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(2*R*,3*R*)-1,4-Dimethoxy-1,1,4,4-tetraphenyl-butane-2,3-diol – Valuable Reagent in the Asymmetric Synthesis of Organoboronates

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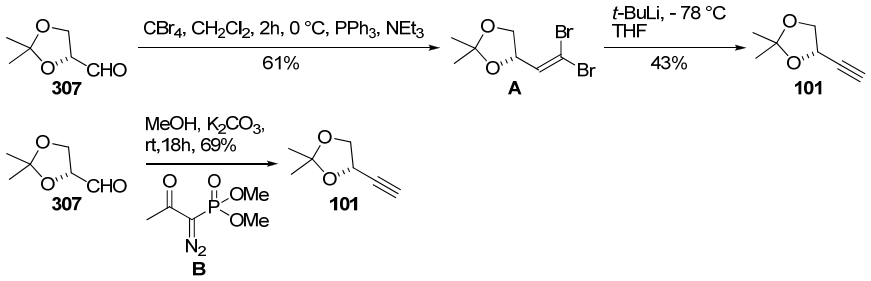
Dedicated to Donald S. Matteson on the occasion of his 80th birthday.

Supporting Information: Table of Contents

SYNTHESIS OF GLYCERALDEHYDE-DERIVATIVE 101

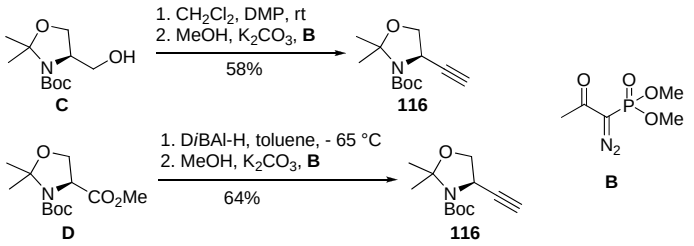
Compound **101** was prepared starting from isopropylidene glyceraldehyde **307**, which was transformed to product **A** by a modified *Corey-Fuchs* reaction sequence first. Product **101** was obtained after reaction with *t*-BuLi.[1, 2] A better yield was obtained when treating aldehyde **307** with *Bestmann-Ohira* reagent **B**.[3-7]



Scheme 1 Preparation of Glyceraldehyde-based Alkyne **101.**

SYNTHESIS OF *GARNER*-ALDEHYDE-DERIVATIVE 116

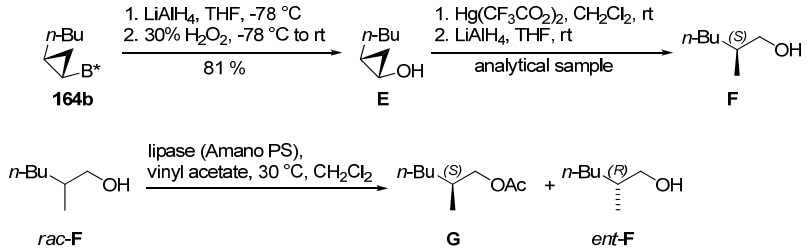
The *Garner*-Aldehyde derivative **116** was synthesized by oxidation of serinol-derivative **C** with *Dess-Martin*-periodinane (DMP) reagent followed by reaction with *Bestmann-Ohira* reagent **B**,[3-5] or the reduction of ester **D** with D*i*BAl-H, followed by treatment with reagent **B**.[8]



Scheme 2 Two Routes to *Garner* Aldehyde-derived Alkyne **116**.

ASSIGNMENT OF ABSOLUTE CONFIGURATION OF CYCLOPROPYLBORONATE 164B BY CHEMICAL CORRELATION

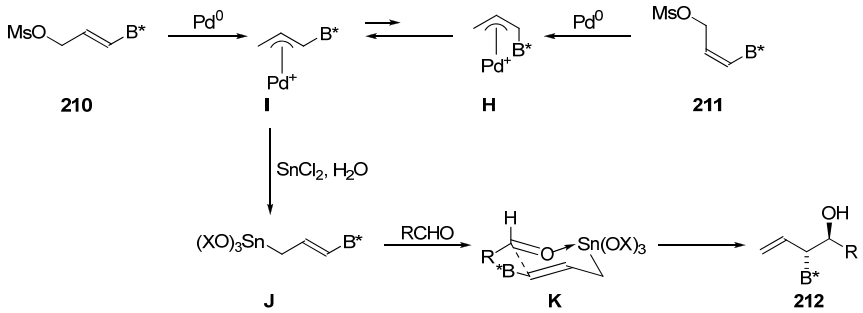
First compound **164b** was transformed to cyclopropanol **E**, and in the subsequent reaction the ring was opened employing $Hg(CF_3CO_2)_2$, followed by a reduction to form alcohol **F** (Scheme 3). The resulting product **F** was correlated *via* chiral GC with a reference sample, which was synthesized by a lipase-catalyzed acetylation of (*rac*)-**F**. Once the configuration of **164b** was assigned, the established method relying on the characteristic ^{1}H-NMR data of the cyclopropylboronic ester was adopted for the *cis*-cyclopropylboronates. Just as for the *trans*-boronates the 3'-H_{trans} proton and carbon C-3' signals were shifted to the downfield region (^{1}H: 0.21-0.44 ppm, ^{13}C: 0.12-1.20) for the major diastereomer in all cases.[9]



Scheme 3 Assignment of Absolute Configuration of **164b** by Chemical Correlation.

MECHANISTIC CONSIDERATIONS ON CARBONYL ALLYLATION OF (E)-AND (Z)-CONFIGURED MESYLATES 210 AND 211

After formation of a η^3-allyl-Pd-complex **H**, the isomers equilibrate. Structure **I** is strongly favored due to its higher stability. By transmetallation with excess tin(II)chloride this complex is transformed to allyltin-intermediate **J**. The presence of water may result in partial cleavage of the Sn(IV)-Cl bonds, thus generating active species **J**. In six-membered transition state **K**, the carbonyl oxygen of the aldehyde substrate coordinates to the Sn(IV)-species, resulting in *anti*-selective formation of allylboronate **212**.[10]



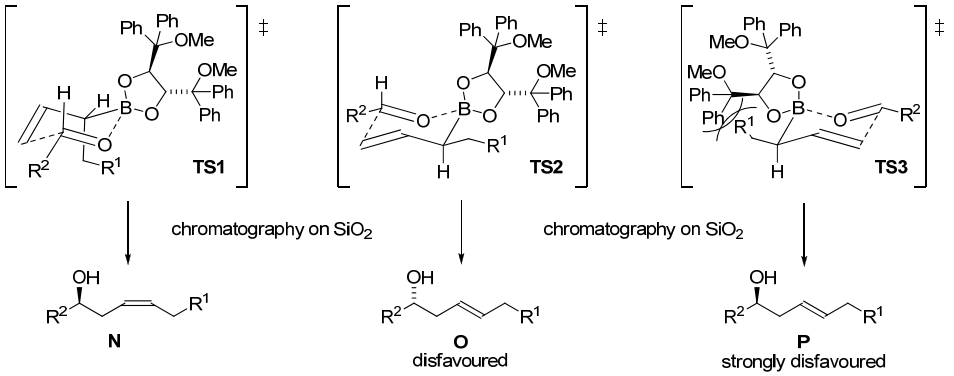
Scheme 4 Mechanism of Carbonyl Allylation Reactions of Mesylates **210** and **211.**

DETAILED ANALYSIS OF THE MECHANISM OF ALLY ADDITION REACTIONS

Stereoselectivity of allylation reactions of allylboronates of type 176/177

Taking a closer look at the allylation reactions discussed, it has to be noted that despite the final isolation of pure (*Z*)-configured products in high yields, in some cases varying amounts of (*E*)-isomer were detected in crude NMR samples. While the addition reactions to benzaldehyde **73** proceeded with exclusive formation of the (*Z*)-isomer, the reactions of PMB-protected glyoxaldehyde **327** and especially 3-phenylpropionaldehyde **322** yielded (*E*)-configured homoallylic alcohols as side-products. In the reaction with PMB-protected aldehyde **327** the (*R*)-series gave (*Z*)-isomers as products exclusively, while in the (*S*)-series' crude products marginal amounts of (*E*)-products were detected. The observation that (*R*)- and (*S*)-series differ in their stereochemical behavior was underlined in the reactions with 3-phenylpropionaldehyde **322** as

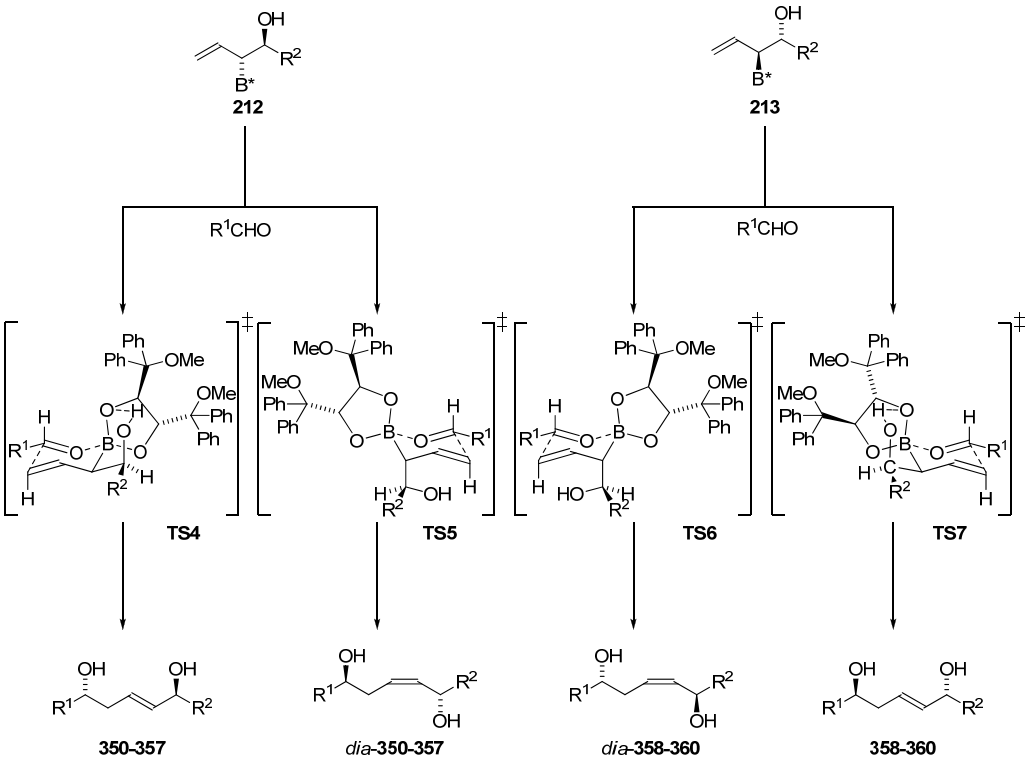
substrate: Except for ethyl-substituted allylboronate **293**, all allylation reagents belonging to the (*S*)-series tested gave considerable amounts of (*E*)-isomer in the crude product mixture (crude **323**: 93%, *Z*/*E* 87:13; crude **326**: 98%, *Z*/*E* 70:30; crude **324**: 89%, *Z*/*E* 87:13). Although plausible transition states for each product isomer can be proposed easily (Scheme 5), the cause for certain substituents to favor transition state **TS2** with pseudo-equatorial position of all substituents while others do not, remains unclear. At least the difference in *E*/*Z*-selectivity between (*S*)- and (*R*)-series can be explained by mechanistic considerations. If a transition state **TS3** analogous to **TS2** is postulated for an allylboronate **M** belonging to the (*R*)-series, one bulky group of the remote auxiliary would interfere with equatorial residue R^1 sterically, thus strongly disfavoring this transition state leading to (*E*)-isomeric products **P**.[11]



Scheme 5 Mechanistic Considerations on *E*/*Z*-Selectivity of Allylation Reactions.

Stereoselectivity of Allylic Additions of Hydroxy-substituted Allylboronates 212 and 213

In general, the obtained results can be rationalized by assuming a six-membered transition state for the allylation reaction (Scheme 6). Unfavorable *gauche* interaction between α-substituents and the bulky boronic ester moiety generally favors formation of (*Z*)-products, while decrease in (*Z*)-selectivity is caused by additional substituents in the side-chain. It was assumed that *syn*-pentane interaction increases with the α-substituent R^2 in pseudoaxial position (transition state **TS5**), therefore transition state **TS4** is favored. X-ray crystal analysis of **212h** led to the consideration that a hydrogen bond between the OH-group and one of the dioxaborolane′s oxygen atoms has additional influence on the reaction outcome. Such interaction might fix the conformation of the α-substituent and activate the boron moiety, resulting in an increased reaction rate and (*E*)-selectivity. In transition state **TS6**, a *syn*-pentane interaction similar to transition state **TS5** can be recognized. The preferred formation of the (*Z*)-isomer corresponding to transition state **TS6** can be explained by the strong steric interaction of the α-substituent R^2 in the pseudoequatorial position and one of the dioxaborolane's bulky CPh_2OMe groups in transition state **TS7**. Higher (*Z*)-selectivity in reactions of one of both diastereomeric "series" of allylboronic esters bearing diol **26** as protective group was already observed for the distinct selectivities of (*R*)- and (*S*)-configured α-substituted allylboronates obtained from [3.3]-sigmatropic rearrangements. According to the experimental results, the steric interactions found in transition state **TS7** are a very influential factor and overrule *syn*-pentane interactions in transition state **TS6**.[10]



Scheme 6 Transition States Leading to (*E*)- and (*Z*)-Products.

MECHANISTIC CONSIDERATIONS ON THE DIASTEREOSELECTIVITY OF *MANNICH* REACTIONS OF SULFONYLIMINE 394

The obtained configurations were discussed on the basis of six- and seven-membered transition states, respectively (Fig. 6). While transition states **TS8** and **TS9** leading to addition from the *re*-face seem likely, transition state **TS10** for the attack from *si*-face should be strongly disfavored due to steric demand of the boronic ester's bulky groups.[12]

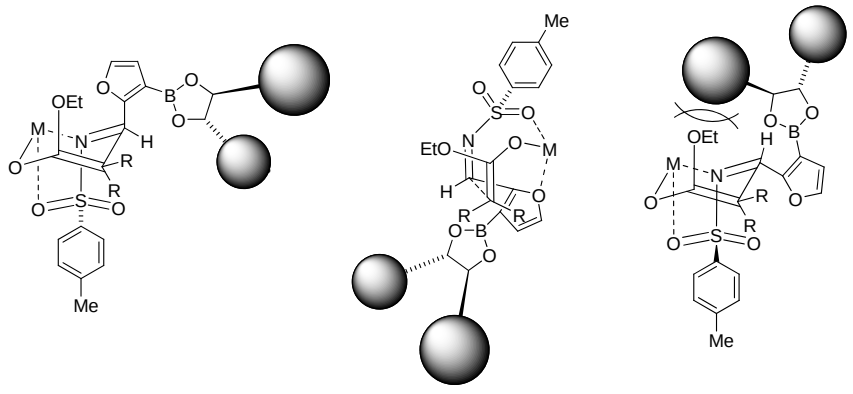


Fig. 1 Transition States for Asymmetric *Mannich* Reactions of Furyl Sulfonylimine **394**.

RECOVERY OF DIOL 26 FROM HYDROXYDIOXABOROLANE 97 OBTAINED FROM ALLYL ADDITION REACTIONS

Dioxaborolane **97** collected during work-up of allyl addition reactions is collected and volatiles are removed *in vacuo*. In a *Schlenk* flask $LiAlH_4$ (4 eq.) is suspended in dry Et_2O and the suspension is cooled to 0 °C in an ice-bath before dioxaborolane **97** is dissolved in Et_2O (2.3 mL/mmol **97**) and slowly added to the suspension *via* transfer cannula or dropping funnel. The reaction mixture is stirred over night at room temperature (the progression can also be checked by TLC). Upon complete consumption of the starting material, H_2O (45 μL/mmol $LiAlH_4$), 15% NaOH (45 μL/mmol $LiAlH_4$) and another portion of H_2O (135 μL/mmol $LiAlH_4$) are carefully added at 0 °C. The mixture is stirred until a filterable precipitate is formed (~30min) which is removed by filtration. The filtrate is dried over $MgSO_4$ and concentrated using rotary evaporator. Thus obtained crude diol **26** is purified by flash column chromatography, yielding pure diol **26** as colorless foam. For full characterization, see: M. Bischop, V. Cmrecki, Ophoven, V. Ophoven, J. Pietruszka. *Synthesis* 2488 (2008). The described method is also applicable to other collected side-products and waste materials containing boronate moiety **18**.

LIST OF ABBREVIATIONS

p-TsOH	*para*-toluenesulfonic acid
2-Me-THF	2-methyl-tetrahydrofurane
AAM	anthranilamide
BHT	butylated hydroxytoluene
Bn	benzyl
Boc	butoxycarbonyl
Bz	benzoyl
CDK	cyclin-dependent kinases
DAN	1,8-diaminonaphthaline
DCC	dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
de	diastereomeric excess
DEAD	diethyl azodicarboxylate
DET	diethyl tartrate
D*i*BAl-H	diisobutylaluminium hydride
DIPEA	*N*,*N*-diisopropylethylamine
DMAP	dimethylaminopyridine
DMDO	dimethoxydioxirane
DME	dimethoxyethane
DMF	dimethylformamide
DMP	*Dess-Martin*-periodinane
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
ee	enantiomeric excess
eq	equivalent(s)
GC	gas chromatography

HOTT	*S*-(1-oxido-2-pyridinyl)-1,1,3,3-tetramethylthiouronium hexafluorophosphate
HPLC	high pressure liquid chromatography
HWE	*Horner-Wadsworth-Emmons*
Ipc	isopinocampheyl
KHMDS	potassium hexamethyldisilazide
LDA	lithium diisopropylamide
LiHMDS	lithium hexamethyldisilazide
MAO	monoaminooxidase
*m*CPBA	*meta*-chloroperbenzoic acid
MIDA	*N*-methyl iminodiacetic acid
MOM	methoxymethyl
MPLC	medium pressure liquid chromatography
Ms	mesyl
MS	molecular sieves
MW	microwave
NaHMDS	sodium hexamethyldisilazide
NBS	*N*-bromosuccinimide
NMO	*N*-methylmorpholine-*N*-oxide
Phth	phthalyl
PIDA	pinene-derived iminodiacetic acid
PMB	*para*-methoxybenzyl
PMP	*para*-methoxyphenyl
TADDOL	α,α,α′,α′-tetraaryl-1,3-dioxolan-4,5-dimethanol
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBHP	*tert*-butylhydroperoxide
TBS	*tert*-butyldimethylsilyl
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxyl
TES	triethylsilyl
Tf	triflyl
TMS	trimethylsilyl
TPAP	tetrapropylammonium perrhutenate
TPS	triisopropylsilyl

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