels of asymmetric induction (ref. 10).

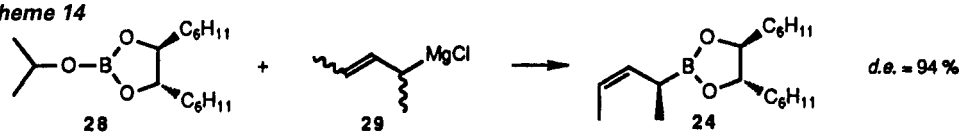
Scheme 13



While the enantioselectivities still have to be improved, the diastereoselectivity in the reaction of the Z-octenyl-boronate **26** with acetaldehyde is noticeably higher than in the reaction of the Z-heptenyl derivative **14**. This is a consequence of the extra methyl group α to the boron atom in **26**, because the pinacol boronate corresponding to **26** showed likewise a diastereoselectivity of 96% on addition to acetaldehyde (ref. 10).

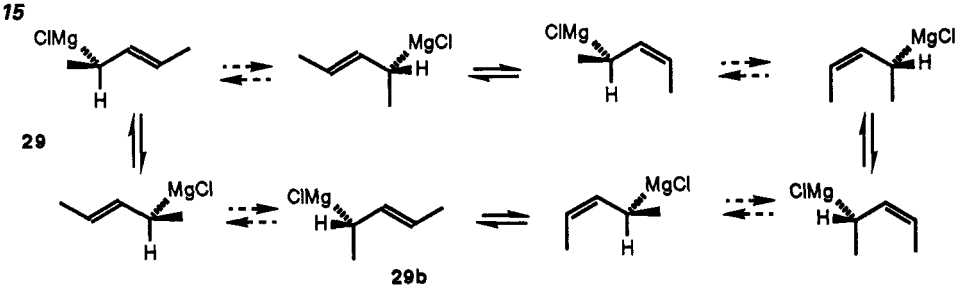
The reagents **24**, **25**, and **26** combine high simple diastereoselection with good to excellent enantioselectivity. However, their preparation is still somewhat circumstantial at present. The more it is gratifying that a truely short access to **24** has been opened (ref. 15): Reaction of the chiral borate ester **28** with the pentenyl-Grignard reagent **29** resulted in **24** with an asymmetric induction of 94% d.e..

Scheme 14



The reaction is remarkable, since the Grignard reagent **29** undergoes fast metallotropic migrations of the MgCl-group. Thus, the Grignard reagent is a rapidly equilibrating mixture of enantiomeric, metallotropic and rotameric forms:

Scheme 15



The chiral borate ester **28** reacted selectively with the form **29b** of the Grignard reagent, eventually converting it all into **24** via a kinetic resolution combined with a rapid enantiomer equilibration of **29**. This way the important reagent **24** can now be obtained in acceptable enantiomeric purity and in good yield on a large scale.

CONCLUSION

The chemistry of crotyl-boronates and in particular of E- and Z-pentenyl boronates **16** and **17** has been developed to allow access to both anti- or syn-homoallyl alcohols **18** and **19**. The chiral reagent **24** is the key to obtaining the homoallyl alcohol **19** in enantiomerically pure form.

Acknowledgement

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