α-Chiral allylboronates: reagents for asymmetric synthesis

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Abstract - Allylboronates as well as crotylboronates add to
aldehydes forming homoallyl alcohols. On addition of chiral
α-heterosubstituted allyl(crotyl)boronates to aldehydes the
chirality is transfered to the new stereocenter of the homo-
allyl alcohol. The asymmetric induction that can be effected
with α-chloro-E-crotylboronates is in the order of 20 - 30 : 1.
α-Methoxy-E-crotylboronates as well as α-methyl-Z-crotyl-
boronates turned out to be even more effective.

INTRODUCTION

Among the carbon-carbon-bond forming reactions, the addition of organometallic
reagents to aldehydes and ketones occupies a prominent position. To this
class of reactions belongs the addition of allylboronates to aldehydes
(ref. 1), a reaction that stands out by its high degree of chemoselectivity,
since ketones, esters, amides, epoxides, nitriles, are not touched under the
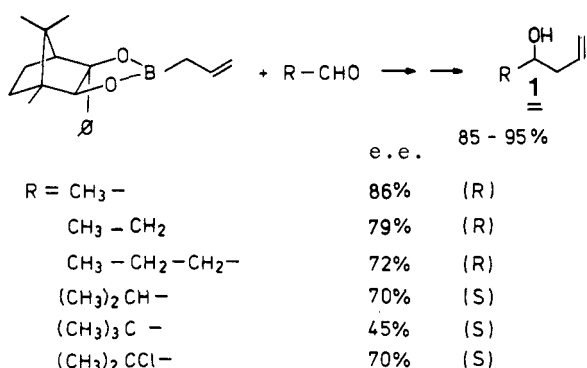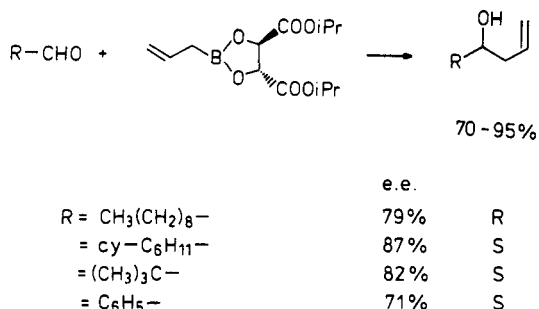usual reaction conditions.

Scheme 1
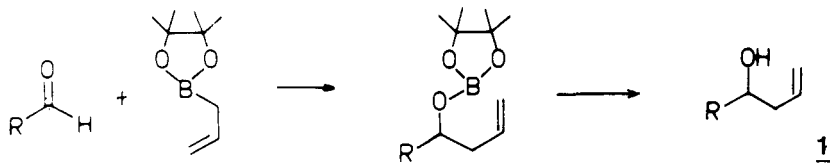
Another desireable factor for a reaction generating new stereogenic centers
is stereoselectivity. Assuming that the addition of the allylboronate to an
aldehyde proceeds via a cyclic sixmembered transition state we reasoned that
the decreased Lewis-acidity of the boron in the allylboronates would corres-
pond to a transition state late on the reaction coordinate and that the
short boron oxygen bond involved should render these transition states
quite compact, amenable to a high degree of stereocontrol. A chirally modi-
fied allylboronate should differentiate the two enantiotopic faces of the
aldehyde and allow an enantioselective formation of the homoallyl alcohols 1.
An obvious point for attachment of the chiral information is the glycol
component of the boronate. Earlier studies (ref. 2) using a camphor derived
chiral glycol were quite encouraging: Scheme (2).

More recently, significant improvements have been realized by others (ref. 3)
using tartrate derived chiral auxiliaries: Scheme (3).

Scheme 2

R =	e.e.	
CH₃ –	86%	(R)
CH₃ – CH₂	79%	(R)
CH₃ – CH₂ –CH₂–	72%	(R)
(CH₃)₂ CH –	70%	(S)
(CH₃)₃ C –	45%	(S)
(CH₃)₂ CCl–	70%	(S)

Scheme 3

| R =	e.e.	
CH₃(CH₂)₈–	79%	R
cy–C₆H₁₁–	87%	S
(CH₃)₃C–	82%	S
C₆H₅–	71%	S

W.R.Roush, J.A.C.S 1985

α-SUBSTITUTED ALLYL BORONATES

However, we felt that an intrinsically better approach to stereocontrol would be to place the element of chirality right onto the core of the transition state (ref. 4), i.e. we became interested in α-chiral allylboronates **2**. These could on reaction with aldehydes transfer their chirality to the newly formed stereogenic center. There are two competing diastereomeric transition states for this process, the energy difference of which determines the level of the asymmetric induction. These transition states differ by the equatorial versus axial arrangement of the group X. There is the useful corrolary that the transition state with an equatorial X leads to the homoallyl alcohol **4** with an E-double bond, whereas the transition state with an axial X leads to **3** with a Z-double bond. Hence, the level of asymmetric induction can already be assessed in the racemic series simply by evaluating the E/Z-ratio of the product homoallyl alcohol: Scheme (4).
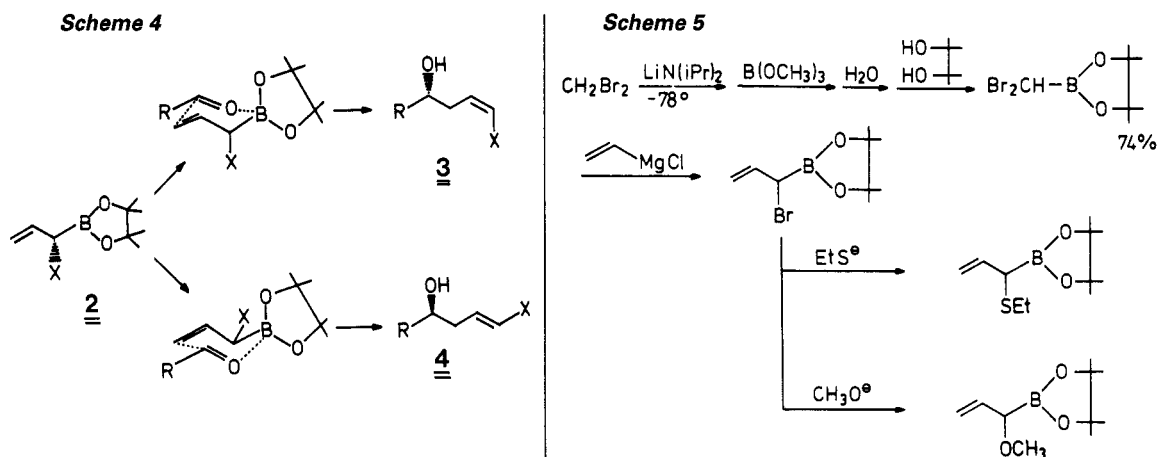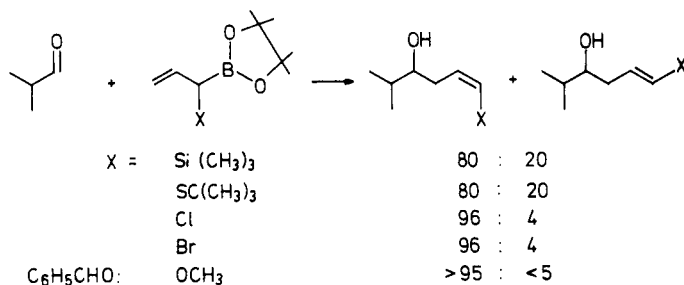
Scheme 4

Scheme 5

A variety of α-hetero-substituted allylboronates were prepared as shown in Scheme (5).

Surprisingly, the addition of the α-bromoallylboronate to aldehydes showed a high preference for the formation of the homoallyl alcohol with a Z-double bond (ref. 5): Scheme (6).
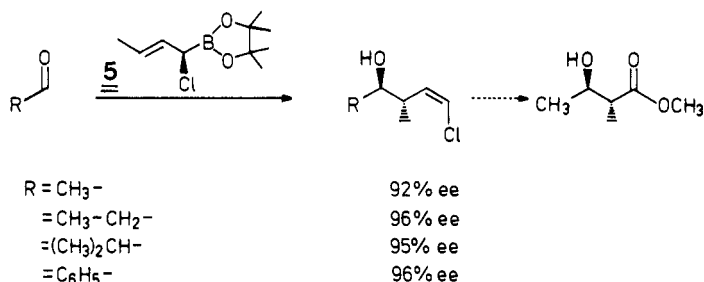
Scheme 6
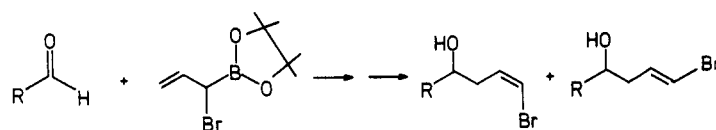
R = CH₃	78%	93 : 7
= CH₃-CH₂	82%	94 : 6
=(CH₃)₂CH	83%	96 : 6
= C₆H₅	80%	97 : 3

Since the E/Z-ratio in the product homoallyl alcohols is equal to the asymmetric induction that would originate from a chiral α-substituted allylboronate, the selectivities recorded in scheme (7) demonstrate that high levels of chirality transfer can be realized using α-chiral allylboronates.

Scheme 7


X =	Si (CH₃)₃	80 : 20
	SC(CH₃)₃	80 : 20
	Cl	96 : 4
	Br	96 : 4
C₆H₅CHO:	OCH₃	>95 : <5

Investigations of other α-hetero-substituted allylboronates showed that in-
creasing polarity of the α-C-X-bond leads to a higher proportion of the pro-
duct being formed via the transition state in wich the X-group occupies an
axial position (ref. 5). An explanation of this fact has to take into account
that complexation of the boron at the carbonyl group of the aldehyde probably
constitutes a rapid preequilibrium, while formation of the C-C-bond is
assumed to be rate determing. This step then amounts to an attack of a weak
electrophile - the δ(+)-carbonyl group - on a π-bond. The spatial disposition
of the C-X-bond with respect to the π-bond determines the energy and coeffici-
ents of the π-orbital (ref. 6). Thus, the most reactive conformation will be
the one in which there is no π-σ*delocalisation, i.e. an axially disposed
C-X-bond, having a dihedral angle between the π-orbital and the σ*-orbital of
ca: 90 °: Scheme (8).

Scheme 8

orthogonal   coplanar

π → σ* Interactions in
Allylsystems

Scheme 9

α-CHIRAL E-CROTYLBORONATES

Of considerable importance for the synthesis of polyketide derived natural
products is the addition of crotylmetallic species to aldehydes (ref. 7).
That of E-crotylboronates proceeds with high simple diastereoselection in
favour of the anti-diastereomer (ref. 8): Scheme (9).

A major aim of our studies was to develop a chiral variant of this reaction.
Ultimately this should allow the assembly of the molecular skeleton of such
natural products under reagent control of diastereoselectivity (ref. 9). In
order to test the viability of this approach a few representative racemic
α-substituted E-crotylboronates were prepared in analogy to scheme (5). On
addition to prochiral aldehydes the direction (forming a Z-double bond) and
the extent of asymmetric induction was fortunately similar to those obtained
with the α-substituted allylboronates: Scheme (10).

Scheme 10

X = CH$_3$	R = Pr	28	:	72	
X = Si(CH$_3$)$_3$	R = Ph	13	:	87	(D.S.Matteson)
X = Cl	R = Ph,Pr	3	:	97	(ref. 10)

Now the stage was set for turning to the optically active α-substituted
crotyl-boronates. The following route was developed as entry into the chloro-
substituted series (ref. 11): Scheme (11).

Scheme 11

95% e.e.   85%   90%   **5**

On reaction of 5 of ca. 95 % e.e. with prochiral aldehydes transfer of
chirality proceeded to our full satisfaction. The relative and the absolute
configuration of the adduct to acetaldehyde has been proven by conversion
into the known methyl α-methyl-β-hydroxy-butyrate: Scheme (12).

Scheme 12

R = CH$_3$-   92% ee
  = CH$_3$-CH$_2$-   96% ee
  = (CH$_3$)$_2$CH-   95% ee
  = C$_6$H$_5$-   96% ee

At first glance the fact that the products contain a vinyl chloride
functionality could be considered as a disadvantage in view of the low re-
activity of this function. On the other hand, as these vinyl chlorides have
a stereohomogenous Z-double bond, there was the challenge to take advantage
of just this particular situation. In consequence, we devised some re-
functionalisation schemes in which the vinyl chloride function is the
starting point for the generation of highly substituted dihydropyran and
tetrahydrofuran rings, c.f. schemes (13) and (14). As a bonus, the creation
of the additional stereogenic centers proceeded under high asymmetric
induction as well.

Scheme 13
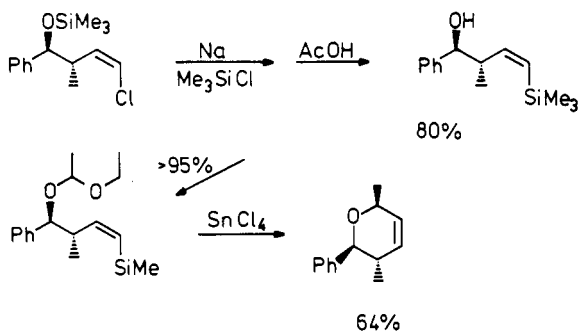
Scheme 14
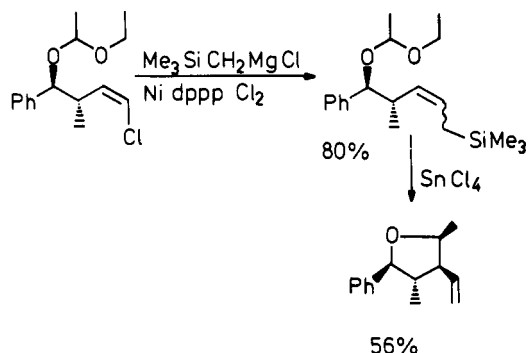
Now let us focus again on th main theme, the reaction of the crotylboronates
with chiral aldehydes. On addition to the aldehyde 6 either triade of stereo-
centers (ref. 12) could be formed with a good level of selectivity. Of course,
high selectivity in the matched pair (ref. 9), in which the asymmetric
induction of the substrate and the reagent cooperate is not difficult to
obtain: Scheme (15).
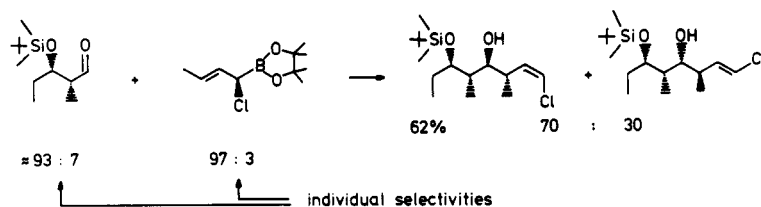
Scheme 15

ds 98%

ds 90%
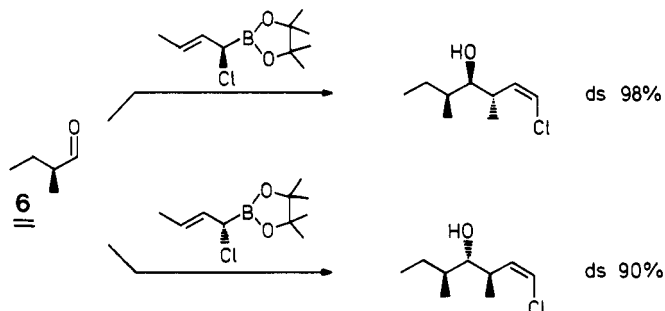
Reagent control of diastereoselectivity in the mismatched pair requires that
the asymmetric induction from the reagent is high enough to override the
asymmetric induction from the substrate aldehyde. An inspection of the $\Delta\Delta G^{\#}$
values involved shows, where the weak points are: Scheme (16).

Scheme 16
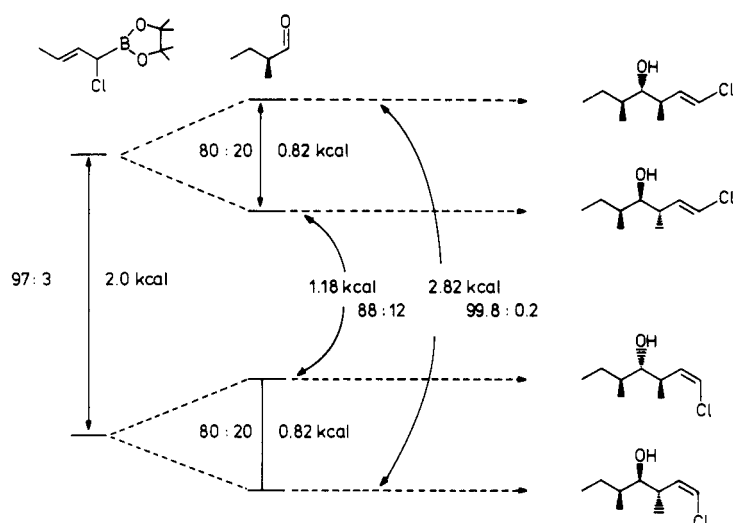
An asymmetric induction of our reagent of 97 : 3 corresponds to only a $\Delta\Delta G^{\#}$ of 2.0 kcal. This becomes insufficient if a strong asymmetric induction of a chiral aldehyde is to be overcome. The following example is indicative of such a situation: Scheme (17).
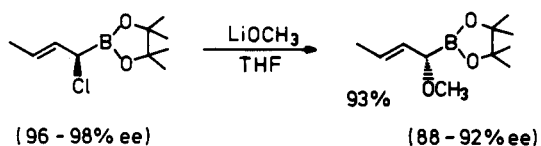
Scheme 17

And in another case the aldehyde remained the winner in the struggle for stereocontrol: Scheme (18).
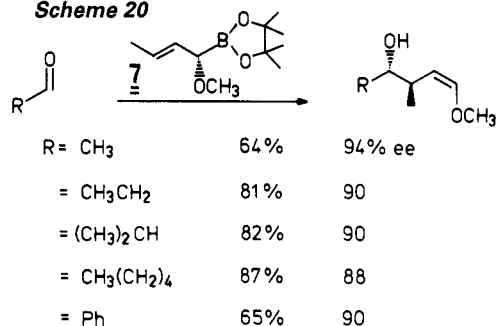
Scheme 18
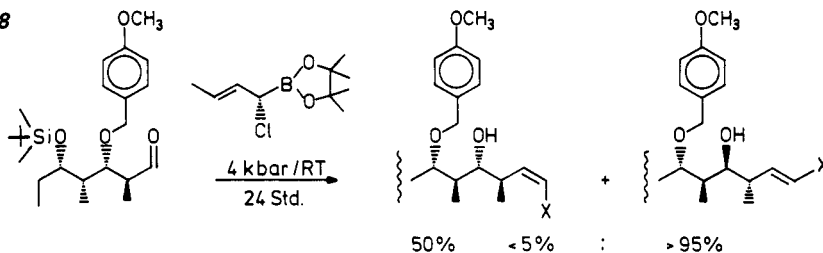
Thus, we were forced to develop other α-heterosubstituted E-crotylboronates with even higher asymmetric induction. In pursuit of this goal we succeeded to realize the following transformation: Scheme (19).

Scheme 19

Scheme 20

R =	CH₃	64%	94% ee
= CH₃CH₂		81%	90
= (CH₃)₂CH		82%	90
= CH₃(CH₂)₄		87%	88
= Ph		65%	90

However, this substitution was accompanied by a loss of 4 - 10 % e.e. by racemisation. Nevertheless we won a reagent which has an asymmetric induction of at least 95 % and hopefully higher. We conclude this from the NMR-spectra of the enol ethers obtained after addition of 7 to aldehydes, which show the presence of solely the Z-configurated product: Scheme (20).

Scheme 21

68%   88   :   12
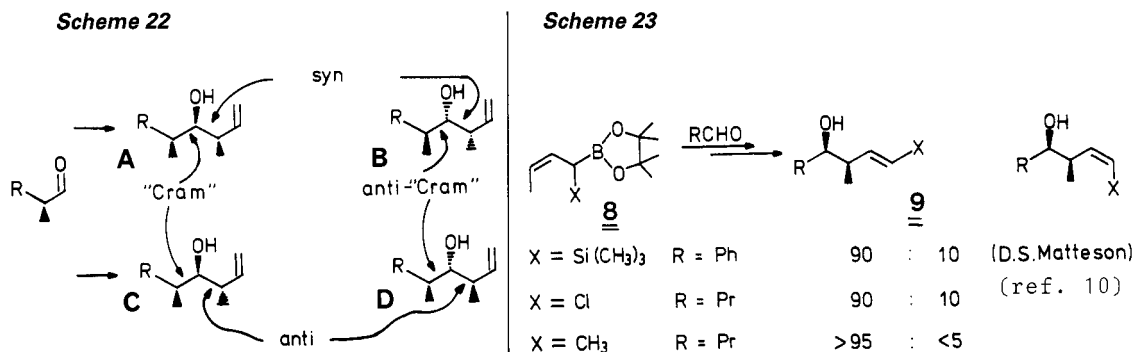

4 kbar/RT
24 Std.

40%   >95%   :   < 5%
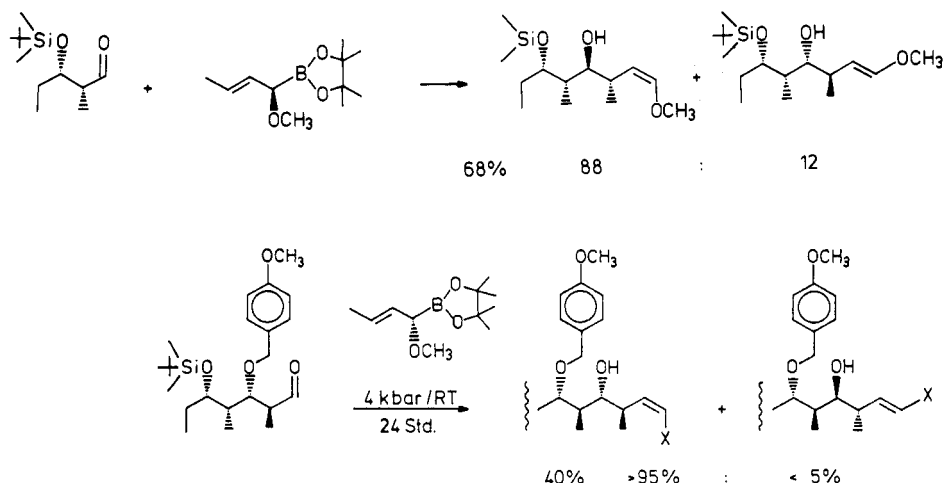
With the reagent 7 in hand we could finally attain a significantly higher
level of reagent control of diastereoselectivity on addition to the
refractory aldehydes studied before: Scheme (21).

One principal aspect of reagent control of diastereoselectivity should not be
overlooked: These reactions, in which the asymmetric induction of the sub-
strate aldehyde has to be overturned proceed more slowly than the reaction of
a matched pair. The reaction of a mismatched pair is forced to use a higher
energy transition state (cf. scheme (16)). This means that in order to get
decent conversions long reaction times or reactions under 4 kbar pressure
had to be applied. Moreover, all kinds of side reactions rear their ugly
heads. The more we feel satisfied with the selectivities that could be
realized in the mismatched cases.

Yet we ought to point out a potentially more economical and easier way:
Instead of fighting uphill using reagent control of diastereoselectivity
to form the product of a mismatched pair, e.g. stereotriade D in Scheme (22),
it could perhaps be easier to generate another stereotriade A, if this happens
to be the product of a matched pair. In this case the product would easily
be generated diastereomerically pure, but it obviously has the undesired
configuration at the hydroxyl bearing carbon. Since the configuration of such
an alcohol can be inverted by a number of ways, this reasoning makes the
development of methods for the diastereo- and enantioselective generation
of syn-ß-methyl homoallyl alcohols even more urgent.

α-CHIRAL Z-CROTYLBORONATES

The stereotriades C and D in scheme (22) have become available using the
α-chiral-E-crotylboronates as described above. In order to reach the other
two stereotriades A and B as well, α-chiral-Z-crotylboronates are required.
First representatives were prepared in the racemic series. On addition to
aldehydes the homoallyl alcohols 9, this time with an E-double bond, were
formed in preference.

Scheme 22   **Scheme 23**

| | X = Si(CH₃)₃ | R = Ph | 90 | : | 10 | (D.S.Matteson) |
| | X = Cl | R = Pr | 90 | : | 10 | (ref. 10) |
| | X = CH₃ | R = Pr | >95 | : | <5 | |

This is a consequence of that fact that the axial position for X in the transition state (cf. scheme (21)) is now seriously crowded causing 1,3-allylic strain. Highest selectivity can, hence, be obtained with the methyl derivative **8**, the methyl group resenting least on stereoelectronic and steric grounds to be in the equatorial position: Scheme (24).
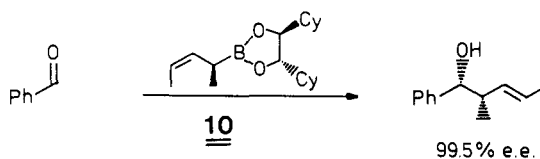
Scheme 24

The pentenyl borate **10** could be obtained in a state of high diastereomeric (enantiomeric) purity making recourse to the method and the kind help of D.S. Matteson (ref. 13):Scheme (25).

Scheme 25
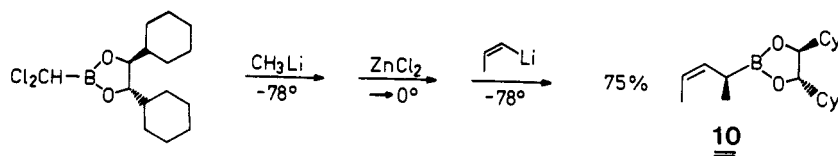
The degree of chirality transfer that can be obtained with this reagent **10** turned out to be rewarding indeed: Scheme (26).
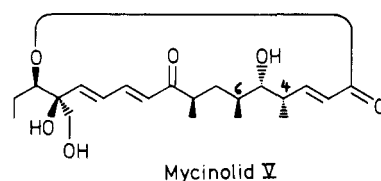
Scheme 26

99.5% e.e.

The relative and absolute configuration of the resulting homoallyl alcohols were established by the application of the reagent **10** to the synthesis of invictolide: Scheme (27).

Scheme 27

67% ds > 95%

$\xrightarrow{\text{KOH}}_{\text{CH}_3\text{OH}}$ $\xrightarrow{\text{pH 2}}$ $\xrightarrow{\text{H}_2}_{\text{Pd/C}}$

(+)-Invictolid

77%
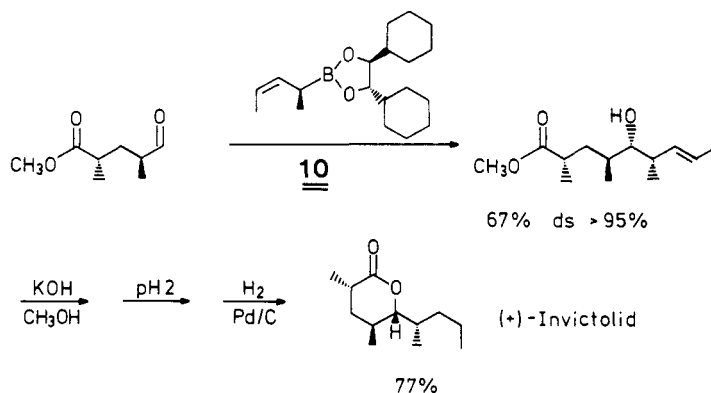
Scheme 28

Mycinolid V

In due course, the reagent **10** has been utilized in the assembly of the stereotriade at C-4 to C-6 in mycinolide V, the aglycon of one of the mycinamycin antibiotics. The synthesis of this macrolide has recently been completed (ref. 14): Scheme (28).

En routo to the C-4/C-6 stereotriade of mycinolide the various crotylboronate reagents have been employed. The results in scheme (29) nicely illustrate the improvement in diastereoselectivity that was realized by changing from an achiral crotylboronate over a chirally modified crotylboronate to the present generation of α-chiral crotylboronates.

Scheme 29
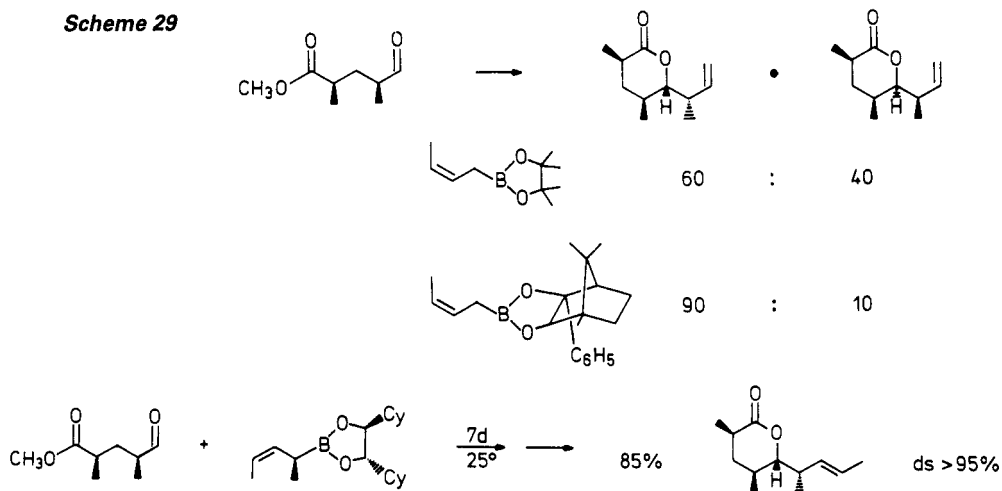
Acknowledgement

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