universität wien

DISSERTATION

Titel der Dissertation

„Synthesis and reactions of chiral, nonracemic compounds with general formula XCHDY and [^{16}O,^{17}O,^{18}O]phosphoenolpyruvate“

Verfasserin

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A huge THANK YOU belongs to Fritz, my supervisor and my mentor for teaching me so much over the years!

Thank you Timinko for always being with me and supporting me all the time.

And last but not least, thank you my family, my colleagues and my friends who stuck with me through all of this.

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1 Introduction

Dear reader, before you start reading my work, I would like to tell you a little about what you can expect on the next 150 or so pages. My doctoral thesis consisted of five parts that at first sight do not have much in common. However, at a closer look one can discover an underlying motif that runs through all of the chapters and that is the chiral methyl group or in the last chapter, the chiral phosphate group.

The first two chapters were kind of a conclusion of my Master's thesis. In chapter 2, the microscopic configurational stability of a chiral silyl-[D_1]methylpalladium complex formed during the Suzuki-Miyaura coupling is investigated, as a continuation of the work I did on the Stille coupling.

In chapter 3, the configurational stability of chiral fluoro-[D_1]methyllithium is studied in order to complete the studies on the configurational stability of various halomethyllithiums that the Hammerschmidt group had been working on for years.

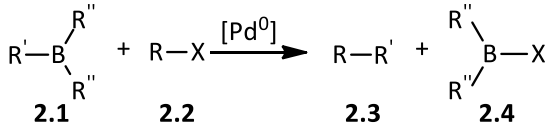
Chapter 4 deals with the attempted synthesis of 1,ω-diols stereospecifically deuterated at each carbon atom by a procedure developed by Matteson where the chain is elongated stepwise by an (*R*)- or (*S*)-configured -CHD- group.

Chapter 5 shows the attempt to separate the enantiomers of bromochlorofluoromethane by the cocrystallization with a potential PET precursor synthesized from allose.

Finally, chapter 6 describes the first direct chemical synthesis of (R_P)- and (S_P)-[$^{16}O_1$,^{17}O,$^{18}O_1$]phosphoenolpyruvate which can be used to study mechanistic aspects of enzymes transferring a phosphate group.

2 Suzuki-Miyaura Cross-Coupling Reaction

The Suzuki-Miyaura cross-coupling reaction, along with the Stille cross-coupling reaction, is one of the most general and selective cross-coupling reactions.[1] It is a reaction between an organoboron compound **2.1** and an organic halide **2.2** catalyzed by palladium(0) under basic conditions (Scheme 2.1). This coupling is popular especially because it tolerates a lot of



Scheme 2.1. Suzuki-Miyaura cross-coupling reaction.

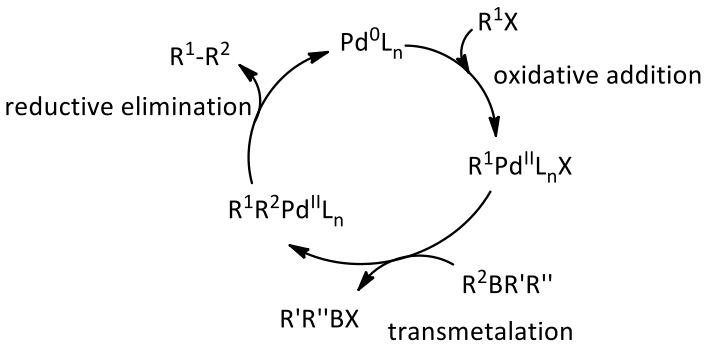
functionalities; it runs under mild conditions, even in presence of water. The starting organoboronic acids and their esters are stable and readily available with many functional groups and the byproducts are nontoxic.[1] It has been successfully used for the cyclization of 5- or 6-membered rings[2] as well as macrocycles,[3] for the synthesis of non-natural amino acids,[4] homoallylic amines[5] and various natural products and their derivatives.[6,7,8,9,10]

A wide variety of $Pd(0)L_n$ catalysts or their precursors, which can be easily reduced to active Pd(0) species, can be utilized, with $Pd(PPh_3)_4$ and $PdCl_2(PPh_3)_2$ being some of the most common ones.[1] Bulky phosphines as ligands or palladium complexes containing fewer than four phosphine ligands are also very useful because they easily form unsaturated Pd complexes that are very reactive towards the first step of the catalytic cycle.[11]

2.1 Mechanism

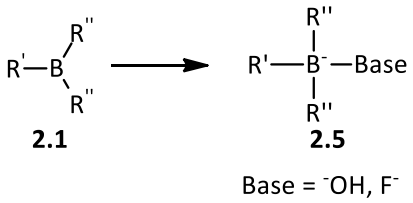
The Suzuki-Miyaura coupling reaction proceeds through a typical cross-coupling mechanism consisting of three main steps (Scheme 2.2). The first and usually the rate-determining step is the oxidative addition of the organic halide to $Pd(0)L_n$ and the formation of a *trans*-σ-palladium(II)L_n complex. The reactivity of halides towards oxidative addition is increased by proximity of electron-withdrawing groups and decreases in order of I >> OTf > Br >> Cl. In case of alkenyl halides this step proceeds with retention of configuration, whereas it proceeds with inversion of configuration for allyl and benzyl halides.[6] Alkyl halides, with the exception of iodoalkanes, are usually useless

because of β-elimination from the formed σ-complex occurring competitively with oxidative addition.[12,13]



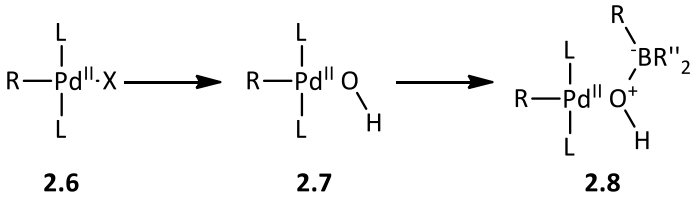
Scheme 2.2. General (simplified) cross-coupling mechanism.

The second and still not completely elucidated step is transmetalation. It is in this step that the presence of a base is necessary, but its role is still being discussed. It is generally known that boronic acids and their esters are not very reactive towards boron-palladium exchange because of low nucleophilicity of the alkyl group on boron. The first mechanism proposed by Suzuki[14] was based on the assumption that the base increases the nucleophilicity of the substituents at boron by creating a negatively charged four-coordinate boron 'ate' complex ('boronate pathway') (Scheme 2.3).[15]



Scheme 2.3. 'Ate' complex formed by the addition of base to the boron starting material.

Later studies show that even though this pathway cannot be completely excluded, more probable is a second pathway, called 'oxo-palladium pathway',[15,16,17] if the one ligand on Pd is a hydroxyl or alkoxy group, but fluoride can also act in the same way (Scheme 2.4).

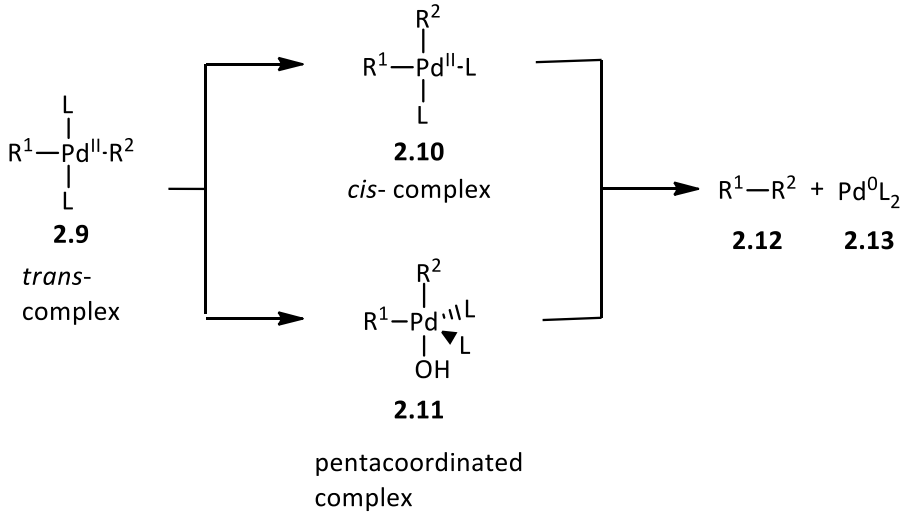


2.6 **2.7** **2.8**

Scheme 2.4. Oxo-palladium pathway.

This is particularly true for couplings of aryl boronic acids with simple aryl halides in aq. DMF, acetone or THF and with PPh_3 as ligands.[15] In this pathway, the base acts as a ligand that displaces the halogen on Pd. The hydroxypalladium species acts as a Lewis base and generates the four-coordinated boron species required for the transmetalation. Transmetalation also proceeds with retention of configuration.[18]

The last step is reductive elimination of two substituents from the complex formed during transmetalation. The product is released and the catalyst is regenerated. Only substituents in *cis*-arrangement get eliminated. If a *trans*-complex is formed, it has to isomerize to the *cis*-complex first which is usually a slow process. A base acting as a ligand accelerates the reductive elimination from *trans*-complex via a pentacoordinated complex (Scheme 2.5).[16]



2.9 **2.10** **2.11** **2.12** **2.13**

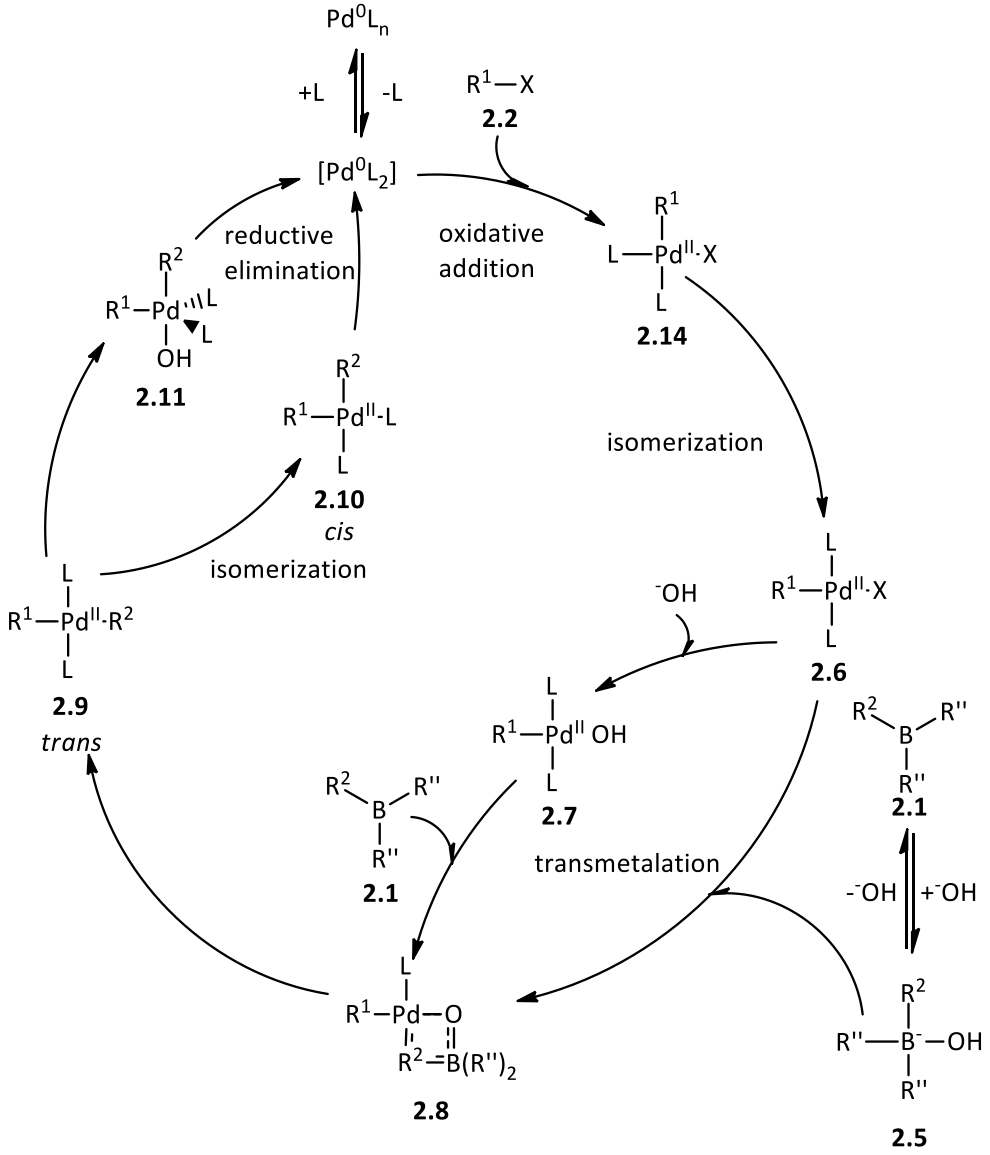
trans-complex

cis- complex

pentacoordinated complex

Scheme 2.5. Two different pathways for reductive elimination.

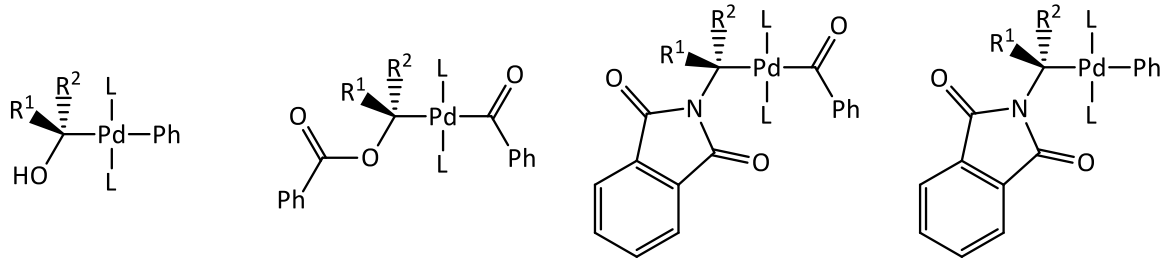
When all of these findings are taken into consideration, the catalytic cycle of the Suzuki-Miyaura coupling reaction looks more complicated that the catalytic cycle shown in Scheme 2.2 (Scheme 2.6).



Scheme 2.6. Complete catalytic cycle of the Suzuki-Miyaura coupling.

2.2 Microscopic configurational stability of silylmethylpalladium complex formed during the Suzuki-Miyaura coupling

I dedicated the majority of my master's thesis to studying the microscopic configurational stability of methylpalladium complexes formed during the Stille coupling in order to widen the scope of reactions that could be used for the preparation of enantiomerically pure deuterated compounds (Figure 2.1).[19]



2.15: $R^1 = R^2 = H$ (*R*)-[D_1]**2.16**: $R^1 = D$, $R^2 = H$ **2.17**: $R^1 = R^2 = H$ **2.18**: $R^1 = R^2 = H$

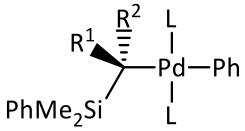
(*R*)-[D_1]**2.15**: $R^1 = D$, $R^2 = H$ (*S*)-[D_1]**2.16**: $R^1 = H$, $R^2 = D$ (*R*)-[D_1]**2.17**: $R^1 = D$, $R^2 = H$ (*R*)-[D_1]**2.18**: $R^1 = D$, $R^2 = H$

(*S*)-[D_1]**2.18**: $R^1 = H$, $R^2 = D$

Figure 2.1. Oxymethylpalladium complexes **2.15** and **2.16**, aminomethylpalladium complexes **2.17** and **2.18** studied.

All reactions with these complexes as intermediates were found to proceed with a net retention of configuration. Methylpalladium complexes **2.15**, **2.16** and **2.17** were found to be at least microscopically configurationally stable at the stereogenic center. However, complex **2.18** was found to be either only partially microscopically configurationally stable or to go through a combination of open and closed transition states during formation. This led to a partially racemic intermediate reflected by the solvent-dependent enantiomeric excess of the product ranging from 52% to 69%.

Encouraged by these successes I decided to briefly study a silyl-[D_1]methylpalladium complex formed as intermediate during the Suzuki-Miyaura coupling to see whether it is also microscopically configurationally stable at the stereogenic center (Figure 2.2).

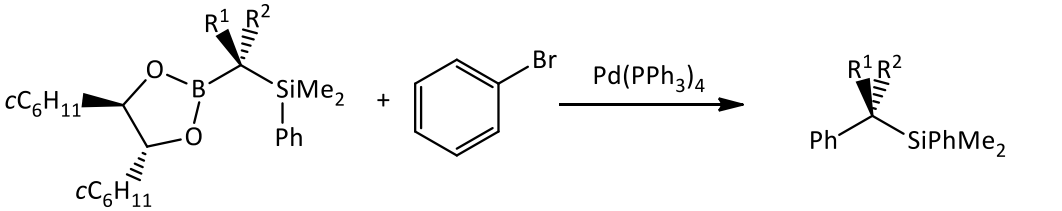


2.19: $R_1 = R^2 = H$
(*R*)-[D_1]**2.19**: $R^1 = D$, $R^2 = H$

Figure 2.2. Silyl-[D_1]methylpalladium complexes **2.19**.

2.2.1 Coupling partners

I decided to study the Suzuki-Miyaura coupling of bromobenzene and boronic ester **2.20** with tetrakis(triphenylphoshine)palladium as catalyst (Scheme 2.7).



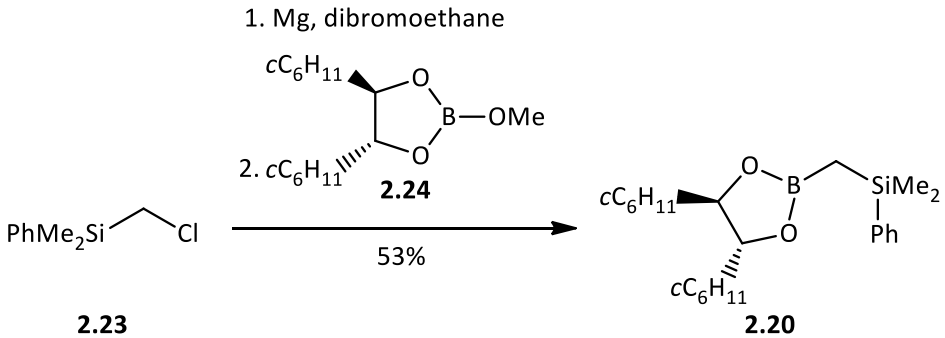
2.20: $R^1 = R^2 = H$
(*S*)-[D_1]**2.20**: $R^1 = H$, $R^2 = D$

2.21

2.22: $R^1 = R^2 = H$
(*S*)-[D_1]**2.22**: $R^1 = H$, $R^2 = D$

Scheme 2.7. Studied Suzuki-Miyaura coupling.

This boronate **2.20** was chosen as a coupling partner because of two reasons. The first one is that the syntheses of both unlabeled[20] and labeled[21] boronates are well established and straightforward. The unlabeled species can be synthesized from (chloromethyl) dimethylphenylsilane (**2.23**) (Scheme 2.8). It is converted into its Grignard reagent with magnesium and then reacted with borate **2.24** to give boronate **2.20** in an overall yield of 53%.

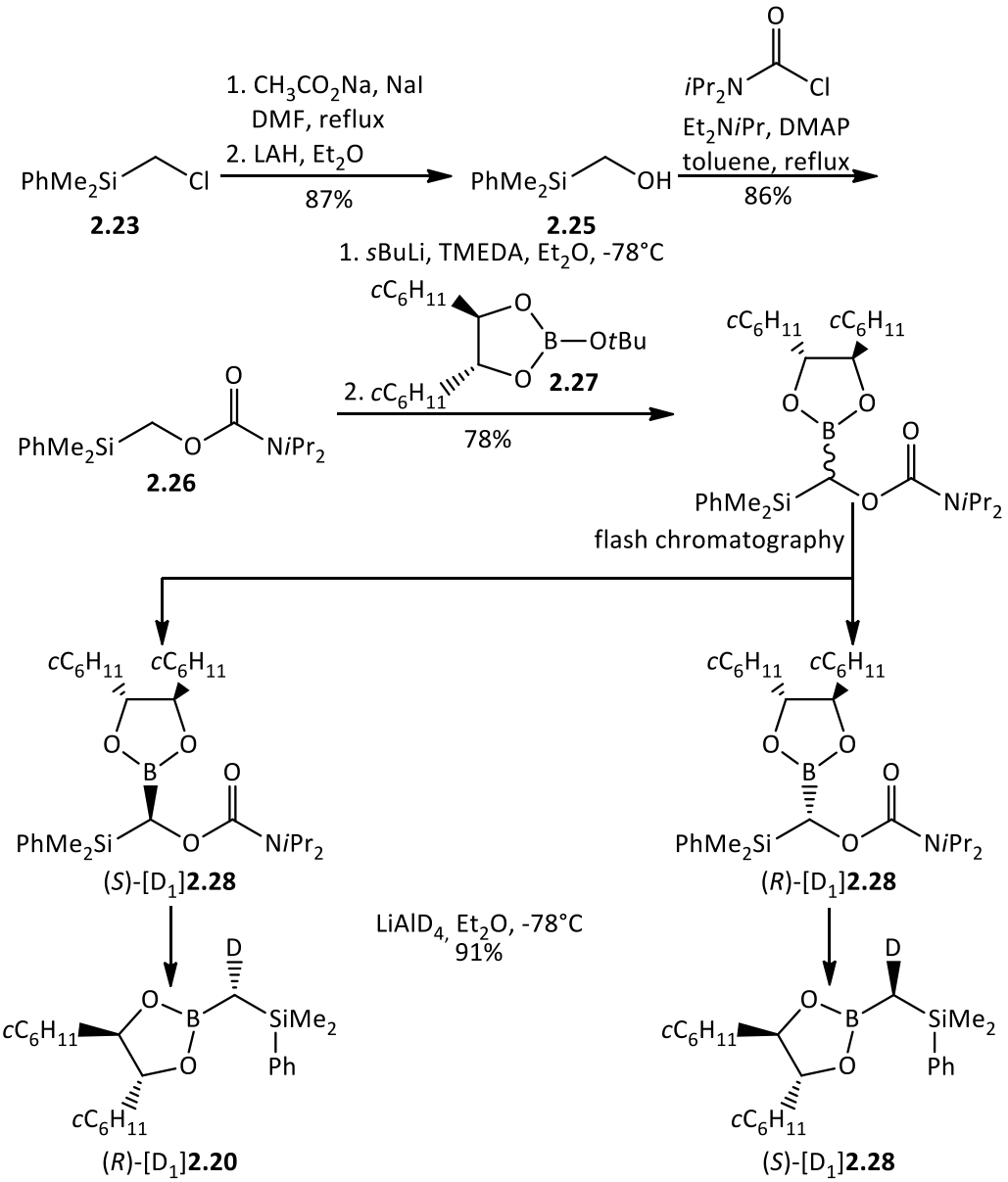


2.23

2.20

Scheme 2.8. Synthesis of the unlabeled boronate **2.20**.

The synthesis of the labeled boronate [D_1]**2.20** is a little more challenging (Scheme 2.9).

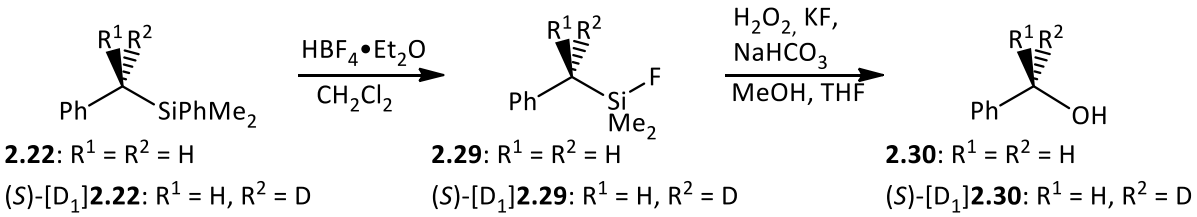


Scheme 2.9. Synthesis of the labeled silylmethylboronates (*R*)- and (*S*)-[D_1]**2.20**.

It starts from the same starting material as the preparation of the unlabeled compound, (chloromethyl)dimethylphenylsilane (**2.23**), that is reacted with sodium acetate in the presence of sodium iodide. The acetate formed is subsequently reduced to (dimethylphenylsilyl)methanol (**2.25**) with $LiAlH_4$ and esterified with with *N*,*N*-diisopropyl carbamoyl chloride. The carbamate **2.26** is deprotonated using *s*BuLi and borylated with the mixed borate **2.27** of (*R*,*R*)-1,2-dicyclohexylethane-1,2-diol and *t*-butanol to form diastereomeric boronates **2.28** that can be separated using flash chromatography. Each diastereomer is reduced separately with $LiAlD_4$ in Et_2O to yield the desired deuterated silylmethylboronates [D_1]**2.20**.

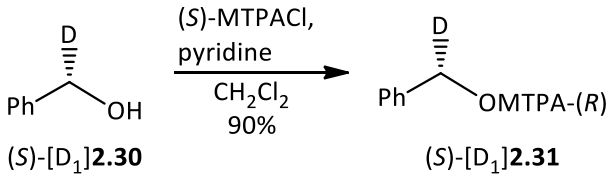
At this point I would like to thank Anna Wieczorek who also used the deuterated boronates [D_1]**2.20** and was kind enough to let me use the material that she no longer needed.

The second reason for using silylmethylboronate **2.20** is that the coupling products, benzylsilanes **2.22**, can be easily converted to benzyl alcohols **2.30** by the Fleming oxidation which proceeds stereospecifically with retention of configuration.[22] The silicon-phenyl bond is much more labile than the silicon-alkyl bonds and can be thus cleaved very easily.[23] The oxidation itself proceeds in two steps. The first is protodesilylation where the Si-Ph bond is broken with an electrophile and the second is the oxidation of the resulting halosilane **2.29** with a peroxide to yield benzylalcohol **2.30** (Scheme 2.10).[24]



Scheme 2.10. Conversion of coupling product **2.22** to benzyl alcohol **2.30**.

The alcohol (*S*)-[D_1]**2.30** can then be converted to the (*R*)-Mosher ester **2.31** and compared by NMR spectroscopy to the previously synthesized (*R*)-Mosher ester of authentic (*R*)-phenyl-[D_1]methanol in order to determine its ee and configuration (Scheme 2.11).



Scheme 2.11. Derivatization of benzyl alcohol (*S*)-[D_1]**2.30** with (*S*)-MTPACl to its (*R*)-Mosher.

2.2.2 Coupling conditions

The hardest part of the synthesis was the coupling itself and its optimization can be found in Table 2.1.

I first tried the standard conditions for the Suzuki-Miyaura coupling found in the literature[25] where only 1 mol% of $Pd(PPh_3)_4$ and 2 eq. of 2M NaOH in toluene were sufficient to give a yield of 86%. Unfortunately, these conditions led to no product in my case (entry 1). Changing the base

Entry	$Pd(PPh_3)_4$ (mol%)	Base (eq. based on 2.20)	Solvent	Reaction time (at 90°C, h)	Yield (2.22, %)	Yield (biphenyl, %)
1	1	NaOH (2)	Toluene	18	0	0
2	1	NaOEt/EtOH (4)	Toluene	7	0	0
3	3	NaOH (2), Bu_4NHSO_4 (5 mol%)	Toluene	8	15	15
4	5	NaOH (2), Bu_4NHSO_4 (5 mol%)	Toluene	17	17	2
5	5	NaOH (2)	Dioxane	18	21	4
6	5	NaOH (2), Bu_4NHSO_4 (5 mol%)	Dioxane	18	35	20
7	5	NaOH (8)	Dioxane	9	41	11
8	5	NaOH (8)	Dioxane	12	46	15
9*	10	NaOH (8)	Dioxane	12	47	37
10*	10	NaOH (8)	Dioxane	24	49	25

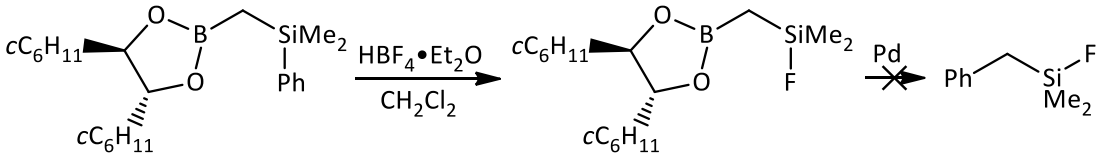
Table 2.1. Optimization of reaction conditions and yields of the desired benzylsilane **2.22** and undesired biphenyl. *Starting material was (*S*)-[D_1]**2.20** instead of unlabeled **2.20**.

from NaOH to NaOEt/EtOH did not lead to the desired product either (entry 2). Simultaneous increase of the amount of catalyst to 3 or 5 mol% and the use of 5 mol% of Bu_4NHSO_4 as additive along with 2 eq. of NaOH finally gave the desired benzylsilane **2.22** although only in 15% and 17% yields, respectively (entries 3 and 4). At this point it was decided to try a different solvent and switched from toluene to 1,4-dioxane in the hope of increasing the yield. With only 2 eq. of NaOH the improvement was not significant (entry 5) but when 5 mol% of Bu_4NHSO_4 were used, the yield was significantly better (35%, entry 6). However, the best results were obtained when 8 eq. of NaOH were used (entries 7 to 10). Entries 7 and 8 were the last experiments performed with the unlabeled material and only differ in reaction time. They show that an increased reaction time only slightly increases the yield. For the coupling of the deuterated silylmethylboronate (*S*)-[D_1]**2.20** I decided to play it safe and use 10 mol% of $Pd(PPh_3)_4$ (entries 9 and 10). There was almost no effect on the yield (entry 9), even when the reaction time was doubled (entry 10).

A side product was formed once the coupling started to yield the desired product. It had the same R_f as the benzylsilane **2.22** in hexanes: CH_2Cl_2 = 2:1 and was identified as biphenyl after it was isolated by flash chromatography with pure hexanes as eluent. It turned out that there was a competing reaction taking place where the transmetalation did not occur between palladium and boron but rather between palladium and silicon which is supported by literature.[26] It might be due to the fact that the boronate cannot be deprotected under the basic conditions to give boronic

acid thus boron is not as easily displaced as the silicon during transmetalation, a prerequisite for high yields.

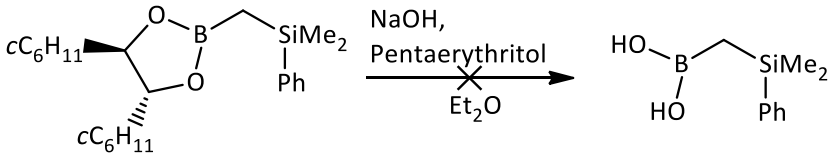
There is no real pattern in how much of biphenyl formed although its yield does seem to increase with increasing catalyst amount. Many changes were tried in order to eliminate the undesired side reaction. The easiest option was tried first. Instead of doing the Fleming oxidation after the coupling, the two reactions were reshuffled. Protodesilylation was performed with $HBF_4 \bullet Et_2O$ before the Suzuki-Miyaura coupling as before, but the fluorosilane **2.32** did not give any product on attempted coupling with bromobenzene under the same conditions (Scheme 2.12).



2.20 **2.32** **2.29**

Scheme 2.12. Attempted coupling of fluorosilane **2.32** derived from **2.20** with bromobenzene.

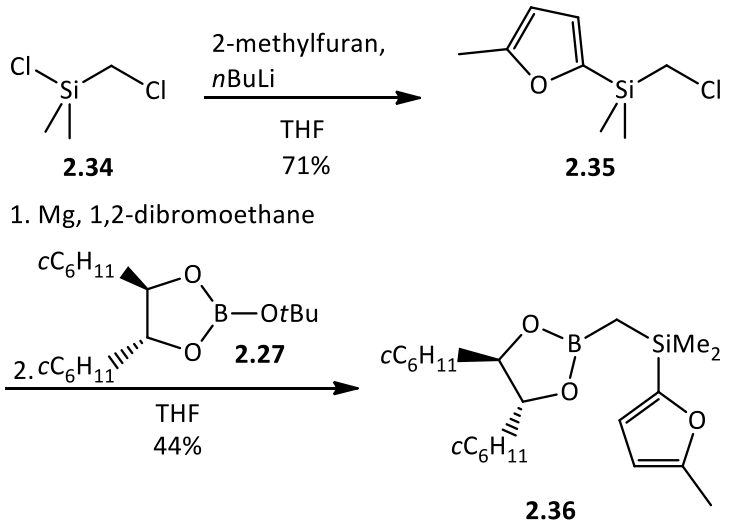
Coupling of the sterically less hindered boronic acid derived from the original boronate **2.20** was attempted next. Simple boronic esters can be normally easily deprotected[27] but the ester of (*R*,*R*)-1,2-dicyclohexylethane-1,2-diol proved to be unreactive under the usual conditions (Scheme 2.13).



2.20 **2.33**

Scheme 2.13. Attempted hydrolysis of boronic ester **2.20**.

Since the Fleming oxidation is not only possible with phenyl as a substituent attached to silicon but also with other aromatic substituents, the phenyl group was replaced by the 5-methylfuran-2-yl group.[24] The boronic ester needed for the coupling was synthesized from chlorosilane **2.34** and 2-methylfuran (Scheme 2.14).



Scheme 2.14. Preparation of boronic ester **2.36** that contained a 5-methylfuran-2-yl substituent on silicon.

However, boronic ester **2.36** was unstable on silica gel so it could not be properly purified. It also did not yield any product when it was coupled with bromobenzene.

The formation of biphenyl as byproduct could not be prevented, but fortunately it did not interfere with the following Fleming oxidation. The biphenyl could be easily removed during the clean-up of the alcohol.

2.2.3 Determination of absolute configuration and enantiomeric excess of deuterated phenylmethanol

The first step of the Fleming oxidation was easily accomplished with $HBF_4 \bullet Et_2O$ in almost quantitative yield and the subsequent oxidation was first unsuccessfully tried with *m*CPBA. When H_2O_2 in the presence of KF and $NaHCO_3$ in MeOH:THF = 1:1 was used instead, the oxidative cleavage of the silicon-carbon bond proceeded smoothly with 67% yield. To determine the configuration and enantiomeric excess of the deuterated phenylmethanol [D_1]**2.30**, it was derivatized with (*S*)-Mosher chloride to give (*R*)-Mosher ester **2.31** (Scheme 2.11).

The ^{1}H NMR spectrum of the (*R*)-Mosher ester **2.31** derived from the Suzuki-Miyaura coupling product was compared to the one derived from authentic (*R*)-phenyl-[D_1]methanol. The former spectrum showed a triplet at 5.29 ppm, the latter at 5.33 ppm. Therefore, the configuration of the phenyl-[D_1]methanol obtained by Fleming oxidation is (*S*) and the same as the configuration of the

starting deuterated silymethylboronate (*S*)-[D_1]**2.20** at the silyl bearing carbon atom. The ee was determined to be 99% (Figure2.3).

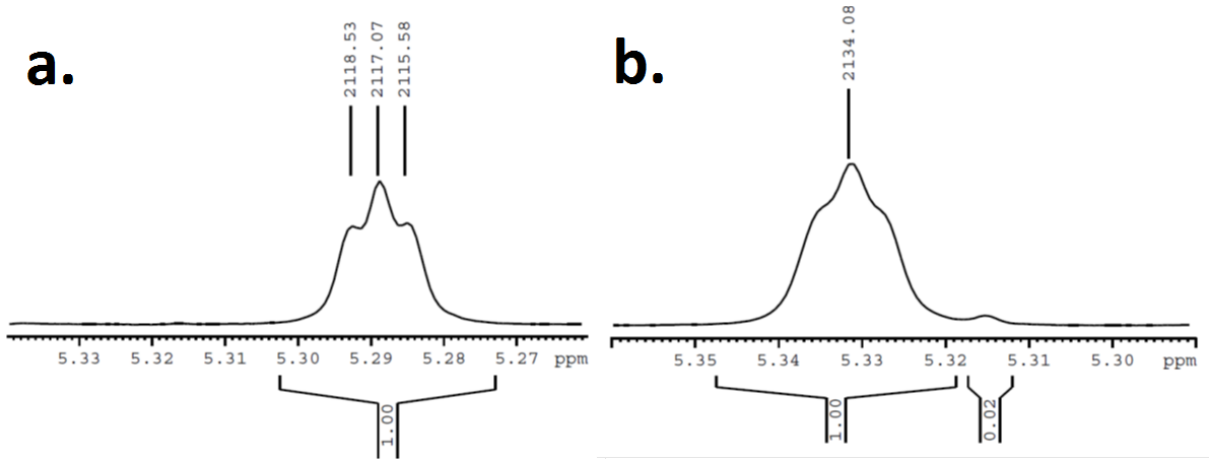


Figure 2.3. Segments of the ^{1}H NMR spectra showing the CHD peak of (*R*)-Mosher ester derived from **a.** the derivatized coupling product (*S*)-[D_1]**2.22** and **b.** authentic (*R*)-phenyl-[D_1]methanol.

The results show that the Suzuki-Miyaura coupling proceeds with net retention of configuration under these conditions and that the palladium complex formed as intermediate during transmetalation is microscopically configurationally stable.

3 Organolithiums

Organolithiums are compounds which contain a carbon atom that is directly bonded to lithium. Due to very high electropositivity of lithium, the negative charge on carbon atom is increased and thus these compounds behave like salts of carbanions.[28]

The term "carbanion" was first used by Wallace and Adams in 1933[29] to describe the reactivity of compounds that have a negative charge on the carbon atom. They exist in several hybridization states (Figure 3.1) and can be stabilized by different substituents on carbon either by polarisability (*tert* > *sec* > *prim*) or by resonance (substituents containing heteroatoms - CN, NO_2, COR).[28]

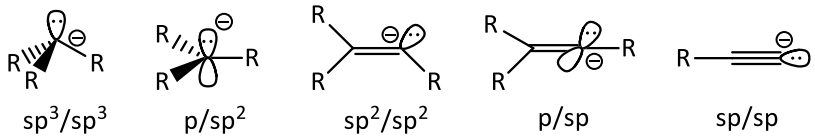


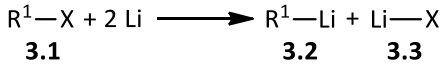
Figure 3.1. Hybridization states of carbanions.

In solution, organolithiums form aggregates - dimers (bulky organolithiums), tetramers (tertiary, secondary and β-branched primary organolithiums), hexamers (simple primary organolithiums) and higher. The aggregation is influenced by the solvent and can be reduced or completely diminished by various ligands (HMPA > PMDTA > (-)-sparteine > DMPU > DME > TMEDA > THF > Et_2O).[30]

3.1 Preparation

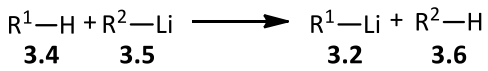
Organolithiums can be prepared in four general ways:[28]

1. Via reductive lithiation with metallic lithium - it is the simplest method, but not very useful for chiral, nonracemic reagents as most of the stereochemical integrity is lost (Scheme 3.1).



Scheme 3.1. Preparation of RLi with metallic lithium.

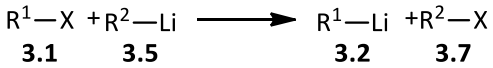
2. Via lithiation (metalation) - it is a common method where the most acidic hydrogen atom gets exchanged for lithium (Scheme 3.2).



3.4 **3.5** **3.2** **3.6**

Scheme 3.2. Hydrogen - lithium exchange.

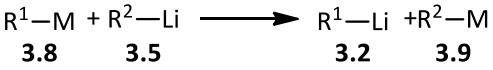
3. Via halogen-metal exchange - this reaction proceeds in the direction of the most stable organolithium formed from the more acidic compound and is useful for converting aryl and alkenyl halides to the respective organolithiums (Scheme 3.3).



3.1 **3.5** **3.2** **3.7**

Scheme 3.3. Halogen-lithium exchange.

4. Via metal-metal exchange (transmetalation) e. g. tin-lithium exchange - this exchange places the most electropositive metal on the most acidic carbon atom (Scheme 3.4).



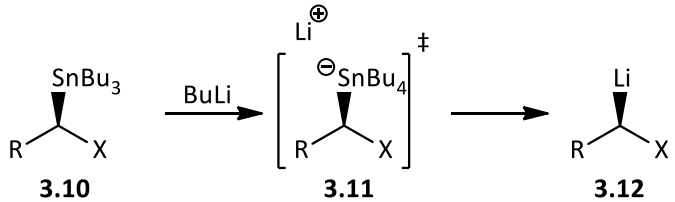
3.8 **3.5** **3.2** **3.9**

Scheme 3.4. Transmetalation.

3.1.1 Tin-Lithium exchange

Tin-lithium exchange is the most important transmetalation reaction because it proceeds stereospecifically with retention of configuration and produces the most stable and salt free organolithium. It is especially useful for synthesizing aryl, vinyl, and α-heteroatom substituted organolithiums because they are more stable than common reagents used for the exchange (MeLi, BuLi).[31]

The reaction goes through an ate complex **3.11** which contains five substituents bound to tin and gives the desired alkyllithium by cleavage of a tin-carbon bond (Scheme 3.5).



3.10 **3.11** **3.12**

Scheme 3.5. Mechanism of the tin-lithium exchange.

A heteroatom in α-position can serve as an anchor for lithium and direct it so that the reaction follows a retentive course.[32,33]

Reich and his team confirmed the formation of ate complex and characterized it by ^{119}Sn NMR spectroscopy in the reaction of tetramethylstannane and MeLi in THF after the addition of HMPA.[34]

3.2 Configurational stability

Configurational stability is not an absolute property of a compound, but it is dependent on many conditions like solvent, reactants, temperature and timescale. Based on the timescale of interest, one can talk about three types:[35]

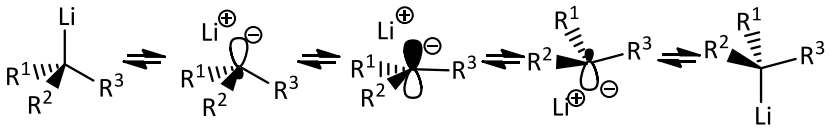
1. Macroscopic - it is measured for compounds that racemize slowly, anywhere from minutes to hours. The macroscopic timescale is determined by the formation of an enantiomerically pure organolithium without the presence of an electrophile in the reaction mixture, its addition to electrophile after a certain time and subsequent determination of enantriomeric excess of the isolated product.
2. Microscopic - it is measured for compounds that racemize quickly, over the course of seconds or less. It cannot be measured precisely as it corresponds to the time it takes the newly formed organolithium to react with an electrophile or to intramolecularly rearrange.
3. Compounds that racemize within 1/10 or 1/100 of a second can be investigated by NMR spectroscopy - peaks of the interconverting diastereomeric signals can be analyzed by line shape analysis at different temperatures.

The configurational stability of organolithiums can be greatly influenced if one hydrogen atom is replaced by a heteroatom. Boche et al. performed theoretical calculations that show, that the configurational stability increases in order of H < S < N < O < F.[36]

3.2.1 Inversion of configuration

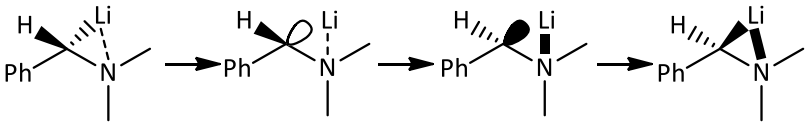
NMR spectroscopy proved to be essential for the mechanistical investigations of enantiomerization and inversion of configuration of organolithiums. Three possible mechanisms have been proposed:[37]

1. Dissociative - the first and rate determining step in this sequence is the dissociation of lithium from the tetrahedral carbon atom to form a solvent-separated ion pair. The carbanion inverts its configuration through a planar transition state and recombines with lithium (Scheme 3.6).



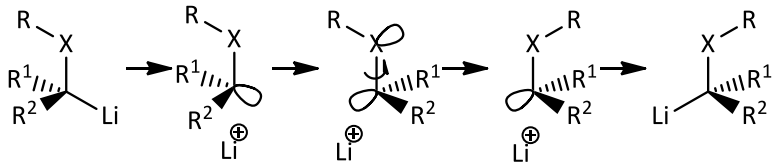
Scheme 3.6. Dissociative mechanism.

2. Conducted tour - lithium is delivered to the other side of the carbanion by coordination to a heteroatom like nitrogen present in the molecule and acting like a Lewis base. In the crystal structure of α-lithio-*N*,*N*-dimethylbenzylamine, the lithium is bridged between carbon and nitrogen atoms which seems to be first step of this mechanism (Scheme 3.7).



Scheme 3.7. Conducted tour mechanism.

3. Bond rotation - this mechanism can be found in organolithiums that contain sulfur or selenium in α-position. Inversion of configuration stems from the rate-determining step which is the rotation around the C-S or C-Se bond (Scheme 3.8).



Scheme 3.8. C-X bond rotation.

3.2.2 Hoffman test

In order to determine the configurational stability of optically active organolithiums, Hoffman developed a test based on kinetic resolution during the electrophilic substitution step that consists of two experiments.[37,38] The first one, the control experiment, is used to decide whether the organolithium is suitable for the test itself. The racemic organolithium is reacted with a racemic

electrophile and if the ratio of formed diastereomers lies between 1.5 and 3, the test can be performed with this chosen electrophile.

The second experiment is performed between the racemic organolithium and the enantiomerically pure electrophile. If the resulting ratio of diastereomes formed is equal to that of the first reaction, then the organolithium is completely labile with respect to this particular reaction. If the ratio is different, the organolithium is at least partially configurationally stable. If the organolithium is completely configurationally stable during this reaction then the diastereomers will form in equal amounts.

The differing results can be easily explained when one looks at the energy diagrams for the two reactions. In case of a configurationally labile organolithium, the inversion barrier for the enantiomers is much lower than the transition state energies for the formation of both diastereomeric products. Consequently, the interconversion of the enantiomers is faster than the reaction with the electrophile (Figure 3.2).

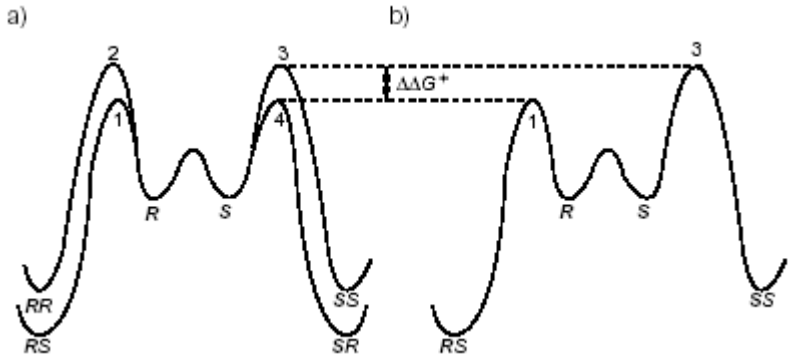


Figure 3.2. Energy diagram for the reaction of a configurationally labile and racemic organolithium. **a**) represents the reaction with racemic chiral electrophile and **b**) with an enantiomerically pure (*S*)-electrophile.

The ratio of the diastereomeric products in reaction a) formed by pathways 1 and 2 or 3 and 4 is only dependent on the transition states energy difference $\Delta\Delta G^{\ddagger}$. The same is true in reaction b) hence the ratios of diastereomeric products are equal in case of configurationally labile organolithiums.

The energy diagram for the reaction of configurationally stable organolithiums differs significantly (Figure 3.3).

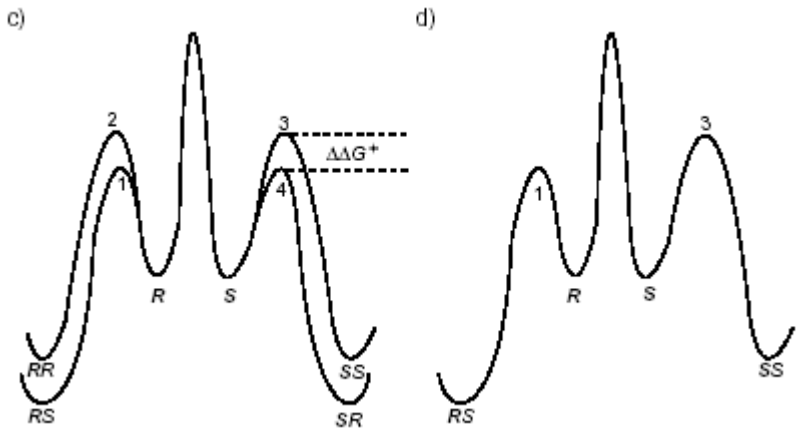
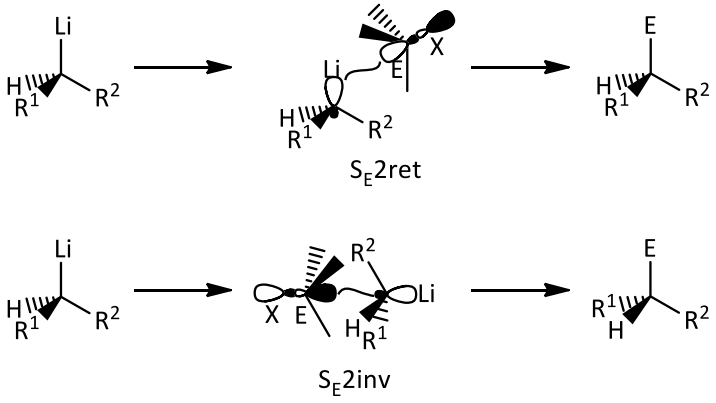


Figure 3.3. Energy diagram for the reaction of a configurationally stable and racemic organolithium. c) represents the reaction with a racemic chiral electrophile and d) with an enantiomerically pure (*S*)-electrophile.

In this case, the inversion barrier is greater than the transition state energies for the reaction with the electrophile and also than their difference in $\Delta\Delta G^{\ddagger}$, so the ratio of diastereomeric products for reaction c) is again determined by $\Delta\Delta G^{\ddagger}$. In case d) however, only one pathway is possible for each enantiomer of the organolithium and thus the resulting product ratio is equal to 1.

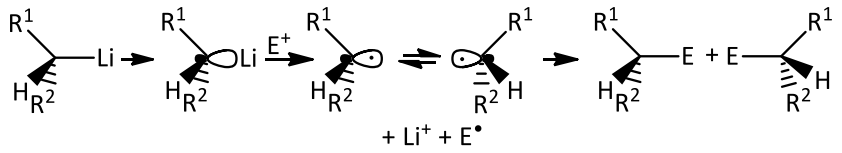
3.3 Reactions of organolithiums

Organolithiums are usually not isolated as products because of their instability, but instead are used as intermediates in various transformations. They undergo substitution reactions with a big variety of electrophiles. The non-stabilized organolithiums usually react with retention of configuration ($S_E2$ret) and stabilized ones with both retention ($S_E2$ret) and inversion ($S_E2$inv) (Scheme 3.9).[31] Both of these pathways are symmetry and energetically allowed.



Scheme 3.9. Retentive and invertive substitution reaction of an organolithium.

If a reaction goes through a radical mechanism, a stepwise single-electron transfer pathway, products can be formed with retention or inversion of configuration (Scheme 3.10).



Scheme 3.10. Radical mechanism of an organolithium.

Organolithiums with (mostly) a halogen in α position act as carbenoids and react in a slightly different way.[39,40,41] At low temperature they add to electrophiles but at higher temperature they start behaving as electrophiles themselves. They insert into C-H bonds, form alkanes by elimination, add to olefinic double bonds to produce cyclopropanes or react with other organolithiums under the formation of a new organolithium and Li-X.[42,43,44]

3.4 Classification of Organolithiums

3.4.1 Unfunctionalized organolithiums

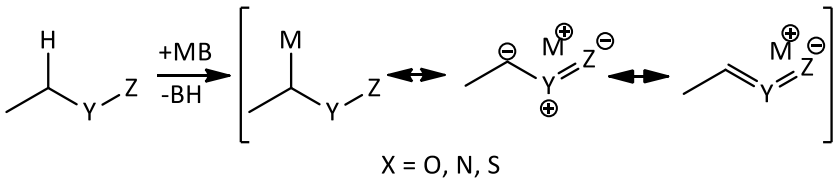
These organolithiums do not contain any heteroatoms in α-position and are more important from the historical point of view than from a synthetic one. The first chiral and nonracemic organolithium, (-)-2-lithiooctane, was prepared with enantiomeric excess of 20% 60 years ago.[45] Their configurational stability increases in order of benzylic < primary < secondary < tertiary < vinylic < cyclopropyllithiums.[31]

3.4.2 α-Heteroatom substituted organolithiums

These organolithiums contain heteroatoms like oxygen, nitrogen, phosphorus, sulfur or halogens and are further divided into two subgroups:

1. Non-dipole-stabilized organolithiums - lithium is attached to a tetrahedral carbon atom. They usually react with retention of configuration and thus are useful in the syntheses of chiral, nonracemic compounds.[30]

2. Dipole-stabilzed organolithiums - the stabilizing effect comes from the ability of a heteroatom Z to induce a positive charge on Y. The dipole stabilizes the carbanionic center (Scheme 3.11).[46]



Scheme 3.11. Stabilization of a carbanion through dipole.

3.4.2.1 α-Oxyorganolithiums

This is the most important group of heteroatom substituted alkyllithiums but they are difficult to form.[30] Oxygen's electron-withdrawing and thus activating effect on the carbon atom is overcome by the repulsion between its electron pairs and the C-Li bond.[46] Non-dipole-stabilized α-oxymethyllithiums like α-MOM-substituted or α-silyloxy-substituted alkyllithiums are synthetically useful because they are configurationally stable during their reactions.[47,48]

Dipole-stabilized α-oxyalkyllithiums, like the ones derived from alcohols protected by carbamoyloxy groups like Cb, Cbx and Cby have been studied extensively and are considered to be one of the configurationally most stable organolithiums (Figure 3.4).[37]

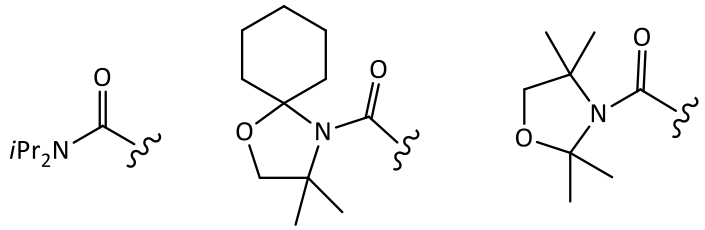


Figure 3.4. *N*,*N*-disubstituted carbamoyloxy protecting groups.

A lot of other α-oxyorganolithiums containing alkyl, heteroalkyl, tertiary allylic or bezylic substituents have been determined to be configurationally stable over long periods of time in the absence of THF.[49]

3.4.2.2 α-Aminoorganolithiums

Organolithiums that contain nitrogen in the α-position are the second most stable organolithiums. This is probably due to the lone pair on nitrogen having a more destabilizing effect than that of oxygen's. In order to receive the same results concerning configurational stability as with their oxygen substituted analogues, lower temperatures and absence of chelating agents during the course of reaction are required.[50]

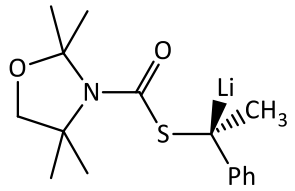
Non-dipole-stabilized analogues usually racemize readily so they are not particularly useful in asymmetric syntheses. The only exceptions are *N*-methyl pyrrolidines and piperidines which are stable for 45 min at -40°C.[50]

Dipole-stabilized ones on the other hand are synthetically more useful, for example as chiral auxiliaries in asymmetric alkylations.[51]

3.4.2.3 α-Thioorganolithiums

Non-dipole-stabilized thioorganolithiums like some α-lithiated sulfides were found to be microscopically configurationally stable in rearrangement reactions or if an electrophile was present in the reaction mixture at the time of their formation. Others, like benzylic lithiated sulfides are unstable on the microscopic timescale.[37]

Dipole-stabilized thioorganolithiums can be macroscopically configurationally stable. Carbanions derived from sulfoxides and sulfones are configurationally stable at low temperatures and lithiated tertiary thiocarbamates like compound **3.13** do not racemize for a few minutes up to a temperature of 0°C(Figure 3.5).[37]



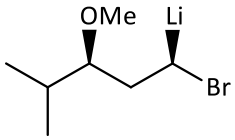
3.13

Figure 3.5. Tertiary dipole-stabilized α-lithiated thiocarbamate **3.13**.

3.4.2.4 α-Haloorganolithiums

The determination of the configurational stability of α-haloorganolithiums is challenging because of the chemical instability of these species. It depends on the type of halogen and the number of halogen atoms a compound contains. If the halogen is bromine, the stability pattern is clear, the

more bromine atoms there are, the more stable the bromoorganolithium is. In case of chlorine, the stability increases in order of *mono* < *tri* < *di*-substituted. Inspite of these limitations, it was found that α-bromoorganolithium **3.14** is configurationally stable below -110°C for up to 10 min (Figure 3.6).[52]

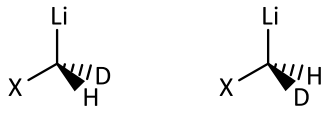


3.14

Figure 3.6. Macroscopically configurationally stable α-bromoorganolithium **3.14**.

3.5 Chiral methyllithiums

The Hammerschmidt group has been carrying out a lot of research in the field of the configurational stability of chiral, nonracemic α-heteroatom-substituted methyllithiums (Figure 3.7). The major part of the investigation was performed by Kapeller[53,54,55,56,57,58,59] and Wieczorek.[60,61]



(*S*)-**3.15** (*R*)-**3.15**

X = O, N, S, I, Br, Cl, F

Figure 3.7. α-heteroatom substituted chiral organolithiums.

3.5.1 Chiral oxy-[D_1]methyllithiums

Kapeller found that silyloxymethyllithiums **3.16** and **3.17**, germyloxymethillithium **3.18** and compound **3.19** are microscopically configurationally stable up to 0°C at the timescale of the *retro*-Brook, *retro*-germyl and [2,3]-Wittig rearrangement respectively. She also found that the most stable oxymethyllithiums were compounds **3.20**, **3.21** and **3.22** - for 10 min at -50°C, 30 s at -35°C and 3 min at -78°C, respectively (Figure 3.8).[53]

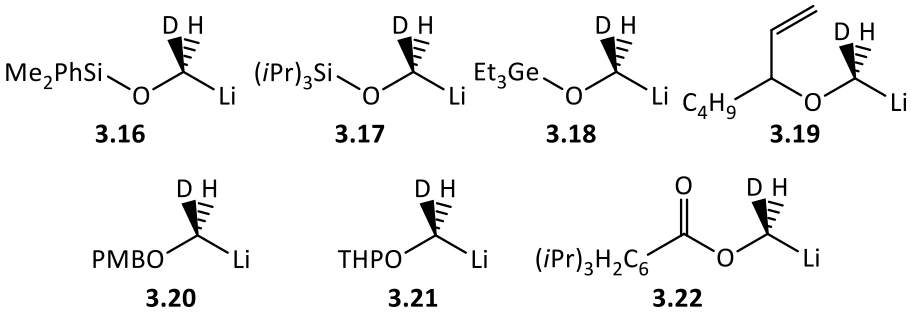


Figure 3.8. Configurationally stable chiral oxy-[D_1]methyllithiums.

3.5.2 Chiral amino-[D_1]methyllithiums

Aminomethyllithiums were experimentally found to be less configurationally stable than oxymethyllithiums. Phosphoramidate **3.23** was found to be microscopically configurationally stable up to 0°C at the timescale of the phosphoramidate-aminophosphonate rearrangement. *N*-protected aminomethyllithium **3.24** was already macroscopically configurationally labile at -95°C after 10 s, but *N*,*N*-dibenzylaminomethyllithium **3.25** was configurationally stable for 15 min at -95°C (Figure 3.9).[53]

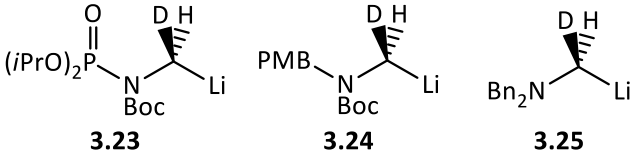


Figure 3.9. Tested chiral amino-[D_1]methlyllithiums.

3.5.3 Chiral thio-[D_1]methyllithiums

Enantiomerically pure thiomethyllithiums studied by Wieczorek were proven to be even more configurationally labile than aminomethyllithiums.[61] Thiomethyllithiums **3.26** and **3.27** were only partially microscopically stable on the timescale of the thiophosphate-mercaptophosphonate (product had 77% ee) and [2,3]-thia-Wittig (72% ee) rearrangement at -95°C, respectively. The benzyl thiol obtained by the [2,3]-thia-Wittig rearrangement of benzylthiomethyllithium **3.28** at -95°C had an ee of 26%. The configurationally most stable compound was allylthiomethyllithium **3.29** which was microscopically configurationally stable at -95°C at the timescale of the [2,3]-rearrangement (Figure 3.10).

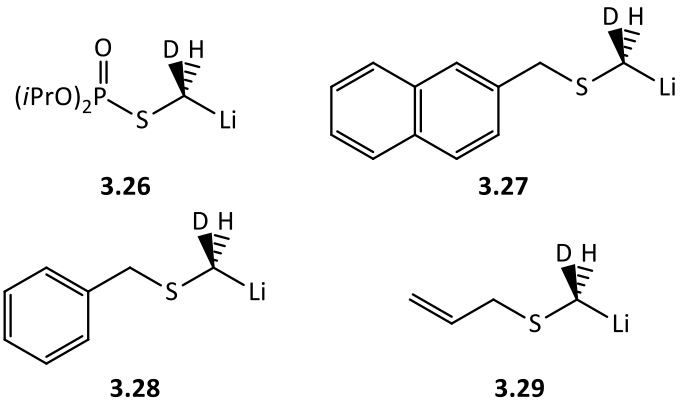
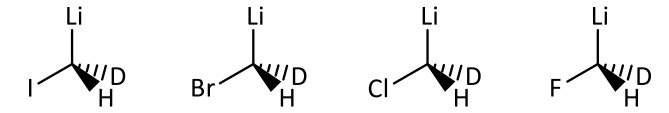


Figure 3.10. Tested thio-[D_1]methyllithiums.

3.5.4 Chiral halogen-[D_1]methyllithiums

Extensive research has been performed on enantiomerically pure [D_1]methyllithiums with halogens (iodine, bromine, chlorine and fluorine) as substituents (Figure 3.11). The results correspond to theoretical calculations that fluorine should be the most stable one.[36]



(*S*)-[D_1]**3.30** (*S*)-[D_1]**3.31** (*S*)-[D_1]**3.32** (*S*)-[D_1]**3.33**

Figure 3.11. Chiral halogen-[D_1]methyllithiums.

3.5.4.1 Chiral iodo-[D_1]methyllithium

Chiral iodo-[D_1]methyllithium ([D_1]**3.30**) was found to be microscopically configurationally labile at the timescale of addition to benzaldehyde even at -95°C, but the iodohydrin formed as product still had an ee of 28% at -30°C.[62]

3.5.4.2 Chiral bromo-[D_1]methyllithium

Chiral, nonracemic bromo-[D_1]methyllithium ([D_1]**3.31**) was found to be microscopically configurationally stable on the timescale of the addition to benzaldehyde even at -78°C, but chemically too unstable to determine its macroscopic stability.[61]

3.5.4.3 Chiral chloro-[D_1]methyllithium

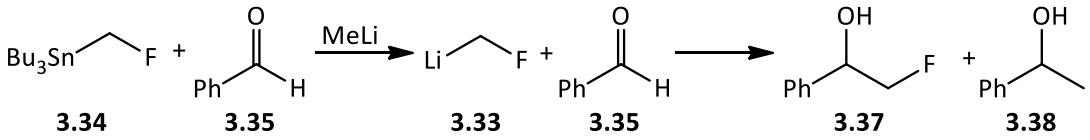
Chiral chloro-[D_1]methyllithium ([D_1]**3.32**) was found to be macroscopically configurationally stable for 30 s at -78°C but it is chemically very labile at this temperature so only traces of the product were isolated.[58]

3.5.4.4 Chiral fluoro-[D_1]methyllithium

Chiral fluoro-[D_1]methyllithium ([D_1]**3.33**) prepared by tin-lithium exchange with MeLi was found to be microscopically configurationally stable at the timescale of the addition to benzaldehyde at -70°C. However, it is chemically very labile even at this low temperature. The side reaction, the addition of MeLi to benzaldehyde, interfered heavily with tin-lithium exchange. Therefore, the yield of fluoromethyllithium formed was low.[53]

3.6 Determination of configurational stability of (*R*)- and (*S*)-fluoro-[D_1]methyllithium

My work in this field is a continuation of Kapeller's doctoral thesis.[53] During the investigation of the microscopic configurational stability of chiral fluoro-[D_1]methyllithium ([D_1]**3.33**) using benzaldehyde (**3.35**) as electrophile, she encountered two problems (Scheme 3.12).



3.34 **3.35** **3.33** **3.35** **3.37** **3.38**

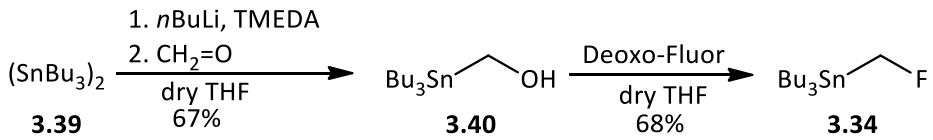
Scheme 3.12. Addition reaction used to study the configurational stability of fluoro-[D_1]methyllithium ([D_1]**3.33**).

The first was the high chemical instability of fluoromethyllihium (**3.33**) which easily decomposes to LiF and carbene. The second was the low yield of the fluorohydrin **3.37** due to the fast addition of MeLi to benzaldehyde as competing reaction to tin-lithium exchange. Because of that she was only able to perform experiments up to -70°C.

To increase the chemical stability of fluoromethyllithium, low reaction temperatures are advantageous. I hypothesized that using a more sterically hindered electrophile than benzaldehyde would decrease the rate of the addition of MeLi to the electrophile in favor of transmetalation. Thus more time would be left for the formation of fluoromethyllithium (**3.33**). If that was the case the amount of byproduct relative to the amount of product derived from fluoromethyllithium would decrease with increasing steric hindrance of the electrophile.

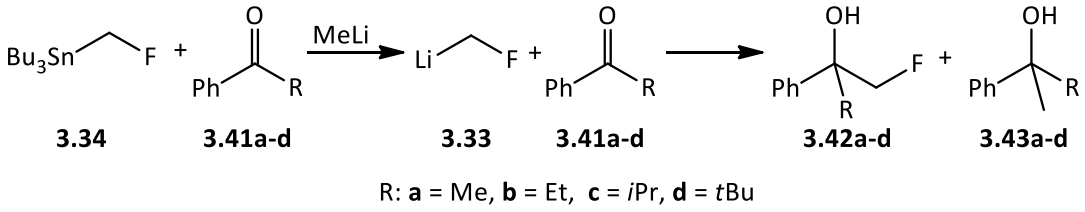
3.6.1 Search for better electrophile than benzaldehyde

Because the deuterated tributyl(fluoromethyl)stannane ([D_1]**3.34**) is difficult to synthesize I optimized the reaction conditions with unlabelled stannane **3.34** synthesized easily from bis(tributyl)tin (**3.39**). It was reacted first with *n*BuLi and then with formaldehyde to yield tributylstannylmethanol (**3.40**), a widely used intermediate in our group in 67% yield. Reaction with Deoxo-Fluor® furnished the unlabeled tributyl(fluoromethyl)stannane (**3.34**) in 68% yield (Scheme 3.13).[53]



Scheme 3.13. Synthesis of unlabeled tributyl(fluoromethyl)stannane (**3.34**).

All experiments performed to optimize the reaction conditions were carried out with 2 eq. of MeLi (commercial 3 M solution in diethoxymethane was diluted to 1 M with dry THF) and 2 eq. of various electrophiles relative to fluoromethylstannane in dry THF at -78° and -95°C (Scheme 3.14).



Scheme 3.14. Experiment used to test the formation of the byproduct.

The experiments were started with acetophenone (**3.41a**) and continued through propiophenone (**3.41b**) and isobutyrophenone (**3.41c**) to 2,2-dimethylpropiophenone (**3.41d**). The results of these experiments can be found in Table 3.1.

R	Entry	T (°C)	OH, Ph, R **3.43a-d**	$MeSnBu_3$ **3.44**	OH, Ph, R, F **3.42a-d**	Bu_3Sn, F **3.34**
Me (a)	1	-95	1.03	1.00	1.00	1.15
	2	-78	3.85	1.00	0.53	5
Et (b)	3	-95	1.79	1.00	0.94	0.85
	4	-78	4.15	1.00	0.91	3.12
***i*Pr (c)**	5	-95	0.75	1.00	0.94	0.60
	6	-78	0.31	1.00	0.93	1.66
***t*Bu (d)**	7	-95	0.87	1.00	0.79	0.40
	8	-78	2.72	1.00	0.66	0.86

Table 3.1. Relative ratios of products formed during the synthesis of fluoromethyllithium and its addition to various nucleophiles.

The ratios were determined by ^{1}H NMR spectroscopy of the crude products after work-up.

The table shows the relative ratios of tertiary alcohols **3.43a-d**, $MeSnBu_3$ (**3.44**) as internal standard set to 1, fluorohydrins **3.42a-d** and starting material (**3.34**). There are a couple of things that can be concluded from the ratios found in the table. They show that there is apparently more to the story about the byproduct formation than just steric hindrance. No trend is visible in the ratios of **3.43a-d** to **3.44** going from acetophenone to 2,2-dimethylpropiophenone at none of the studied temperatures other than in general less byproduct formed at lower temperature (entries 1,3,5,7 and 2,4,6,8).

Chart 3.1 illustrates the results a little clearer than the table itself. It shows the relative amount of the byproducts, the tertiary alcohols **3.43a-d**, [y-axis, compared to $MeSnBu_3$ (**3.44**) set to 1] dependent on the electrophile [x-axis, labeled by the substituent attached to PhC(O)].

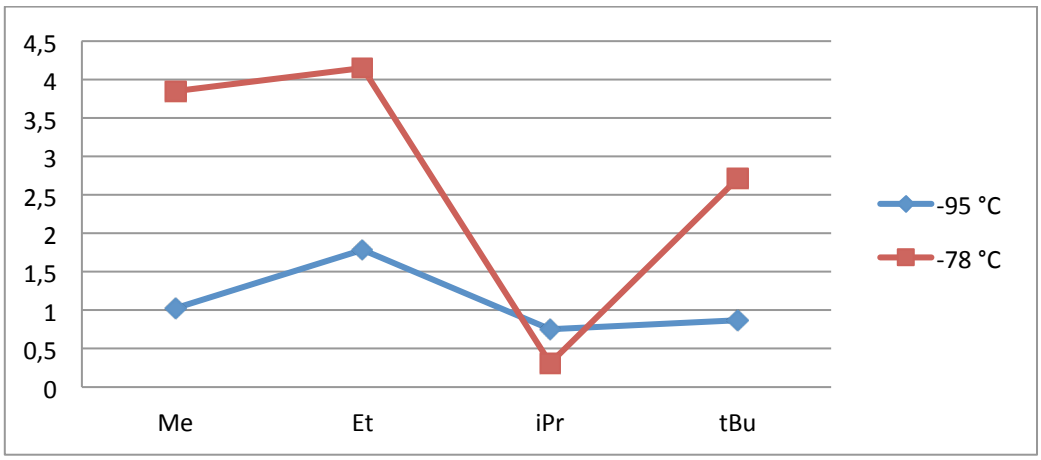


Chart 3.1. Relative amount of tertiary alcohols **3.43a-d** formed dependent on the electrophile at -78°C and -95°C compared to $MeSnBu_3$ (**3.44**) which is set to 1.

The best results in terms of the lowest byproduct yield were obtained with isobutyrophenone at both temperatures (entries 5,6) followed by 2,2-dimethylpropiophenone at -95°C (entry 7), acetophenone at -95°C (entry 1), propiophenone at -95°C (entry 3) followed by 2,2-dimethylpropiophenone at -78°C (entry 8), acetophenone at -78°C (entry 2) and propiophenone at -78°C (entry 4).

Chart 3.2 shows the chemical stability of fluoromethyllithium dependent on the electrophile and temperature.

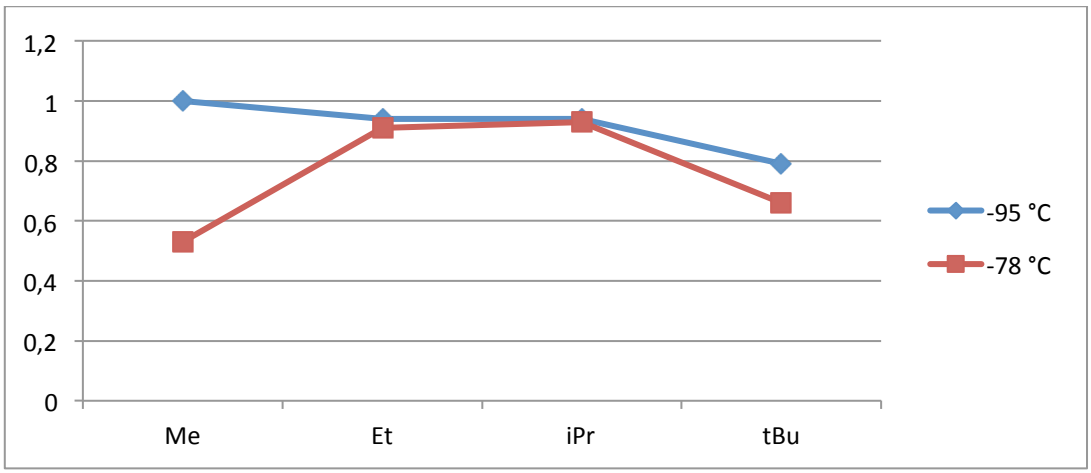


Chart 3.2. Relative amount of product **3.42a-d** dependent on the electrophile compared to $MeSnBu_3$ (**3.44**) which is set to 1. No decomposition is observed when the relative amount of product is equal to 1.

Fluoromethyllithium is chemically stable when the relative amount of fluorohydrin **3.42** is equal to 1, indicating that all fluoromethyllithium formed is reacting with the electrophile. As fluorohydrins **3.42** are more volatile than $MeSnBu_3$ (**3.44**), their amount could be somewhat lower than 1 even when the fluoromethyllithium (**3.33**) is chemically stable at the timescale of its addition to the ketone. Here the trend is a little more pronounced and as expected. At -95°C, the chemical stability decreases with increasing steric hindrance of the electrophile because the reaction rate for the addition gets lower. Consequently, the life span of the fluoromethyllithium (**3.33**) gets longer and the chance for decomposition increases. At -78°C the trend is identical except when acetophenone is the electrophile. This experiment with acetophenone at -78°C was repeated a few times. The results were reproducible meaning that there must be another (unknown) factor influencing the product formation. Presumably the addition of MeLi to the electrophile is faster than transmetalation.

The last chart 3.3 shows the relative amount of starting material (**3.34**) left after the reaction was quenched compared to the amount of $MeSnBu_3$ (**3.44**).

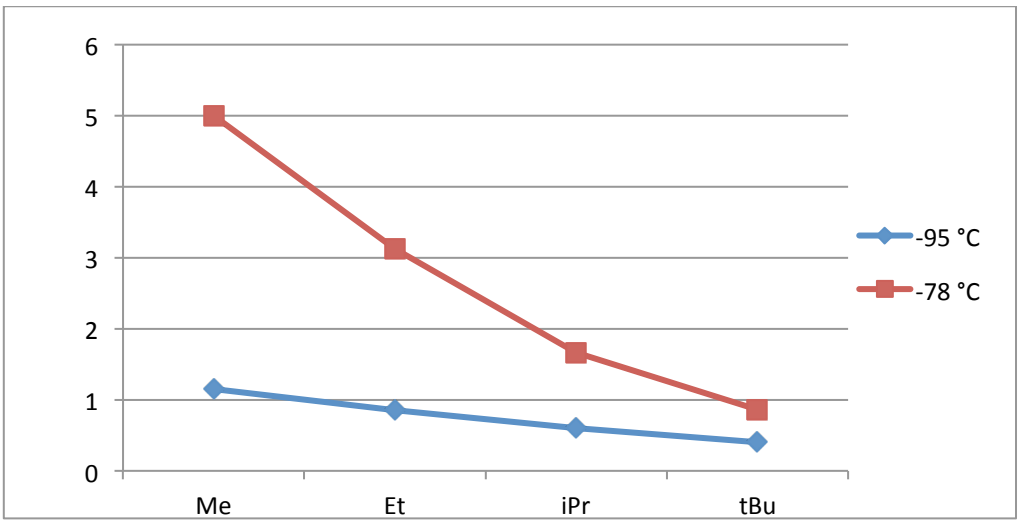
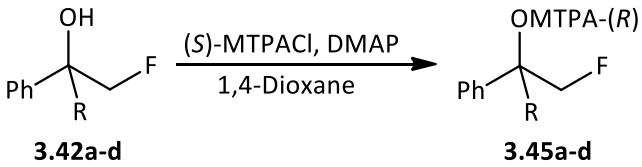


Chart 3.3. Relative amount of starting material **3.34** left dependent on the electrophile.

The amount of recovered starting material decreased with increasing steric hindrance of the electrophile. When the rate of addition of MeLi to the electrophile was slowed down, more MeLi was available for transmetalation and consequently less starting material is left.

These results suggest that the best electrophile was isobutyrophenone but before using it to intercept chiral fluoro-[D_1]methyllithium ([D_1]**3.33**), esterification of the respective fluorohydrin **3.42c** had to be checked with (*S*)-Mosher chloride. If the esterification did not work as it is a tertiary alcohol, isobutyrophenone would have to be replaced by another ketone, possibly acetophenone. The "ee" at the halogen bearing carbon atom of chloro- and bromohydrins derived from chiral halo-[D_1]methyllithium and benzaldeyhde could be determined easily by ^{1}H NMR spectroscopy of the Mosher esters. Unfortunately, this reaction only worked with the fluorohydrin **3.42a** derived from acetophenone. (Scheme 3.15).



3.42a-d **3.45a-d**

R: **a** = Me, **b** = Et, **c** = *i*Pr, **d** = *t*Bu

Scheme 3.15. Attempted derivatization of flurohydrins **3.42a-d** with (*S*)-Mosher chloride.

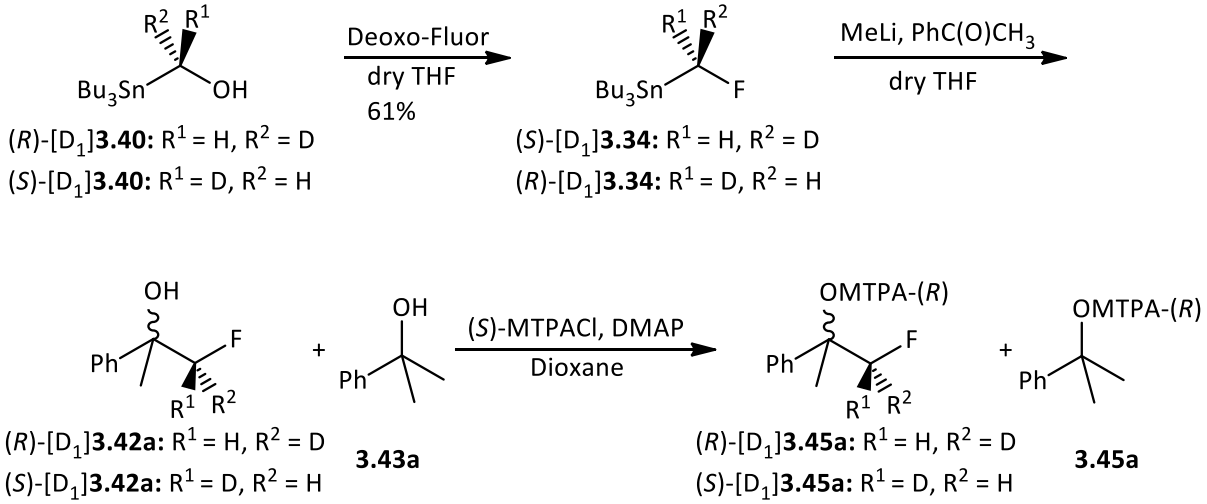
Fluorohydrins **3.42a-d** have two stereogenic centers. Separation of the diastereomers with (*R*)- and (*S*)-configuration at the carbon atom bearing the hydroxyl group should be possible, irrespective of the configuration at the deuterium bearing carbon atom.

^{1}H NMR spectroscopy of each sample would give the quantities of the diastereomers with the same configuration at the hydroxyl bearing carbon atom, but opposite configuration at the deuterium bearing carbon atom. HPLC of **3.42b-d** however did not give the desired results, because the two peaks were overlapping too much on an HPLC column with a chiral stationary phase (Chiralcel OD-H®) to be useful. Therefore, acetophenone had to be used as electrophile for studying the configurational stability of fluoro-[D_1]methyllithium ([D_1]**3.33**).

3.6.2 Experiments with deuterated tributyl(fluoromethyl)stannane [D_1]3.34

The experiments in the labeled series with deuterated stannane [D_1]**3.34** were performed in the same way as in the unlabeled series. I also wanted to increase the temperature as far as possible to see its effect on yield and ee.

Stannane [D_1]**3.34** was prepared from tributylstannyl-[D_1]methanol ([D_1]**3.40**) in analogy to the unlabeled compound by reaction with Deoxo-Fluor® and transmetalated. The fluoro-[D_1]methyllithium ([D_1]**3.33**) and methyllithium were added to acetophenone to yield fluorohydrin [D_1]**3.42a** and 1-phenylethanol (**3.43a**) as a byproduct, respectively. The two tertiary alcohols could not be separated before conversion to their Mosher ester, but afterwards (Scheme 3.16).



(*R*)-[D_1]**3.40:** R^1 = H, R^2 = D
(*S*)-[D_1]**3.40:** R^1 = D, R^2 = H

(*S*)-[D_1]**3.34:** R^1 = H, R^2 = D
(*R*)-[D_1]**3.34:** R^1 = D, R^2 = H

(*R*)-[D_1]**3.42a:** R^1 = H, R^2 = D
(*S*)-[D_1]**3.42a:** R^1 = D, R^2 = H

3.43a

(*R*)-[D_1]**3.45a:** R^1 = H, R^2 = D
(*S*)-[D_1]**3.45a:** R^1 = D, R^2 = H

3.45a

Scheme 3.16. Preparation of fluoro-[D_1]methyllithium ([D_1]**3.33**), its addition to acetophenone and esterification of alcohols [D_1]**3.42a** and **3.43a** with (*S*)-Mosher chloride.

As the enantioselectivity of the addition of the chiral fluoro-[D_1]methyllithium to acetophenone is zero, (*R*)- and (*S*)-configuration at C-1 were always formed in equal amounts, resulting in products with zero "ee" at C-1. The "ee" at C-2 is determined by the configurational stability of fluoro-

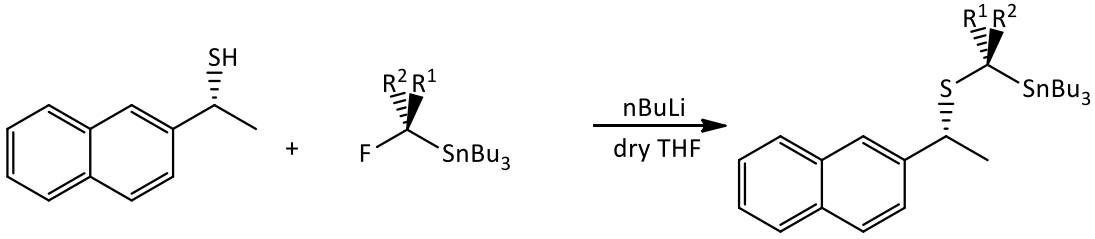
[D_1]methyllithium ([D_1]**3.33**) and could vary from 0% (racemization) to 100% (configurational stability at the time scale of the addition to acetophenone).

Experiments with both (*R*)- and (*S*)-fluoromethylstannanes [D_1]**3.34** at -78°C, -50°C and -30°C were performed. The results in Table 3.2 suggest that fluoromethyllithium is not microscopically configurationally stable at any temperature studied.

Sample	T (°C)	Enantiomeric excess (%)
(*R*)-[D_1]**3.34**	-78	90
(*S*)-[D_1]**3.34**	-78	88
(*R*)-[D_1]**3.34**	-50	93
(*R*)-[D_1]**3.34**	-30	93
(*S*)-[D_1]**3.34**	-30	90

Table 3.2. Enantiomeric excess of (*R*)-Mosher ester of [D_1]**3.42a** derived from either (*R*)- or (*S*)-[D_1]**3.34**.

What did not make sense is the fact that configurational stability did not decrease with increasing temperature. This would be expected of a configurationally labile species. It was suspected that the starting material was not enantiomerically pure. This was confirmed by the S_N2 reaction with homochiral thiol (*R*)-**3.46** used for the determination of the ee of (halomethyl)stannanes (Scheme 3.17).[53]



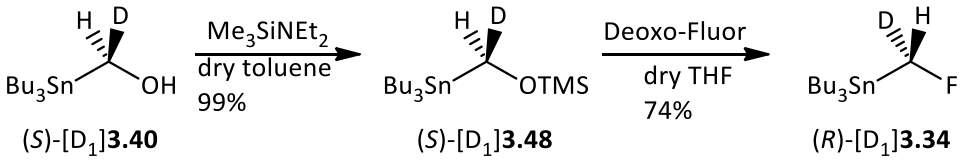
(*R*)-3.46

(*S*)-[D_1]**3.34:** R^1 = H, R^2 = D
(*R*)-[D_1]**3.34:** R^1 = D, R^2 = H

(*R*)-[D_1]**3.47:** R^1 = H, R^2 = D
(*S*)-[D_1]**3.47:** R^1 = D, R^2 = H

Scheme 3.17. Determination of ee of [D_1]**3.34**.

The ee of the thiol (*R*)-[D_1]**3.47** was found to be 86% and that of (*S*)-[D_1]**3.47** 89%. In order to prove that fluoro-[D_1]methyllithium was indeed microscopically configurationally stable at the time scale of its addition to acetophenone, enantiomerically pure (*R*)-[D_1]**3.34** was prepared. (*S*)-tributylstannyl-[D_1]methanol was silylated and then reacted with Deoxo-Fluor® (Scheme 3.18).[53]



(*S*)-[D_1]**3.40** (*S*)-[D_1]**3.48** (*R*)-[D_1]**3.34**

Scheme 3.18. Preparation of enantiomerically pure (*R*)-[D_1]**3.34**.

Fluorohydrins (*S*)-[D_1]**3.42a** formed from this material were derivatized again with (*S*)-MTPACl and their enantiomeric excess was determined to be ≥99% at temperatures ranging from -78°C to 0°C (Table 3.3).

Sample	T (°C)	Enantiomeric excess (%)
(*S*)-[D_1]**3.42a**	-78	98
(*S*)-[D_1]**3.42a**	-30	98
(*S*)-[D_1]**3.42a**	0	98

Table 3.3. Enantiomeric excesses of fluorohydrins (*S*)-[D_1]**3.42a** formed at various temperatures.

The chemical instability of fluoro-[D_1]methyllithium interfered with the yield, but the (very) small amounts of deuterated fluorohydrins [D_1]**3.42a** were enough for the determination of "ee". The ratios of fluoro-[D_1]methyllithium {(*S*)-[D_1]**3.33**} generated by transmetalation with release of $MeSnBu_3$ and fluorohydrins (*S*)-[D_1]**3.42a** at various temperatures are given in Table 3.4.

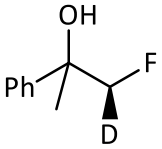
Temperature (°C)		$MeSnBu_3$
-78	0.43	1
-30	0.34	1
0	0.04	1

Table 3.4. Relative yields of fluorohydrin (*S*)-[D_1]**3.42a** representing the survival of (*S*)-fluoro-[D_1]methyllithium {(*S*)-[D_1]**3.33**} compared to $MeSnBu_3$ representing the total of (*S*)-fluoro-[D_1]methyllithium {(*S*)-[D_1]**3.33**} formed set to 1.

Encouraged by the fact that 4% of the fluoro-[D_1]methyllithium ([D_1]**3.33**) formed survived at 0°C I also tried to investigate its macroscopic configurational stability as well. At first, a preliminary

experiment was performed in the unlabeled series at -120°C in Me_2O (because THF freezes by -108°C). The fluoromethyllithium (**3.33**) was aged for 60 seconds and then 2,2-dimethylpropiophenone (**3.41d**) was added. The second and last experiment was performed at -95°C under standard conditions (dry THF, 2 eq. of MeLi). The fluoromethyllithium (**3.33**) was aged for 30 seconds before acetophenone was added. Unfortunately, no fluorohydrin (**3.42a**) was formed in either reaction, although some of $MeSnBu_3$ (**3.44**) was formed. Therefore, fluoromethyllithium (**3.33**) is chemically too unstable and too short-lived to investigate its macroscopic configurational stability.

In conclusion, fluoro-[D_1]methyllithium ([D_1]**3.33**) was found to be microscopically configurationally stable relative to its addition to acetophenone up to 0°C.

These results were also published in Chemistry – A European Journal.[62]

4 Boronic esters

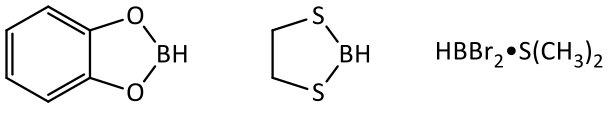
Triethylborane and ethylboronic acid, the first organic compounds containing carbon-boron bonds, were described in 1860.[63] Although no natural organoboronic acid was isolated as natural product so far, boric acid is important as a micronutrient for plants[64] and is a component of the antibiotics aplasmomycin[65] and boromycin.[66] The carbon-boron bond is weaker than the carbon-oxygen bond by about 125-165 kJ/mol meaning that the functional groups on boron bound through a carbon atom can be treated without affecting the alkoxy ligands.[67]

Boronic acids and their esters are very useful reagents in organic (especially asymmetric) synthesis due to their chemical stability, steric properties, low toxicity and overall simple handling.[68] They are relatively air stable but have to be protected from moisture. Another advantage of boronic esters, especially the ones derived from bulky cyclic diols, is that they can be treated - extracted, distilled and chromatographed like usual organic compounds. They are especially useful for the Suzuki-Miyaura coupling already described in chapter 2, the synthesis of unsaturated compounds, asymmetric reductions and for chiral CHCl insertions.

4.1 Synthesis

A few syntheses of boronic acids and their esters are known, but two of them are the most used and general:[68,69]

1. Via lithium or Grignard reagents - classical and efficient method, where lithium or Grignard reagents react with trialkyl borates to form either boronic acids or their esters based on the borate and reaction conditions.
2. Via hydroboration - during this reaction catecholborane (**4.1**), dithiaborolane (**4.2**) or dibromoborane-dimethyl sulfide (**4.3**) (Figure 4.1) add to multiple bonds.

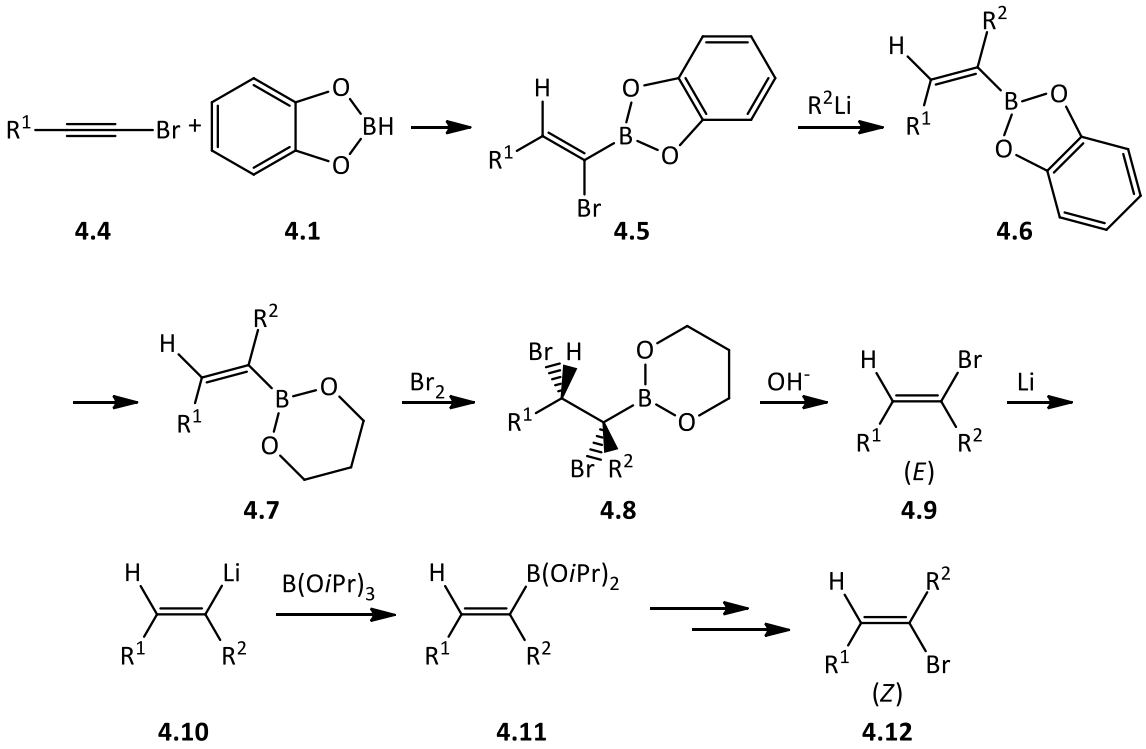


4.1 **4.2** **4.3**

Figure 4.1. Boranes used for hydroboration.

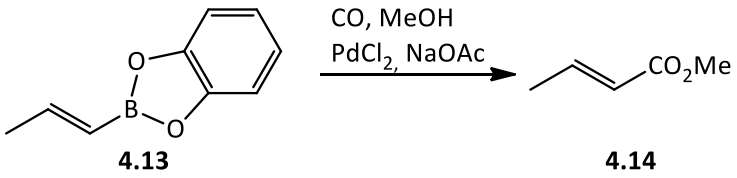
4.2 Uses in organic synthesis

Boronic esters are used for the stereospecific preparation of haloalkenes **4.9** and **4.12** of *E* or *Z* geometry (Scheme 4.1).



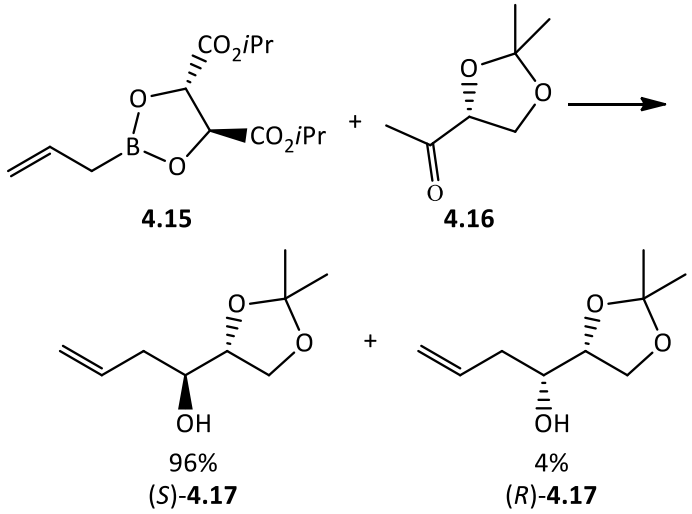
Scheme 4.1. Preparation of *E* and *Z* haloalkenes **4.9** and **4.12** through boronic esters **4.5** and **4.11**.

These can be synthesized from bromoalkynes **4.4** or vinyllithiums **4.10** where the *E* and *Z* geometry can get interconverted through a boronic ester as intermediate.[68,70] Organoboronic compounds **4.13** can be coupled with carbon monoxide with palladium as catalyst in the presence of an alcohol to form carboxylic esters that have the same geometry as the starting boronic esters (Scheme 4.2).[71]



Scheme 4.2. Coupling of boronate **4.13** with CO in presence of a Pd catalyst.

Chiral nonracemic allylboronic esters derived from (+)-phenylboranediol or diisopropyl tartrate **4.15** act as chiral directors in reactions with aldehydes. One of the alcohols is formed with high diastereoselectivity (Scheme 4.3).[72]

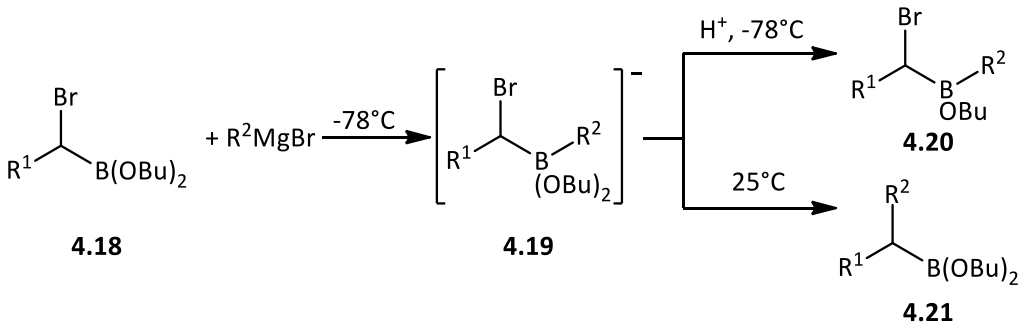


4.15 **4.16**

Scheme 4.3. Allylboronic ester **4.15** derived from diisopropyl tartrate acts as chiral director.

4.2.1 α-Haloboronic esters

Matteson first described α-bromo- and chloroboronic esters in 1959 when he prepared them through radical addition to dibutyl ethyleneboronate (**4.18**).[73] When these esters were reacted with a nucleophile, two products were formed from the same intermediate **4.19** depending on the temperature. At room temperature, the substituent R^2 added to boron via Grignard reagent migrated to the α-carbon atom and replaced the halide to form **4.21**. However, at lower temperatures one BuO at boron was substituted to form **4.20** (Scheme 4.4).[74,75]

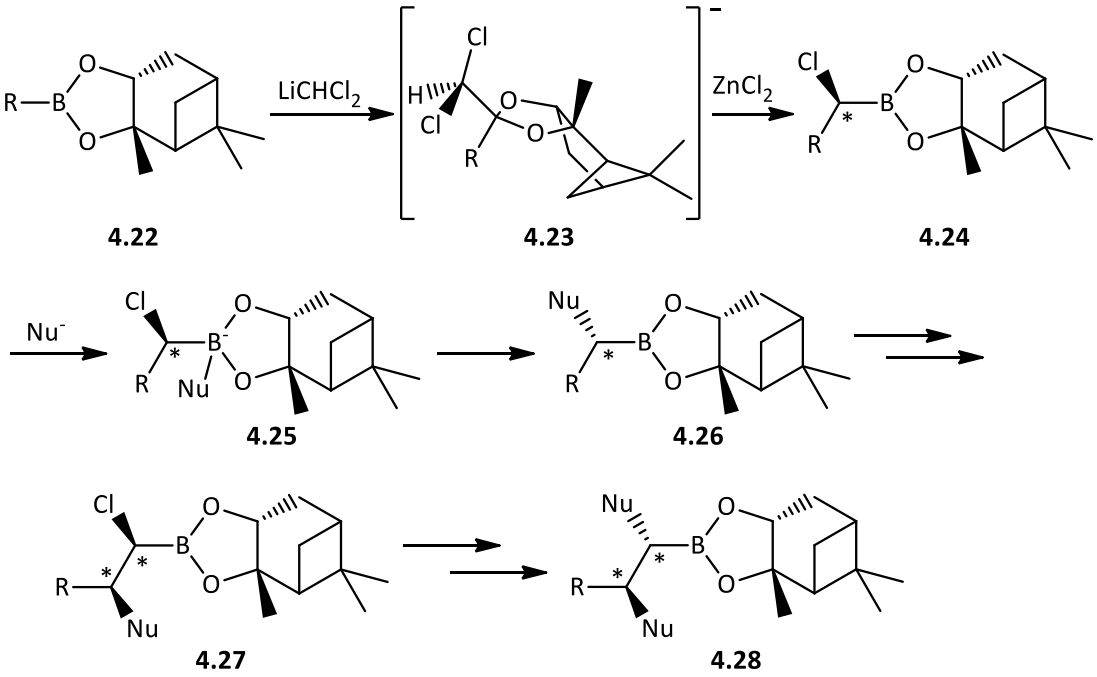


4.18 **4.19** **4.20** **4.21**

Scheme 4.4. Reaction pathways of boronate **4.18** with a nucleophile depending on the reaction temperature.

During the migration, the configuration of the carbon atom with the halide gets inverted whereas the configuration of the migrating group stays the same.

In 1980, Matteson reported the synthesis of α-chloroboronic esters **4.24** by homologation of boronic esters **4.22** (Scheme 4.5).[76]

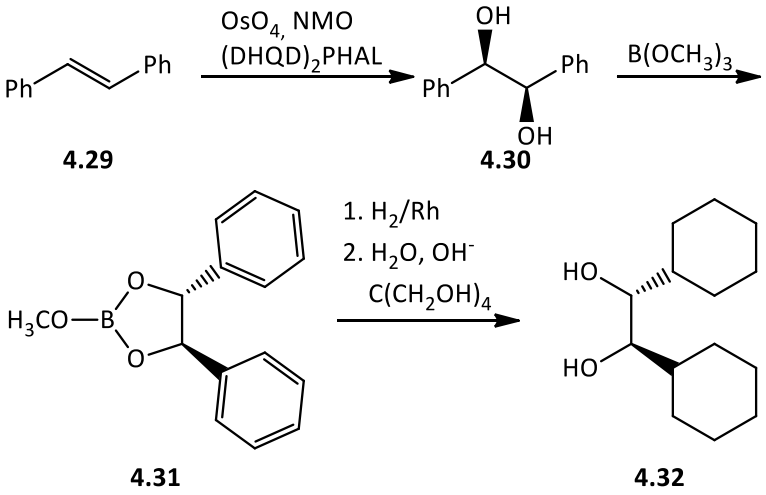


Scheme 4.5. Mechanism of the homologation of boronates with $LiCHCl_2$ and subsequent substitution of the halide with a Nu^-. Asterisk denotes new asymmetric center.

He reacted esters **4.22** with (dichloromethyl)lithium at -100 °C. The ate complex **4.23** formed rearranged to the desired α-chloroboronic ester **4.24** upon warming to room temperature. The rearrangement was later optimized and made much more efficient with zinc chloride as catalyst which complexes the chloride ions. When chiral nonracemic boronic esters **4.22** derived from (+)-pinane-2,3-diol were used in combination with zinc chloride, the diastereomeric ratios of the α-chloroboronates **4.24** were significantly improved. The halogen can be stereospecifically substituted with different nucleophiles with inversion of configuration.[77] The new asymmetric center is marked by a star and is formed highly diastereoselectively (ratio 100:1).

The reaction tolerates primary, secondary, tertiary or cyclic alkyl, alkenyl, allylic, arylic and benzylic substituents at boron.[78] The stereochemistry of the new asymmetric center depends on the stereochemistry of the chiral diol as director attached to boron. It is also possible to change chiral directors by hydrolysis of the boric ester, which is not trivial, and repeated esterification with a different diol for each new asymmetric center so that more complex molecules can be

synthesized. Apart from pinanediol, (*R*)-(*R**,*R**) and (*S*)-(*S**,*S**)-1,2-dicyclohexyl-1,2-ethanediol **4.32** were successfully used as a chiral director. Their advantages are easy preparation - they can be prepared from *trans*-stilbene via Sharpless dihydroxylation in enantiomerically pure form (Scheme 4.6).[75]

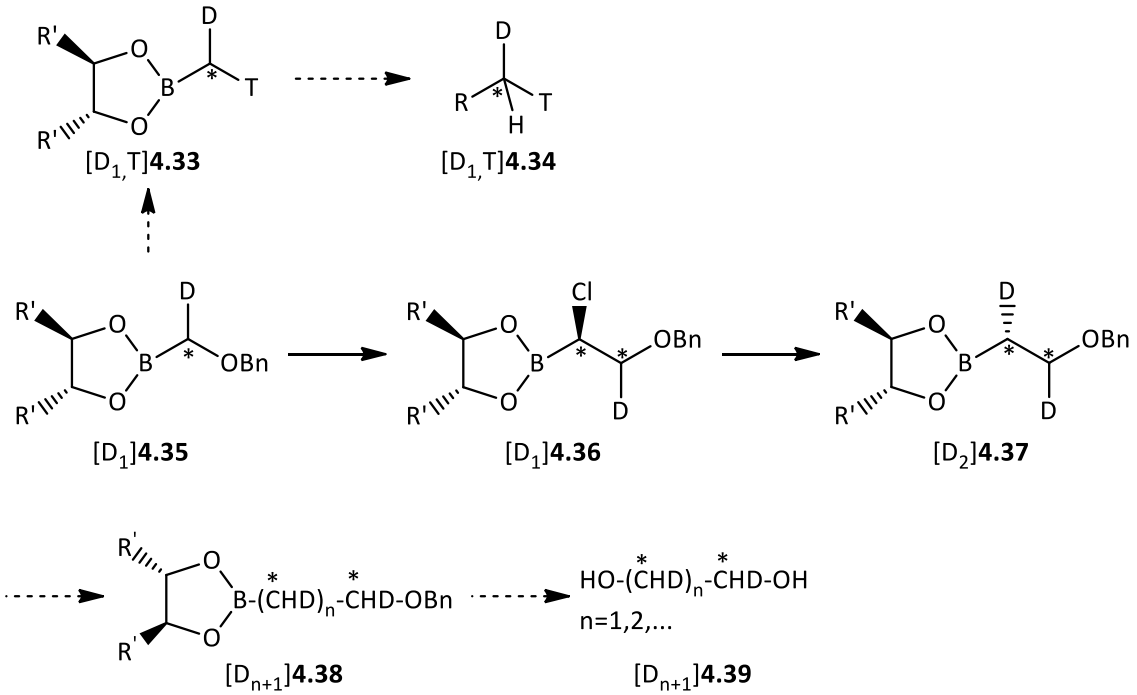


Scheme 4.6. Synthesis of (*R*)-(*R**,*R**)-1,2-dicyclohexyl-1,2-ethanediol (**4.32**).

The usefulness of this method has been shown by the total synthesis of many natural products, among them carbohydrates[79] and pheromones like stegobinone and stegobiol.[80,81]

4.3 Attempted preparation of deuterated 1,ω-diols through α-halo boronic esters

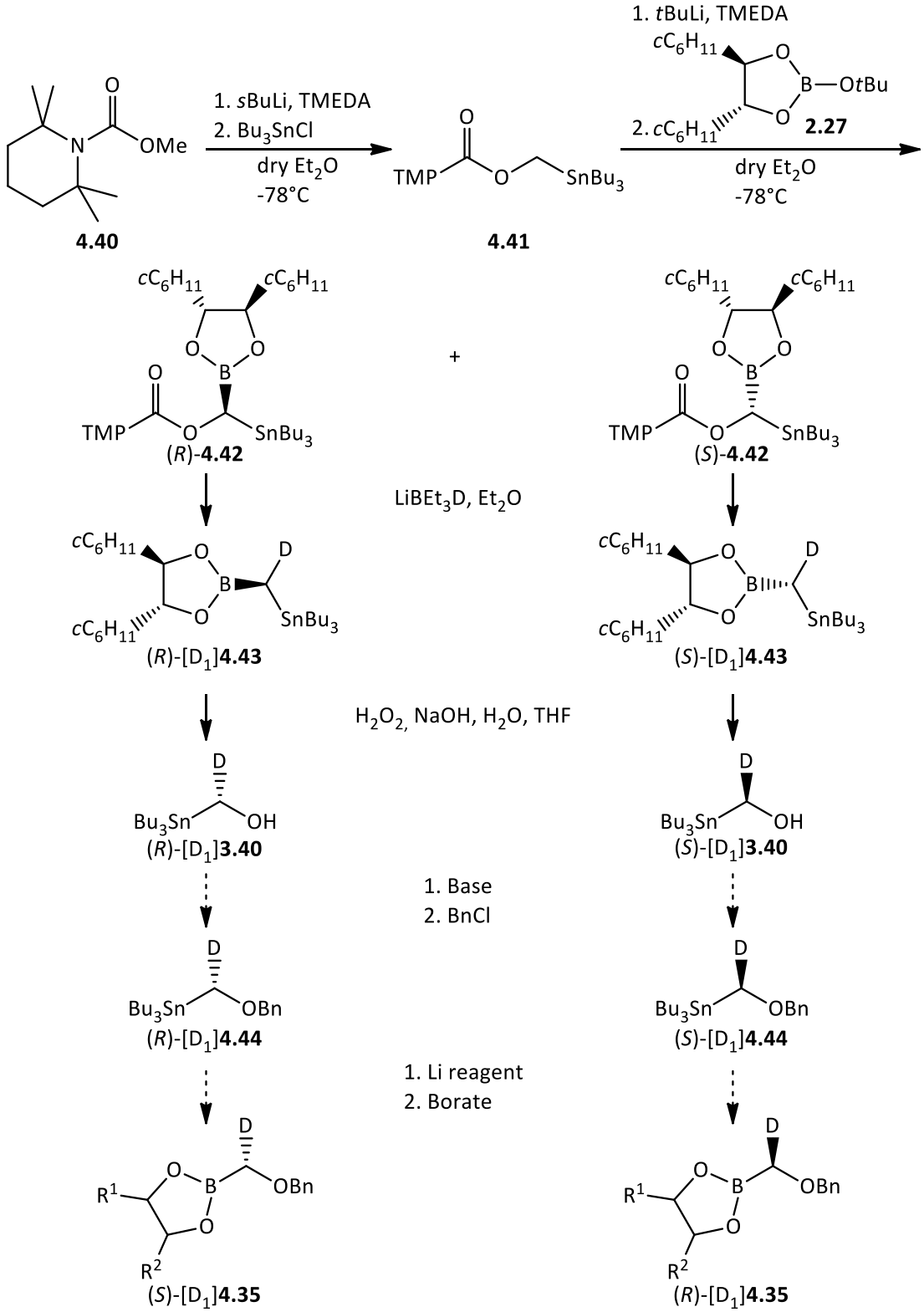
I thought that I could use the methodology developed by Matteson et al. for the synthesis of 1,ω–diols with various chain lengths and stereospecifically deuterated at each carbon atom. It was reasoned that it would be possible with benzyloxy-[D_1]methylboronate [D_1]**4.35** with (*R*)- or (*S*)-configuration at the deuterium bearing carbon atom as starting material (Scheme 4.7).



Scheme 4.7. Synthesis of 1,ω-diols [D_{n+1}]**4.39** stereospecifically deuterated at each carbon atom with asterisk showing chiral carbon atoms.

A highly stereoselective homologation with $LiCHCl_2$ followed by substitution of chloride with deuteride will give a certain configuration depending on the 1,2-diol used for the esterification of the boronate. Homologation with $LiCDCl_2$ and reduction with a hydride source will give the opposite configuration. A repetitive combination of the two sequences and finally oxidative cleavage of the boron-carbon bond will yield 1,ω-diols of any length in principle. Benzyloxy-[D_1]methyloronate [D_1]**4.35** could also be possibly used for the synthesis of chiral methylboronate [D_1,T]**4.33** being chiral at the methyl group by virtue of the isotopes hydrogen, deuterium and tritium.

The chirally deuterated 1,ω-diols and the chiral methylboronate could be very useful starting materials for the preparation of substrates for enzymes to address stereochemical problems.

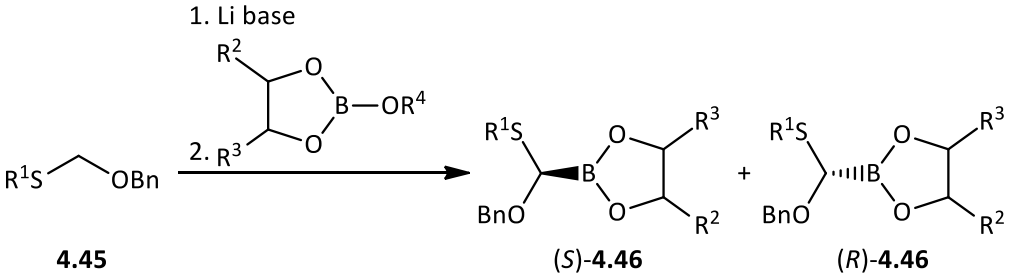


Scheme 4.8. Potential synthesis of deuterated boronic esters [D_1]**4.35**, precursors for the homologation.

Enantiomerically pure deuterated benzyloxy-[D_1]methylboronate [D_1]**4.35** could be prepared by a quite lengthy and laborious sequence through enantiomerically pure tributylstannyl-[D_1]methanol ([D_1]**3.40**) (Scheme 4.8).

Its synthesis starts with methyl carbamate **4.40** which is stannylated to compound **4.41** and subsequently borylated using tributyltinchloride and a homochiral borate **2.27**[56], respectively, as electrophiles. The diastereomeric boronates formed (*R*)- and (*S*)-**4.42** are separated by flash chromatography. The deuterium is introduced via $LiBEt_3D$. The carbamoyloxy group is reductively replaced by D^- to form boronates (*R*)- and (*S*)-[D_1]**4.43** which are oxidatively converted with H_2O_2 and NaOH to deuterated tributylstannyl methanols (*R*)- and (*S*)- [D_1]**3.40**.[56] These alcohols could then be theoretically benzylated, tin-lithium exchanged and borylated with a borate derived from an enantiomerically pure 1,2-diol.

As this synthesis is quite long, it was decided to try to develop a shorter one. The benzyl protecting group on oxygen was chosen because it can be easily removed by catalytic hydrogenation. I thought that a thioacetal of type **4.45** would be an appropriate starting material that could be metalated and borylated to give diasteromeric boronates (*R*)- and (*S*)-**4.46**. A sulfur-containing substituent is necessary to allow metalation because acetals cannot be deprotonated due to the repulsion of lone pairs belonging to the oxygens and the C-Li bond (Scheme 4.9).[46]

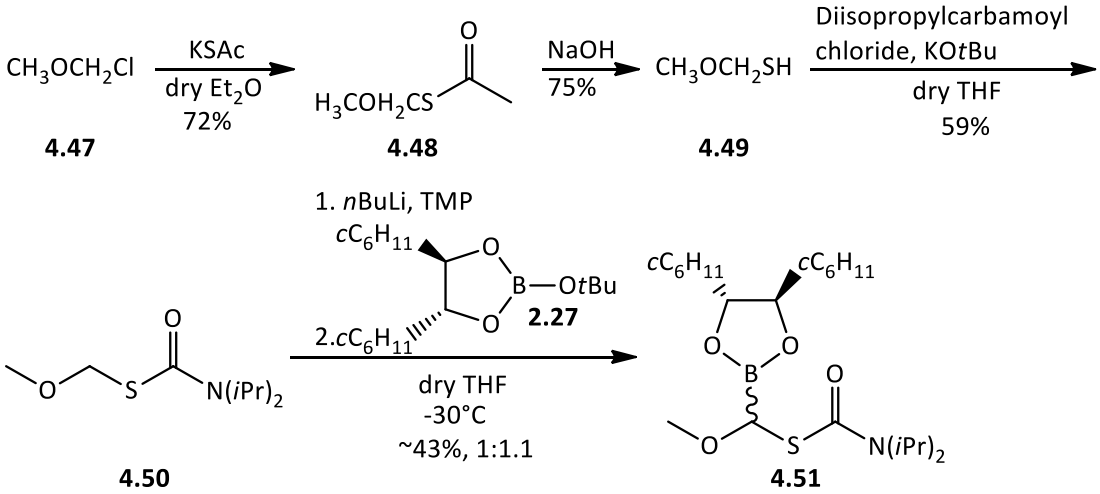


Scheme 4.9. Proposed synthesis of diastereomeric boronates **4.46**.

Since the homologation is known from literature, my attention was first focused on the preparation of enantiomerically pure benzyloxy-[D_1]methylboronates from various diastereomeric boronates that could be reduced with $LiBEt_3D$ or $LiAlD_4$.

4.3.1 Diastereomeric boronates containing a carbamothioyl substituent

The synthesis of the first diastereomeric boronates **4.51** started with chloromethyl methyl ether (**4.47**) (Scheme 4.10).



Scheme 4.10. Synthesis of diastereomeric boronates **4.51**.

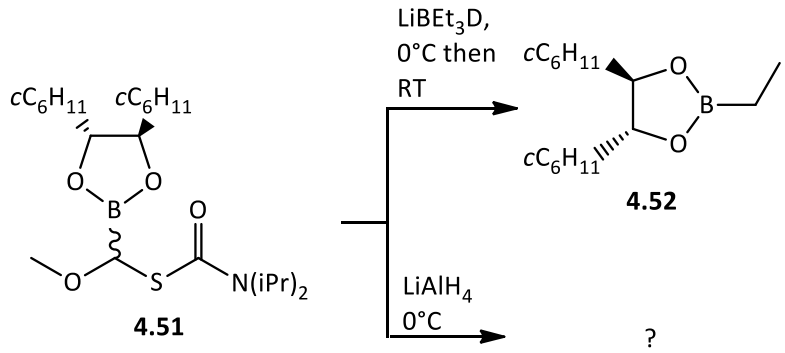
It was reacted with potassium thioacetate to form thioacetate **4.48** in 72% yield, which was hydrolysed with NaOH to form thiol **4.49** isolated as a solution in toluene. The yield was assumed to be 75%.[82] The thiol was esterified with diisopropylcarbamoyl chloride to form *S*-alkyl carbamate **4.50**. Since I was not sure what the best deprotonation conditions are, I had to optimize the reaction conditions (Table 4.1).

Entry	T (°C)	Time (min)	D-content (%)
1	-78	30	45
2	-78	60	27
3	-78	120	40

Table 4.1. Various deprotonation/metalation conditions.

The *S*-alkyl thiocarbamate was metalated with *s*BuLi and TMEDA at -78° but the time was varied. The reaction was then quenched with D_2O and the yield was calculated from the ^1H NMR spectrum of the crude product. Since none of these conditions yielded impressive results, I decided to use LiTMP prepared from *n*BuLi and TMPH instead, which did not yield such impressive results either.[56] The *S*-alkyl thiocarbamate was deprotonated and coupled with the borate ester **2.27**[56] derived from (*R*,*R*)-1,2-dicyclohexane-1,2-ethanediol. Only an impure mixture of

diastereomeric boronates **4.51** (ratio: 1:1.1) could be obtained by flash chromatography in 43% yield. The diastereomers were unstable on SiO_2 and thus could not be properly separated and characterized so they were only identified by a couple of significant peaks in the ^1H NMR spectrum. The reduction of the mixture of boronates was attempted with both $LiBEt_3D$ and $LiAlH_4$ but unfortunately none gave the desired methoxy-[D_1]methylboronate. When $LiBEt_3D$ was used, the boronate was evidently converted to ethylboronate **4.52**. It could not be properly characterized as it was unstable on SiO_2 too and the spectrum was very messy. When $LiAlH_4$ was used, only an unidentified product formed (Scheme 4.11). At this point I decided not to pursue the synthesis of diastereomers **4.51** any more and look for more stable compounds.



Scheme 4.11. Attempted reduction of mixture of diastereomeric boronates **4.51**.

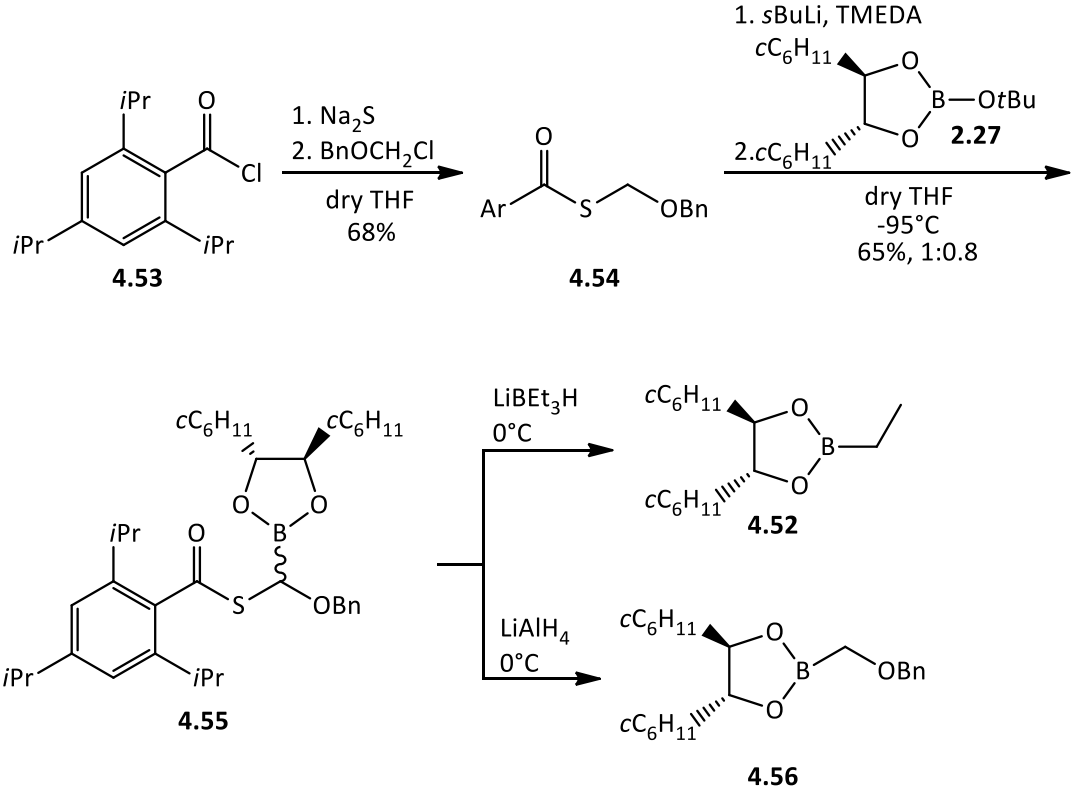
4.3.2 Diastereomeric boronates containing a 2,4,6-triisopropylbenzoylthioyl substituent

The synthesis started from 2,4,6-triisopropylbenzoyl chloride (**4.53**) that was reacted with sodium sulfide and benzyl chloromethyl ether to yield 68% of benzyl ether **4.54** (Scheme 4.12).
The following reaction, metalation of thioacetal **4.54** with *s*BuLi and TMEDA was again optimized (Table 4.2).

Entry	T (°C)	Time (min)	D-content (%)
1	-78	30	15
2	-95	90	100

Table 4.2. Metalation/deuteration of **4.54**.

The right conditions were fortunately found very quickly, so diastereomers **4.55** derived from borate ester **2.27**[56] formed from (*R*,*R*)-1,2-dicyclohexyl-1,2-ethanediol and tri(*tert*-butyl) borate could be isolated as a mixture in 65% yield. Unfortunately, they were again unstable on SiO_2 and also not separable.



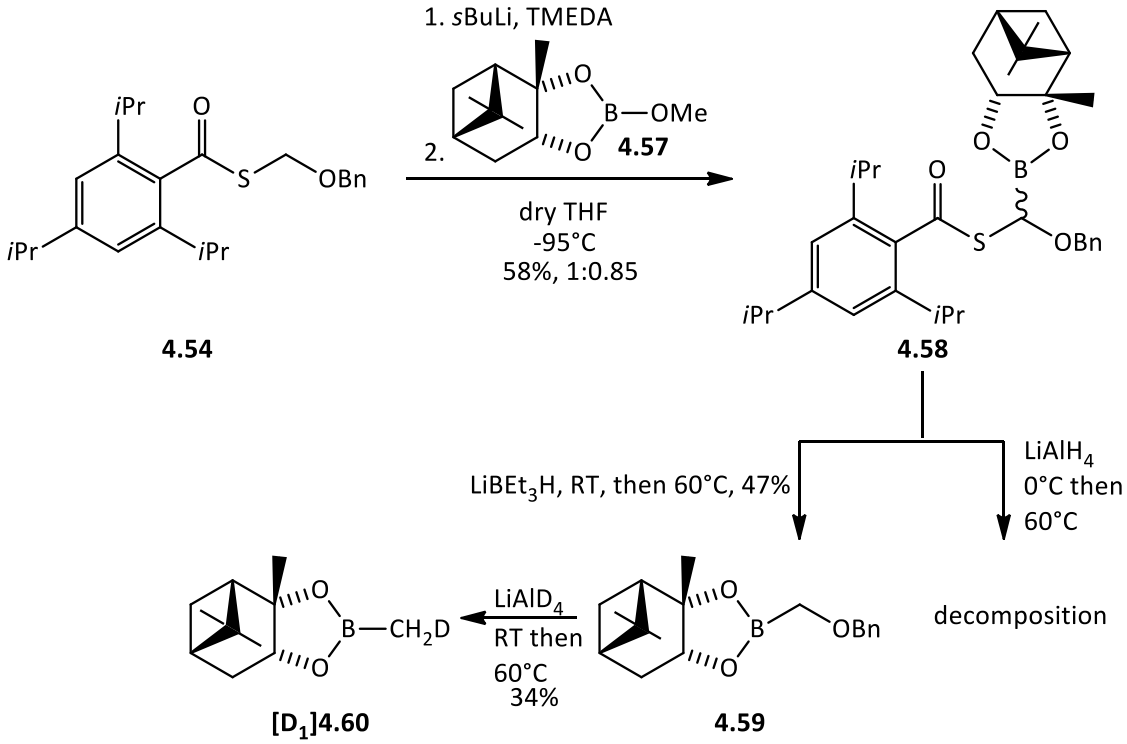
Scheme 4.12. Synthesis and reduction of diastereomeric boronates **4.55**.

Their reduction was attempted, but with $LiBEt_3H$ the same result as with diastereomers **4.51** was obtained. Reduction with $LiAlH_4$ on the other hand was successful and the desired benzyloxymethylboronate **4.56** was formed in 50 % yield.

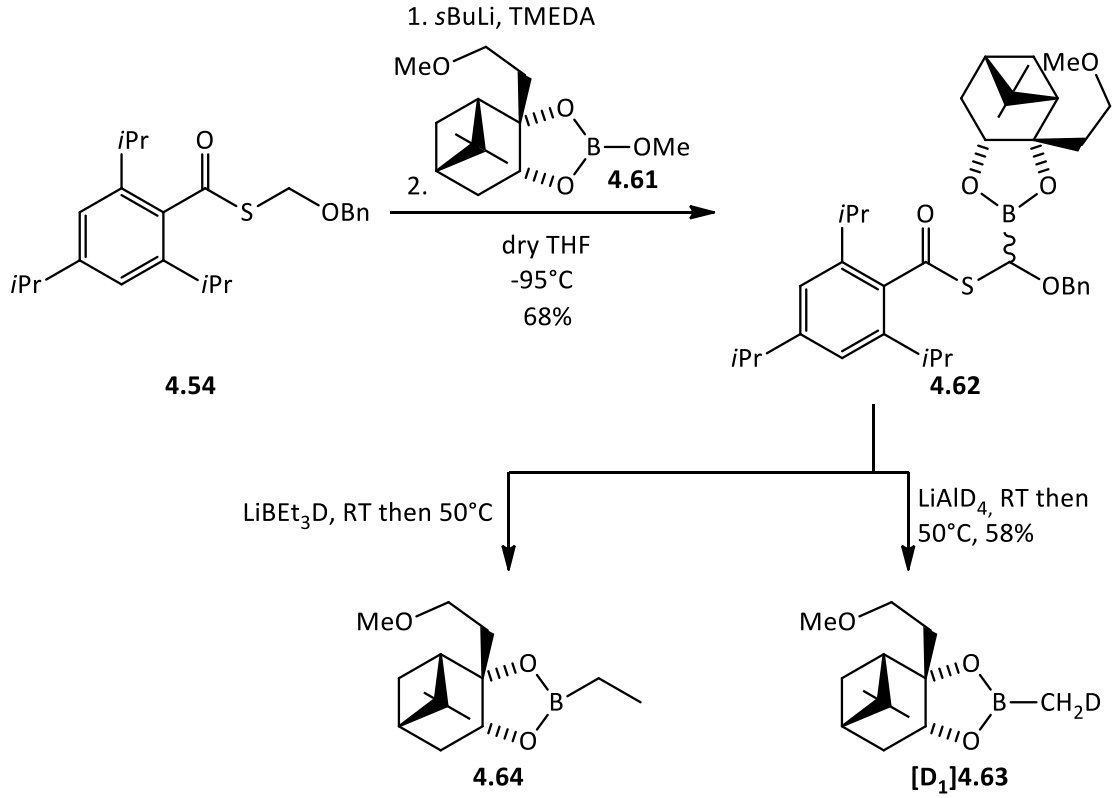
To see if the stability of boronic esters **4.55** could be increased by using a different diol, borate **4.57**[83] derived from (+)-2,3-pinanediol and trimethyl borate was used for the borylation of **4.54** under the same conditions as before (Scheme 4.13).

The diastereomeric boronates **4.58** were obtained as an impure mixture in 58% yield. They were a little more stable than diastereomers **4.55** derived from (*R*,*R*)-dicyclohexyl-1,2-ethanediol, but still too unstable and not separable on silica gel. This time, the reduction with $LiBEt_3H$ was successful and the desired benzyloxymethylboronate **4.59** was obtained in 47% yield (it could not be purified because an impurity was present virtually in all fractions collected during flash chromatography). No ethylboronate was found as byproduct. Reduction with $LiAlH_4$ led to decomposition.

Fortunately, benzyloxymethylboronate **4.59** was reduced with $LiAlD_4$ to the desired [D_1]methylboronate [D_1]**4.60**, although in low yield (34%).



Scheme 4.13. Synthesis and reduction of diastereomeric boronates **4.58**.



Scheme 4.14. Synthesis and reduction of diastereomeric boronates **4.62**.

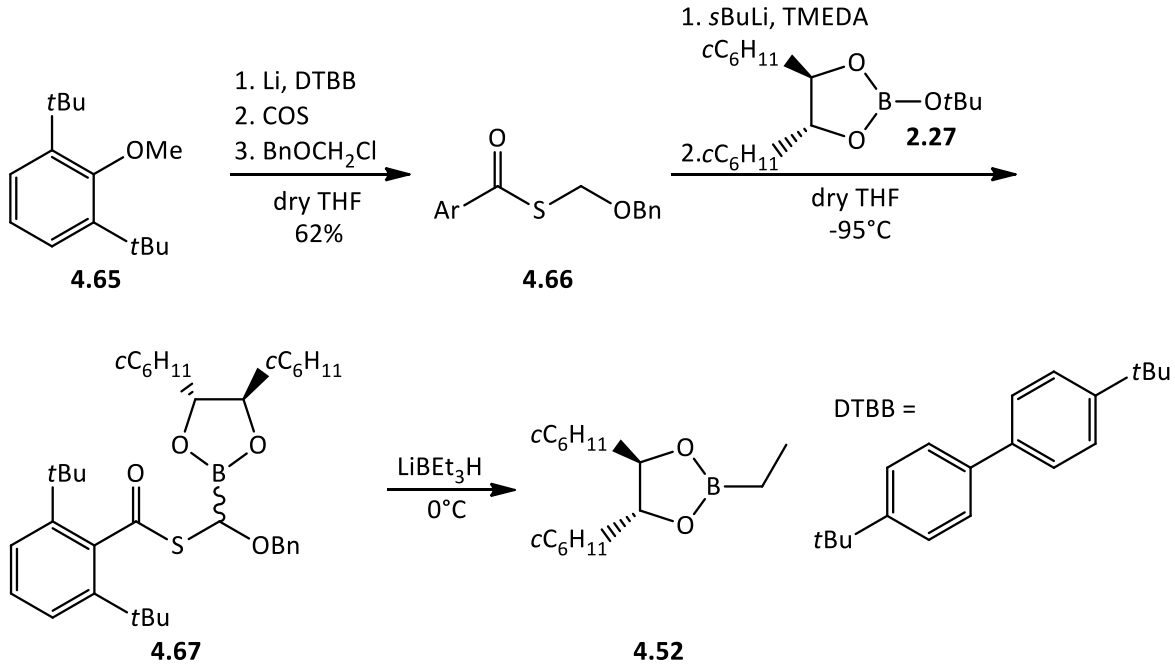
Encouraged by these results, (+)-pinane-2,3-diol was replaced by the diol derived from nopol in hope that the methyl ether will increase the chemical stability of the formed boronates **4.62** even more (Scheme 4.14).

They were obtained in 68% yield and even though they were still unstable on silica gel, they were the most stable and separable ones. Unfortunately, the reduction with $LiBEt_3D$ only yielded the ethylboronate **4.64** but with $LiAlD_4$ gave the possibly useful methylboronate [D_1]**4.63**.

At this point I decided to see whether the diastereomers could be made more stable by altering the aromatic substituent.

4.3.3 Diastereomeric boronates containing a 2,6-di-tert-butylbenzoythioyl substituent

The synthesis of the precursor for these boronates was prepared from 2,6-di-tert-butylanisol (**4.65**) according to a literature procedure (Scheme 4.15).[84]

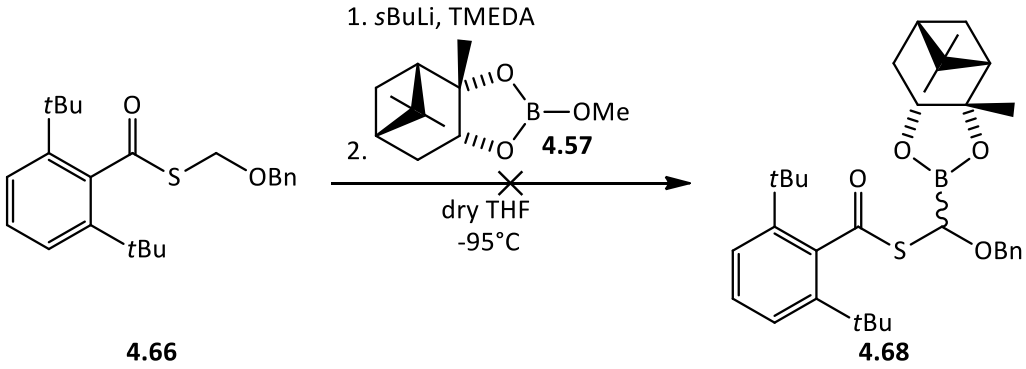


Scheme 4.15. Synthesis and reduction of diastereomeric boronates **4.67**.

It was reductively converted to 2,6-di-tert-butylphenyllithium and then reacted with carbonyl sulfide and benzyl chloromethyl ether. The yield of the *S*-benzyloxymethyl thiobenzoate **4.66** was 62%, but it was unfortunately not pure enough for complete characterization even after two flash chromatographies. The diastereomeric boronates **4.67** obtained by borylation of the lithiated *S*-

benzyloxymethyl thiobenzoate **4.66** by the borate ester **2.27**[56] derived from (*R*,*R*)-1,2-dicyclohexyl-1,2-ethanediol were still very unstable on silica gel and not separable at all. Reduction of their mixture with $LiBEt_3H$ was also unsuccessful and resulted only in ethylboronate **4.52**.

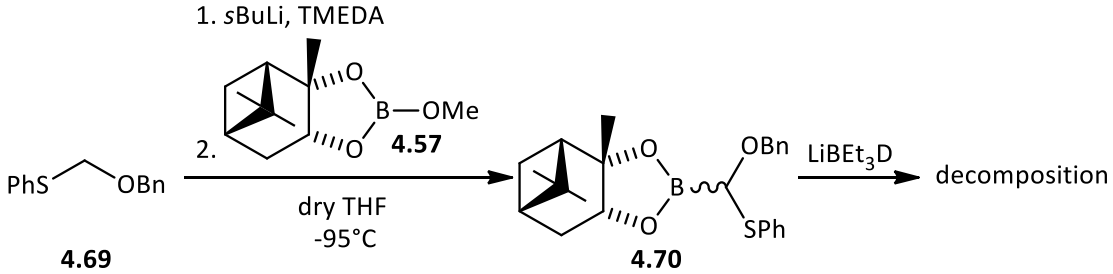
When I tried to prepare diastereomers **4.68** with the borate ester **4.57**[83] derived from (+)-pinane-2,3-diol and trimethyl borate under the same conditions, the reaction did not work (Scheme 4.16).



Scheme 4.16. Attempted synthesis of diastereomeric boronates **4.68**.

4.3.4 Diasteromeric benzyloxyphenylthiomethylboronates 4.70

I gave this ''group'' of compounds a last chance and prepared benzyloxymethyl phenyl thioether (**4.69**) from thiophenol and chloromethyl benzyl ether.[85] The thioether was metalated with sBuLi/TMEDA and borylated with the borate **4.57**[83] derived from (+)-pinane-2,3-diol. The boronates formed were the most unstable of all boronates prepared so far. Therefore, they were not purified at all and the product mixture was not reducible with $LiBEt_3D$ (Scheme 4.17).



Scheme 4.17. Synthesis and reduction of diasteromeric boronates **4.70**.

At this point I unwillingly accepted that diastereomeric methylboronates having a benzyloxy and a sulfur-containing substituent at the methyl group are too unstable for preparative purposes. The most promising seemed to be diastereomers **4.58** where both reductions to **4.59** and [D_1]**4.60**

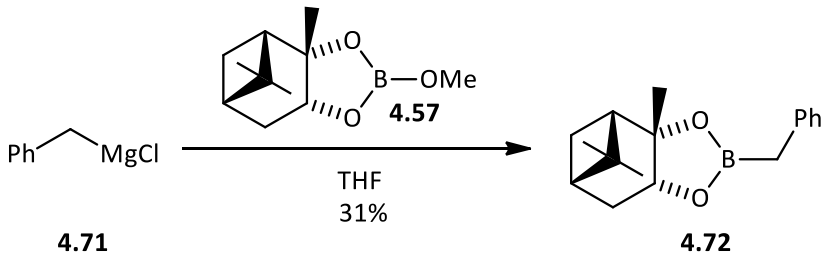
worked. It could be potentially advantageous to try to separate the diastereomers at low temperature (-78°C). However, before doing that I wanted to optimize homologation to see whether it was worth the trouble at all.

4.3.5 Homologation of boronates

There are several methods how to perform the homologation described in the literature.[76,79,86,87,88] Apparently, the procedure was always altered slightly even though the reported yield was always high (around 80-90%). The halomethyllithiums, the temperature and the presence and amount of $ZnCl_2$ were all varied at some point.

The homologation of boronates **4.35** was described in at least three articles.[89,86,79] The first one,[89] described the unsuccessful attempt with $LiCHCl_2$ derived from CH_2Cl_2 at -100°C, which did not give any product. In the second article,[86] homologation was achieved in 90% yield with $LiCH_2Cl$ derived from ICH_2Cl at -78°C. In the third article,[79] homologation was successful thanks to a combination of $LiCHBr_2$ generated from CH_2Br_2 and $ZnCl_2$ that catalyzed the rearrangement at boron and also led to higher diastereoselectivities. The overall yield was 82%.

The homologation experiments were performed with two starting materials - unlabeled boronic ester **4.59** prepared by a literature procedure[79] and unlabeled boronic ester **4.72** prepared from benzylmagnesium chloride and borate **4.57**[83] (Scheme 4.18).



Scheme 4.18. Preparation of boronic ester **4.72**.

A lot of experiments were performed, some of them repeatedly to make sure I did not miss anything, especially the ones already described in literature. The best results with each method are summarized in Table 4.3.

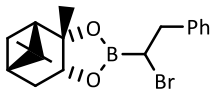
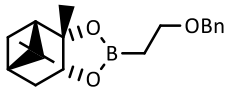
Entry	Ester (eq.)	Source of halolithium (eq.)	Li-reagent (eq.)	LiCHX	T (°C)	$ZnCl_2$ (eq)	Product	Yield[1] (%)
1	**4.72** (1)	CH_2Br_2 (8)	LDA (1.5)	$LiCHBr_2$	-78	0.8	 **4.72**	0
2	**4.59** (1)	ICH_2Cl (1.2)	*n*BuLi (1.2)	$LiCH_2Cl$	-78	0	 **4.73**	<10
3		Bu_3SnCH_2Cl (1.2)	MeLi (1.2)	$LiCH_2Cl$	-78	0		29
4		Bu_3SnCH_2Cl (1.2)	MeLi (1.2)	$LiCH_2Cl$	-95	0		<29

Table 4.3. Optimization of homologation. [1]Yield after flash chromatography.

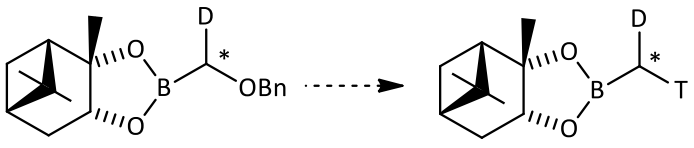
The reaction in entry 1 was performed with ester **4.72**, CH_2Br_2 and LDA as base at -78 °C in THF for 1h. Afterwards the reaction mixture was concentrated in vacuo at 0 °C. A solution of anhydrous $ZnCl_2$ in THF was added to the residue at -78 °C and the mixture was stirred overnight according to the literature.[79] Even though the reported yield was 82%, no homologated boronate could be detected in the crude product mixture by ^1H NMR spectroscopy.

The next reaction was also performed according to literature[86] with ester **4.59** but the yield was anything but satisfying (entry 2). Finally, $LiCH_2Cl$ was generated salt-free by tin-lithium exchange from Bu_3SnCH_2Cl with MeLi at -78 °C, which resulted in a 29% yield of the homologated boronate (entry 3). When this experiment was repeated at -95 °C, the ^1H NMR spectrum of the crude product looked even worse so the product was not isolated (entry 4).

Since these results were rather unsatisfactory, the utilization of benzyloxymethylboronate for the preparation of chiral [D_1,T]methylboronates was pursued.

4.3.6 Reduction of benzyloxy-[D_1]methylboronic ester [D_1]4.59 to methylboronic ester [D_1,T]4.60

Benzyloxy-[D_1]methylboronic ester [D_1]**4.59** needed for the synthesis of a chiral methyl group attached to boron could be prepared by a lengthy sequence described in Scheme 4.8 and then reduced stereospecifically by $LiBEt_3T$ (Scheme 4.19).



[D_1]**4.59** [$D_{1,}$T]**4.60**

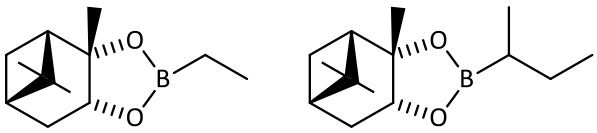
Scheme 4.19. Stereospecific reduction of deuterated benzyloxymethylboronate [D_1]**4.59** to methylboronate [D_1,T]**4.60**. The asterisk denotes the asymmetric center.

The reduction was already performed with $LiAlD_4$ as can be seen in Scheme 4.13. As the yield of 34% was not satisfactory, other reducing agents were tested. The preliminary experiments were all performed with 1 eq. of boronic ester **4.59** that showed the most potential in previous experiments and are summarized in Table 4.4.

Entry	Reducing agent (eq.)	T (°C)	Time (h)	SM : P : BP[1]	Yield[2] (%)
1	$LiBEt_3H$ (2.3)	0 -> RT -> 50	1 -> 2.5 -> 1	1:0.3:0.7	<10
2	$LiBEt_3H$ (1.3)	0 -> RT	3 -> 2	1:4.2:1.4	40
3	$LiBEt_3H$ (3)	0	24	0:0.9:0.1	51
4	$LiBEt_3H$ (2)	RT	5	0:0.9:0.1	45
5	LiD (1.3)	RT	2	1:18.4	19
6	LiD (1.3)	-78->RT	21	1:0	0
7	L-Selectride (1.3)	-30->10	5	1:0.1:0.1	<19
8	L-Selectride (3)	-78->RT	7	1:0.7:0.2	<20

Table 4.4. Reduction of benzyloxymethylboronate **4.59** with different reducing agents. [1]SM: starting material, P: product and BP: byproduct that will be described in more detail in text. The ratio was calculated based on ^{1}H NMR of the crude product before flash chromatography. [2]The yield is given for product after flash chromatography.

The first experiments were performed with Superhydride at various temperatures for various reaction times (entries 1-4). The crude product of the first experiment contained a lot of starting material and a byproduct, which was presumably boronate **4.75** (Figure 4.2). However, the structure of the byproduct was assigned tentatively, because it was never obtained pure. It could not be separated from the desired product or starting material on silica gel. It was formed by the addition of an ethyl group from Superhydride to boron. The best results (51% yield) were obtained when 3 eq. of Superhydride were used and the reaction was stirred at 0°C for a day (entry 3). In order to get rid of the byproduct, LiD was tried as reducing reagent (entries 5 and 6).



4.75 **4.76**

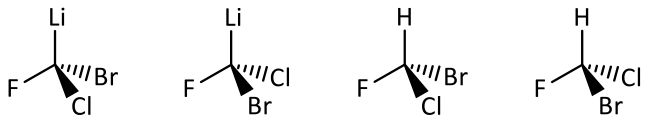
Figure 4.2. Byproducts of the reduction of benzyloxymethylboronate **4.59** with Superhydride (**4.75**) and L-Selectride (**4.76**).

Unfortunately, mostly decomposition took place as is obvious from the poor (entry 5) and virtually nonexistent yield (entry 6). Since this was not the right way to go, I tried whether a bulkier group on the reducing agent would be less prone to addition to boron. Therefore, L-Selectride was used as an alternative to Superhydride, because it contains *sec*-butyl groups instead of the ethyl groups (entries 7 and 8). Unfortunately, even though the formation of the byproduct was mostly blocked, so was the reduction itself. The yields were difficult to calculate because the methylboronate could not be separated from the starting material and byproduct, this time boronate **4.76**. Only the maximum possible yield (based on the assumption that the product was homogeneous after flash chromatography) was given.

Disappointed by these results and the time I spent on this project I finally decided not to pursue the homologation, reduction or synthesis of diastereomeric boronates any further.

5 Bromochlorofluoromethyllithium

The group of Hammerschmidt has been studying the configurational stability of various α-heteroatom-substituted organolithiums for a long time. The most interesting ones are the halo-[D_1]methyllithiums. Bromochlorofluoromethyllithium (Figure 5.1) is a synthetic challenge because it contains three different halogens attached to a carbon atom. So far it has only been studied theoretically in order to determine its equilibrium structure.[90]



(*S*)-**5.1** (*R*)-**5.1** (*S*)-**5.2** (*R*)-**5.2**

Figure 5.1. (*R*)- and (*S*)-bromochlorofluoromethyllithium (**5.1**) and (*R*)- and (*S*)-bromochlorofluoromethane (**5.2**).

The enantiomerically pure methyllithium **5.1** has to be prepared from enantiomerically pure (*R*)- and (*S*)-bromochlorofluoromethane (**5.2**, Figure 5.1) using a lithiated reagent that does not undergo lithium-halogen exchange, like LDA. The starting material is one of the simplest optically active compounds that was discovered by Swarts in 1893.[91] It has been used for the verification of the theory of asymmetric carbon atom proposed independently by Le Bel and van't Hoff in 1874 as well as being used as a model for testing the theories of optical activity and parity violation.[92]

5.1 Parity violation

Louis Pasteur, the discoverer of molecular chirality suggested that it is connected with fundamental physics.[93] About 25 years later, van't Hoff and Le Bel simultaneously elaborated on this concept and van't Hoff proposed "exact mechanical symmetry" between enantiomers which means that their enthalpy, entropy and Gibbs energy are equal.[94] If the symmetry is perfect, then the absolute geometric handedness of enantiomers cannot be observed, we can only define the relationship of opposition between the two.[95] Hund proposed that enantiomers are kinetically stable because the barrier to interconversion gives tunneling times of millions of years.[96] Until 1950's it was assumed that parity, a quantity that expresses the behavior of the wave function of any system of particles when the spatial coordinates *x, y, z,* of the wave function are reflected through the origin to $-x, -y, -z$[97] is conserved as a constant of motion - parity conservation.[98] Lee

and Yang noted in 1956 that there was no definitive proof of parity conservation.[99] It was soon discovered that the so called parity violation indeed exists, at least for the weak force (responsible for the β-decay of radionuclides).[100] In 1966 Yamagata formulated the connection between one of the biggest mysteries in chemistry, the appearance of homochirality in biochemistry of life (DNA, RNA, amino acids...) and the concept of parity violation.[101] Even a very small energy difference between enantiomers could explain the preference of L-amino acids and D-sugars. It would also mean that two enantiomers have slightly different and not identical spectra as previously assumed. The result of parity violation is a nonzero enthalpy for the stereomutation of enantiomer from (*R*) to (*S*) and vice versa:[102]

$$S = R.\Delta_r H_0^0 \approx N_A \Delta_{pv} E$$

Equation 5.1. Entropy of stereomutation dependent on parity-violating energy difference $\Delta_{pv}E$ and Avogadro's number.

A lot of theoretical calculations have been performed in order to predict the parity-violating energy difference. The latest calculations hint at a value in the order of 10^{-17} kT which should theoretically be measurable by absorption spectroscopy with high enough resolution.[103] Up until now there has been no experimental evidence for parity violation mainly due to low sensitivity and resolution of instruments and also due to complicated synthesis, handling and resolution of enantiomers needed for spectroscopic analysis. Various compounds, among them some Os and Au complexes, have been suggested for the study of parity violation. Unfortunately, these compounds are unstable at high temperature in the gas phase. The best type of molecules for quantum chemists and physicists studying parity violation are small chiral molecules containing atoms such as bromine and iodine. They should be volatile and chemically stable at the temperatures needed for the measurement.[103] In 1976, enantiomerically pure CHBrClF was suggested as a good candidate for the observation of $\Delta_{pv}E$ induced by weak force.[104]

5.2 Synthesis of racemic CHBrClF and its resolution

Because the parity-violating energy difference for two enantiomers is so small, synthesis of enantiomerically pure compounds is of utmost importance.[105] Unfortunately, the quest for the

synthesis of enantiomerically pure (*R*)- and (*S*)-bromochlorofluoromethane [(*R*)- and (*S*)-**5.2**] is still ongoing.

As already mentioned in the introduction, racemic bromochlorofluoromethane (**5.2**) was first synthesized by Swarts from dibromochloromethane with (Br_2+SbF_3) fluorinating agent at the end of the 19th century.[91] Since then there have been numerous other syntheses[106,107,108] until 1971, when (+)-**5.2** and (-)-**5.2** were synthesized and partially separated by complexation with brucine with ees (calculated later when the value of optical rotation of pure enantiomers was determined) of 11% and 7% respectively.[109] The determination of enantiomeric excess became possible thanks to Collet et al. who calculated the maximum optical rotation to be α^{25}_{589} = 3.0 deg.dm^{-1} or $[\alpha]^{25}_{589}$ = 1.6 deg.kg^{-1}.dm^{2}.[110] He succeeded to determine the ee of chiral, nonracemic mixtures of CHBrClF by ^{1}H NMR spectroscopy, using (-)-cryptophane-C as chiral host (and simultaneously as a chiral shift reagent). As the optical rotation of the sample was known, the ee of enantiomerically pure bromochlorofluoromethane could be predicted. (Figure 5.2).

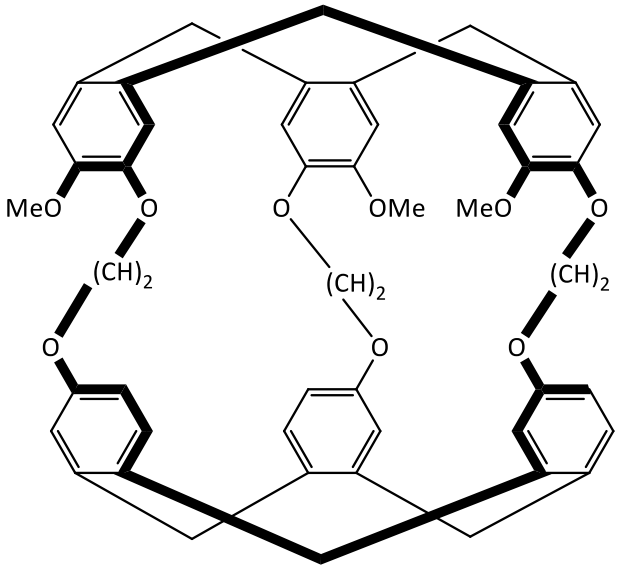
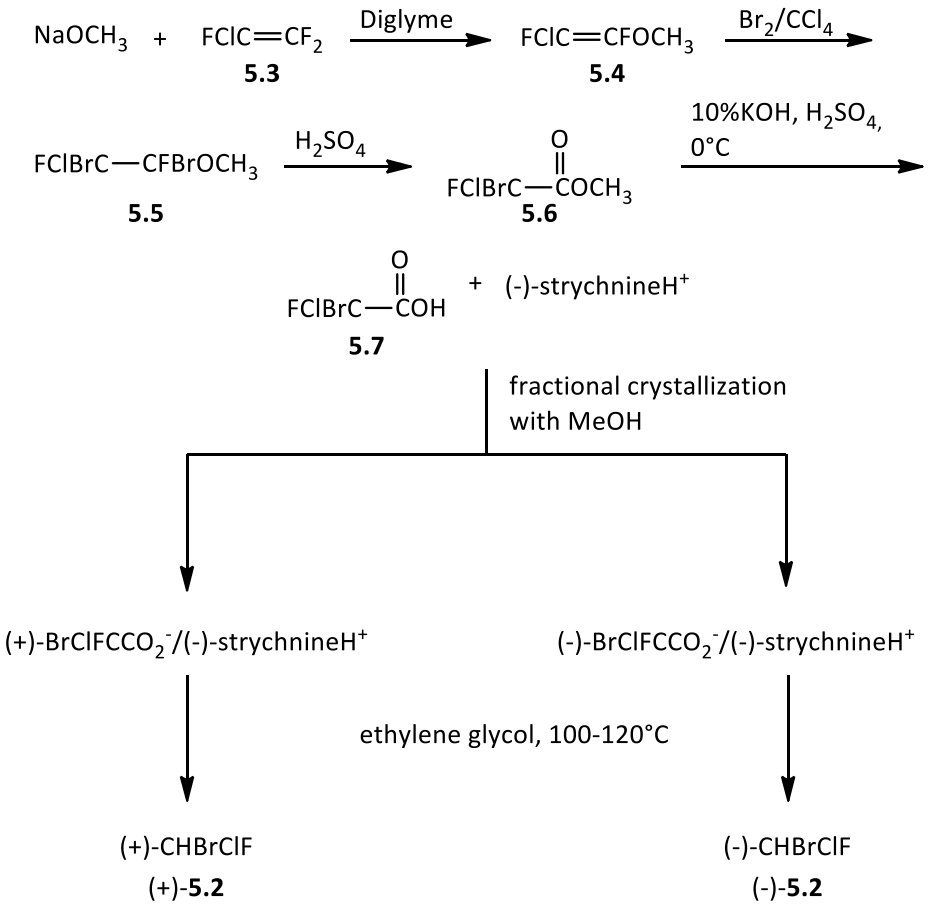


Figure 5.2. (-)-Cryptophane-C.

Doyle and Vogt prepared (+)-**5.2** and (-)-**5.2** with ees of 60% and 31% respectively by enantioselective decarboxylation of chiral, nonracemic bromochlorofluoroacetic acid (**5.7**) synthesized from 1,1,2-trifluoro-2-chloroethylene (**5.3**) and resolved with strychnine (Scheme 5.1).[111,112]



Scheme 5.1. Synthesis of enantiomerically enriched CHBrClF **5.2**.

With the optimized protocol for the resolution with strychnine it is now possible to prepare (+)-**5.2** and (-)-**5.2** with ees of 72% and 56% respectively.[105] The absolute configuration was determined in 1997 using Raman Optical Activity (ROA) and molecular modelling of the enantioselective molecular recognition process of CHBrClF by chiral crypthophane-C.[113,114] It was found that the levorotary and dextrorotary enantiomer have (*R*)- and (*S*)-configuration, respectively.

During the course of their work, Hammerschmidt and his coworker stumbled upon an interesting observation when they were preparing precursors for ^{18}F-containing PET tracers to image hypoxia.

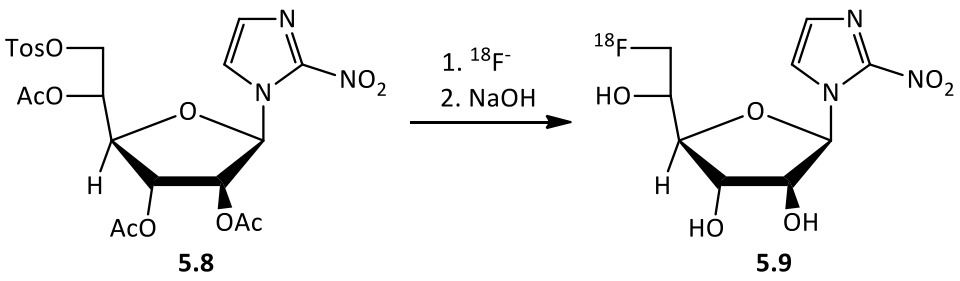


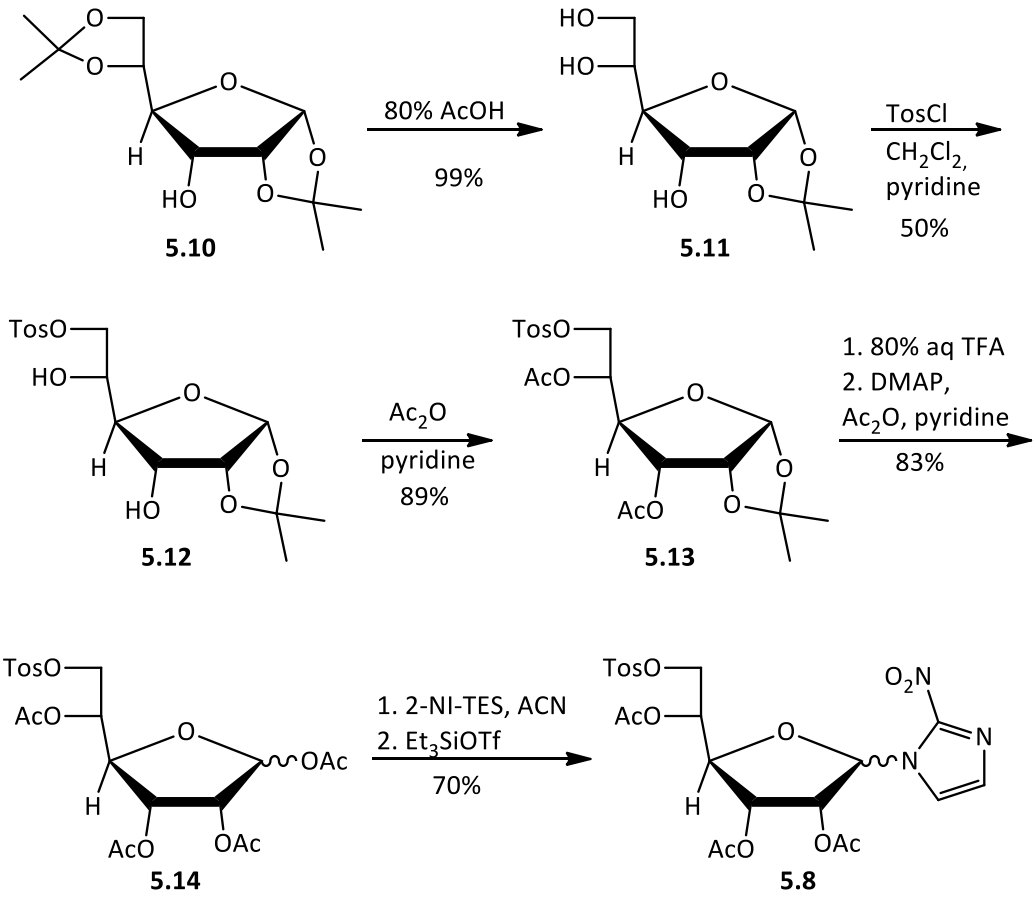
Figure 5.3. D-Allose-based PET-precursor 1β-D-(2´,3´,5´-Tri-*O*-acetyl-6-*O*-p-toluenesulfonyl-allofuranosyl)-2-nitroimidazole (**5.8**) and the corresponding hypoxia tracer **5.9**.

They found that the β-nucleoside **5.8** is a crystalline compound and cocrystallizes with methylene chloride, chloroform and even ethyl acetate (Figure 5.3).

Therefore, it deemed worth to test, if the β-anomer would selectively cocrystallize with (*R*)- or (*S*)-bromochlorfluoromethane, when the racemate is a component of the solvent mixture for crystallization.

5.3 Synthesis of 1α- and 1-β-D-(2´,3´,5´-tri-*O*-acetyl-6-*O*-p-toluenesulfonyl-allofuranosyl)-2-nitroimidazole (5.8)

Most of the synthesis of the D-allose-derived precursor was developed by Anna Woschek,[115] but not yet published because some steps had to be optimized, especially the last one. She started the synthesis from commercially available 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**5.10**) by removal of the 5,6-O-isopropylidene group with aqueous 80% acetic acid to afford triol **5.11** (Scheme 5.2).

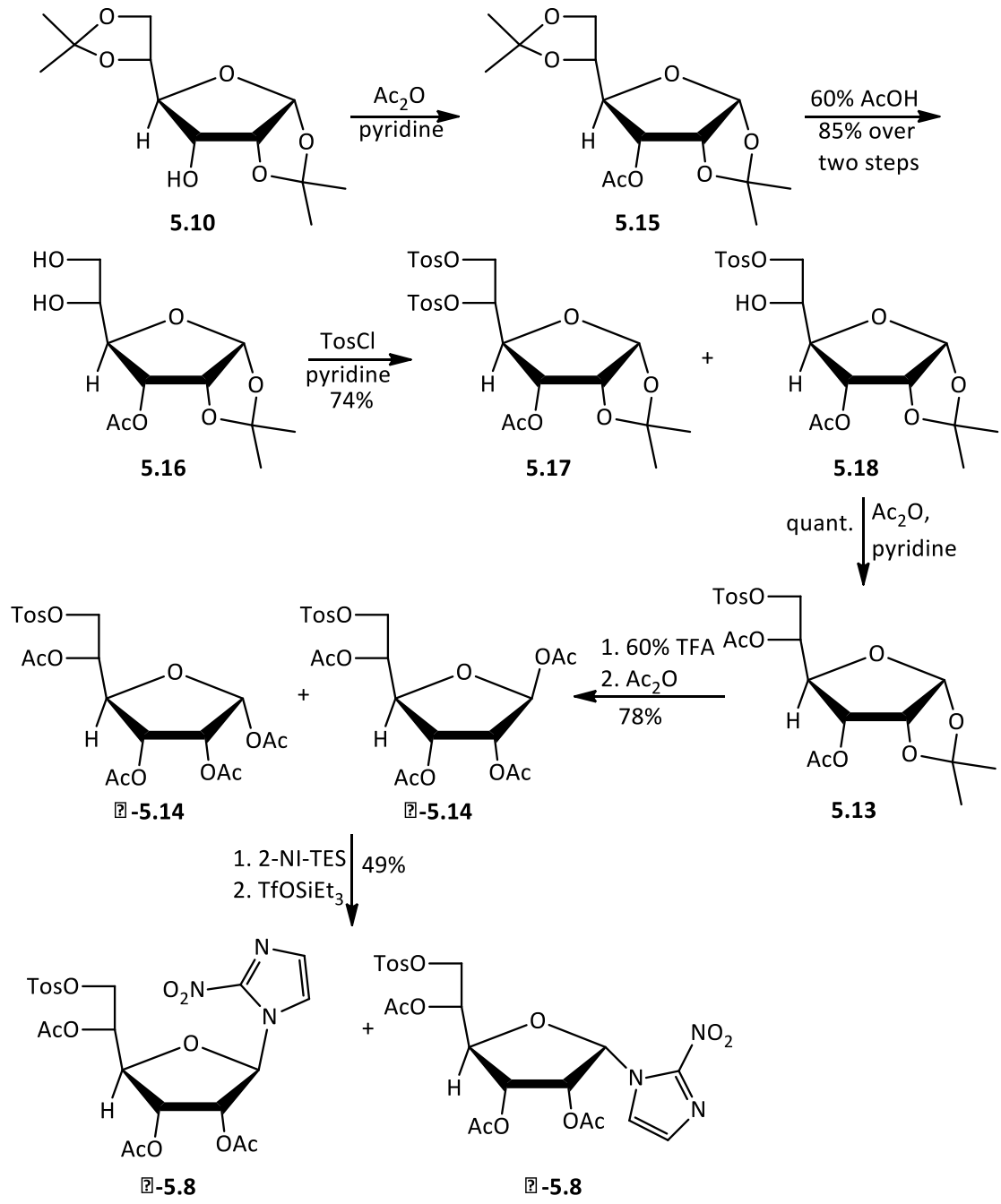


Scheme 5.2. Woschek's synthesis of 1α- and 1-β-D-(2´,3´,5´-tri-*O*-acetyl-6-*O*-p-toluenesulfonyl-allofuranosyl)-2-nitroimidazole (**5.8**).

She then tosylated the primary C-6 hydroxyl group of the triol **5.11** to form **5.12** with 50% yield, and acetylated the free C-3 and C-5 hydroxyl groups to obtain tosylate **5.13** in 89% yield. Deprotection of the hydroxyls at C-1 and C-2 to obtain diol had to be performed with trifluoroacetic acid. This diol was then acetylated to form diacetoxytosylate **5.14** which was then

coupled with TES-silylated 2-nitroimidazole to form a mixture of 1-α- and 1-β-D-(2′,3′,5′-tri-*O*-acetyl-6-*O*-p-toluenesulfonyl-allofuranosyl)-2-nitroimidazole (**5.8**).

The synthesis is straightforward and basically a series of protecting and deprotecting reactions ending with a coupling reaction (Vorbrüggen method) to form **5.8**. One of the critical steps was the tosylation that was performed at -78 °C. The reaction mixture was warmed to room temperature over the course of 18 hours because the 5,6-ditosylate was formed as byproduct in almost 20% yield and the desired 6-monotosylate in 50% yield.



Scheme 5.3. Improved synthesis of 2-nitroimidazole nucleosides **5.8**.

I modified the beginning of the synthesis to improve the yield for the diacetoxytosylate **5.13** (Scheme 5.3). Therefore, the 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**5.10**), the same starting material that Woschek used, was acetylated with Ac_2O/pyridine[116,117] and then the 5,6-O-isopropylidene group was removed selectively with 60% acetic acid[116] to yield diol **5.16** in 85% combined yield for the two steps.

The yield of the selective tosylation at C-6 was increased to 74%. The desired hydroxytosylate **5.18** was formed without ditosylate **5.17** as byproduct.[118] This was achieved by performing the reaction at -25 °C for 40 h. At 4°C for 18 h, the monotosylate **5.18** was formed in 66% yield along with 18% of ditosylate **5.17**. Tosylate **5.18** was acetylated again with acetic anhydride to **5.13** and the 1,2-O-isopropylidene group was removed hydrolytically with TFA.[119] The two resulting hydroxyl groups were acetylated to yield an anomeric mixture of tetraacetates **5.14**. The final step in this sequence was the coupling of tetraacetates **5.14** with TES-silylated 2-nitroimidazole with TfOTES as catalyst (Vorbrüggen method). The mixture of nucleosides **5.8** was separated by flash chromatography.[120]

Unfortunately I was not able to reproduce Woschek's results (70% yield for the coupling) as the highest yield I got was 49%. The ratios of anomers were not reproducible at the same temperature and at comparable reaction times, even when I performed the reaction more than once (Table 5.1).

Conditions	**α:β**	
	Woschek`s experiments	**New experiments**
0°C	only β	0.04:1
RT	1:3.5	1:1.09 / only β / 1:0.27 / 1:0.15 / 0.04:1

Table 5.1. Ratio of anomers in reactions performed by Woschek (old) and me (new).

5.4 Crystallization with halogenated compounds and attempted separation of enantiomers of CHBrClF (*R*)- and (*S*)-5.2

When a solution of the β-nucleoside β-**5.8** in CH_2Cl_2/*i*Pr_2O was allowed to cool from room temperature to 4°C very slowly in a Dewar, crystalls formed. After drying for 3 h (1 mbar/room temperature), they contained 0.3 eq. of CH_2Cl_2.

When a solution of the β-nucleoside β-**5.8** in $CHCl_3$/*i*Pr_2O was allowed to slowly cool from room temprature to 4°C, very thin colourless needles formed, containing 0.46 eq. of $CHCl_3$ after drying

for 1 h at room temeprature at 1 mbar. After heating a sample for NMR spectroscopy for 1 h at 50°C at 1 mbar, the sample looked unchanged, but the $CHCl_3$ contents had fallen to 0.4 eq. When a sample was heated for 1 h at 70°C at 1 mbar, its colour had changed to faint brownish and it contained only 0.23 eq. of $CHCl_3$.

The β-nucleoside β-**5.8** crystallized by slowly cooling a solution in racemic CHBrClF (**5.2**)/*i*Pr_2O from room temperature to -78°C and formed colourless needles, containing 0.4 eq. of CHBrClF (**5.2**) after drying for 15 min at room temerature at 1 mbar. GC analysis was performed on a Lipodex A column at 26°C to determine the ee of the cocrystallized CHBrClF (**5.2**). Unfortunately, β-**5.8** differenciates between (*R*)- and (*S*)-**5.2** only slightly, as the ee of the cocrystallized **5.2** with the higher retention time was 11% and this method is thus not useful for the separation of (*R*)- and (*S*)-**5.2**. However, I would like to thank Prof. Dr. Jürgen Stohner for providing the racemic **5.2**.

6 Chiral phosphate group

The transfer of a phosphate group is catalyzed by various enzymes. Phosphatases transfer the phosphate group from a phosphate ester onto water as acceptor and kinases from a nucleotide triphosphate to an acceptor. Phosphomutases move the phosphate group within the same molecule from one functional group to another. Virtually every energetically unfavorable metabolic process is fuelled by displacement of a phosphate group from phosphoric anhydride or monoester.[121] In order to study these processes in detail, a way of accessing what is happening at the phosphorus during the course of these reactions is necessary. One way of achieving that is making the phosphate group chiral.

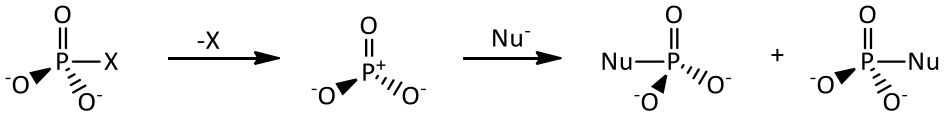
6.1 Assignment of configuration

Although no naturally occurring phosphates chiral at phosphorus are known, chirality at phosphorus can be introduced synthetically by using sulfur or heavy isotopes of oxygen (^{17}O, ^{18}O) to make all of the groups on tetrahedral phosphorus different.[122,123] The assignment of absolute configuration is based on the slightly modified Cahn, Ingold and Prelog rules.[124] Bond orders are ignored during the assignment because they are fractional instead of single or double and so are the delocalized negative charges, otherwise the CIP rules are followed. The priority of the substituents bound to phosphorus is assigned on the basis of atomic mass. If the most immediate atoms of more functional groups bound to phosphorus are the same, the next atom in line is evaluated and so on until a difference is found.[122]

6.2 Phosphoryl transfer mechanisms

There are three mechanisms that have been proposed for enzymatic phosphoryl transfers, which could be investigated with the help of enantiomerically pure chiral phosphate groups:[125]

1. Dissociative mechanism: analogous to the S_N1 mechanism for substitution reactions at sp^3 hybridized carbon atoms with a planar intermediate; the nucleophile can be added from both sides to the phosphorus atom and the product will be racemic if the phosphorus atom of the starting material is a stereogenic center (Scheme 6.1).

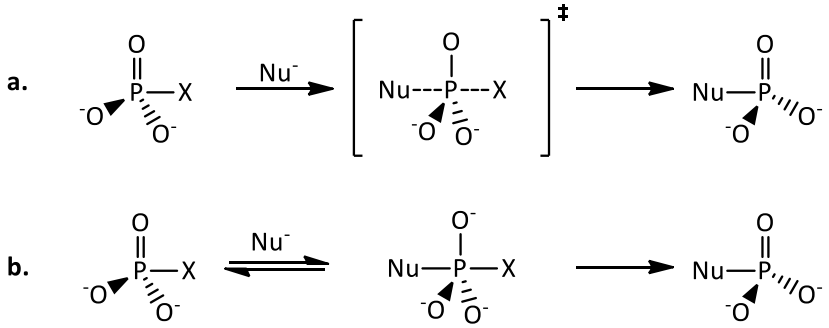


Scheme 6.1. Dissociative mechanism for phosphoryl transfer.

2. Associative mechanism:

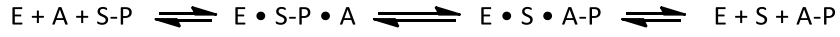
   a. concerted - analogous to S_N2 reaction resulting in inversion of configuration

   b. addition - elimination mechanism with a trigonal bipyramidal intermediate, resulting in inversion of configuration (Scheme 6.2).



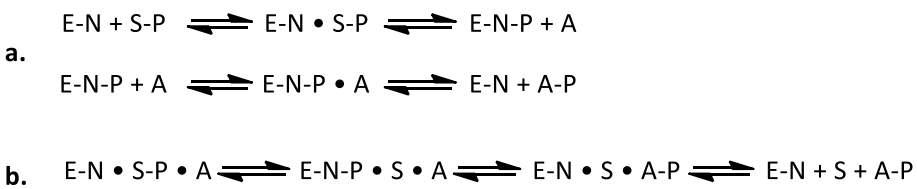
Scheme 6.2. Two associative mechanisms for phosphoryl transfer.

To complicate things further, substitution at phosphorus can also proceed either through a single or double displacement mechanism. During a single displacement reaction, the enzyme does not form a covalent bond to the phosphoryl group but rather binds to the substrate (S) and acceptor (A) in proximal positions and facilitates the direct transfer (Scheme 6.3).[122]



Scheme 6.3. Single displacement mechanism where E stands for enzyme, S for substrate, A for acceptor and P for phosphoryl group.

Double displacement goes through either a ping-pong bi-bi mechanism where the enzyme is covalently bound to the phosphoryl group through a nucleophilic amino acid and then reacts with the acceptor or through two ternary complexes and the transfer again takes place due to an enzymatic nucleophilic group (Scheme 6.4).[122]



Scheme 6.4. Double displacement mechanisms - a. ping-pong bi-bi reaction and b. mechanism containg two ternary complexes.

6.3 Nucleoside phosphorothioates

Phosphorothioates are phosphate analogues where one oxygen atom is replaced by sulfur which leads to minimal structural changes, but relatively big change in chemical reactivity of the natural nucleotides. Phosphorothioates are more stable towards hydrolysis and usually react somewhat slower with enzymes compared to regular phosphates.[126] When three other non-identical residues are attached to the phosphorus atom, a stereogenic center is created. This makes the compound containing it very useful for mechanistic investigations of enzymes. They can even be relatively easily incorporated into DNA and RNA.[127]

Many phosphorothioate analogues of ATP, ADP, cyclic nucleotides and dinucleotides have been synthesized (Figure 6.1).[127]

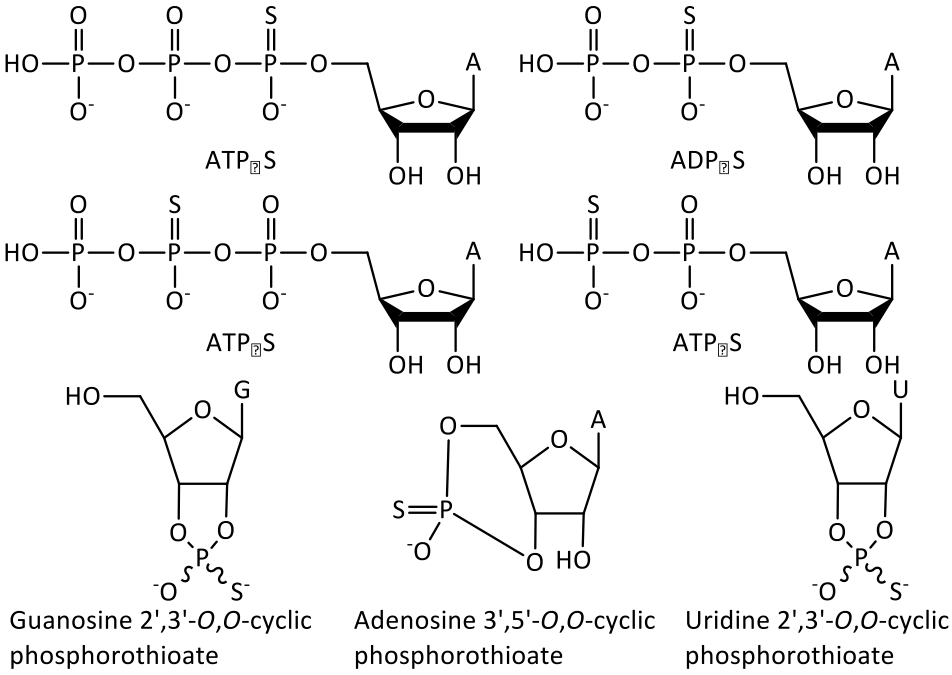
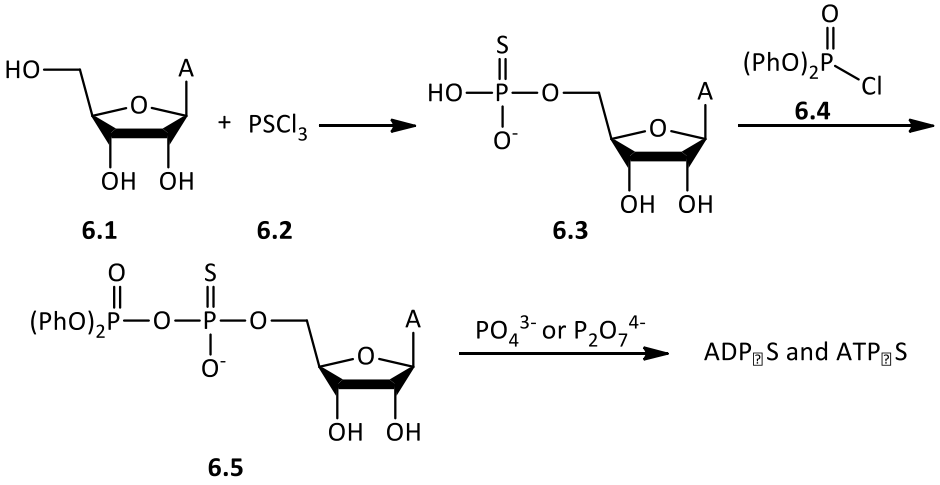


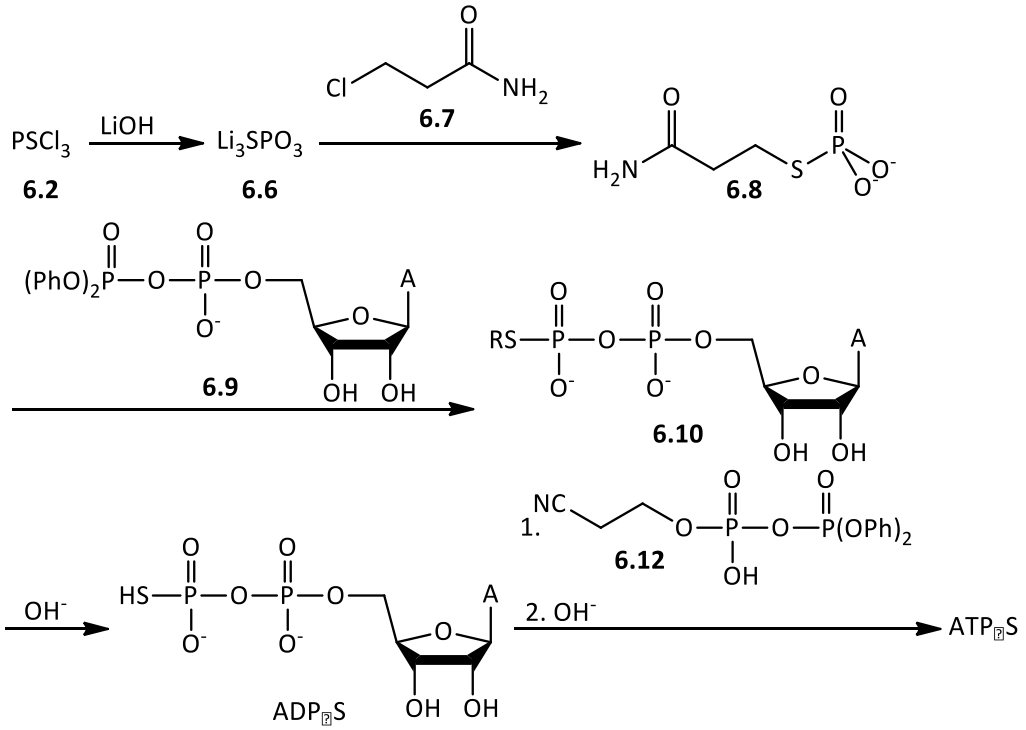
Figure 6.1. Various nucleoside phosphorothioates, A = adenine, G = guanine and U = uracil.

Sulfur can be incorporated into any position of a triphosphate chain and thus all α-, β- and γ-substituted analogues of AMP, ADP and ATP can be prepared.[128,129] AMP was prepared from adenosine (**6.1**) and thiophosphoryl chloride (**6.2**) in good (65%) yield.[130] $ADP_{\alpha}S$ and $ATP_{\alpha}S$ are prepared from AMPS (**6.3**) activated with diphenyl phosphorochloridate (**6.4**) and phosphoric or pyrophosphoric acid respectively (Scheme 6.5).[129]



Scheme 6.5. Preparation of AMPS, $ADP_{\alpha}S$ and $ATP_{\alpha}S$.

The synthesis of $ADP_{\beta}S$[128] and $ATP_{\beta}S$[129] starts from trilithium phosphorothioate (**6.6**) (Scheme 6.6).



Scheme 6.6. Synthesis of $ADP_{\beta}S$ and $ATP_{\beta}S$.

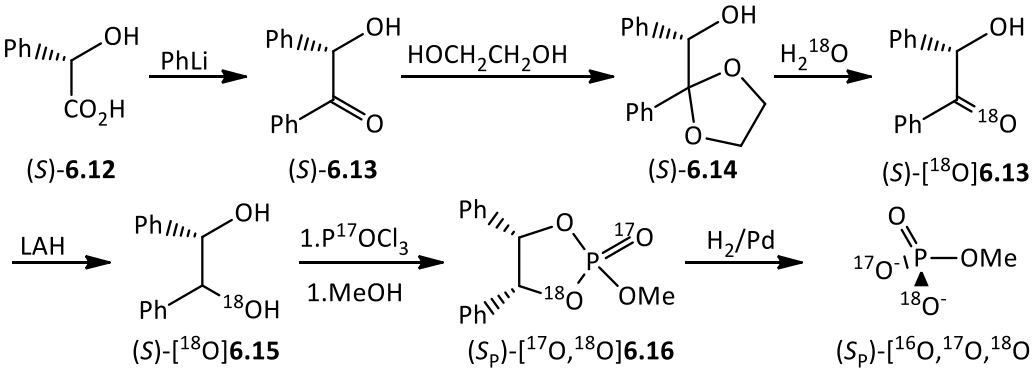
It is derived from lithium hydroxide and thiophosphoryl chloride (**6.2**),[131] that reacts with 3-chloropropionamide (**6.7**) to form (*S*)-2-carbamoylethyl phosphorothioate (**6.8**). It is then reacted with *P*^{1}-diphenyl *P*^{2}-adenosine *5'*-pyrophosphate (**6.9**) to form protected ADP$_{\beta}$S (**6.10**) that is deprotected under basic conditions to yield ADP$_{\beta}$S. ATP$_{\beta}$S is formed by the reaction of ADP$_{\beta}$S with 2-cyanoethyl phosphate (**6.12**) and diphenyl phosphorochloridate.

The diastereomers are separated either by HPLC or by selective enzymatic reactions with various kinases that only convert one of the diastereomeric phopshorothioates. If AMPS is used as a substrate for pyruvate kinase and adenylate kinase then only one isomer of ATP$_{\alpha}$S is formed and there is no need for separation.[127] Sulfur can be activated by oxidation with cyanogen bromide,[132] *N*-bromosuccinimide[133] or bromine[134] and substituted for ^{17}O or ^{18}O using $H_2{}^{17}O$ or $H_2{}^{18}O$.

6.4 [^{16}O,^{17}O,^{18}O]Phosphate

Although nucleoside phosphorothioates have been useful for the investigation of many enzymatic reactions, they have a few disadvantages. The question arises whether the stereochemical course of their reactions is the same as the one of the oxygen analogues. Independent research with chiral phosphates has shown that this was true, but one should always take this assumption with a grain of salt. Another setback is that phosphorothioates are not accepted as substrates by many intriguing enzymes. Therefore, phosphates chiral by virtue of the oxygen isotopes ^{16}O, ^{17}O and ^{18}O became important.[123]

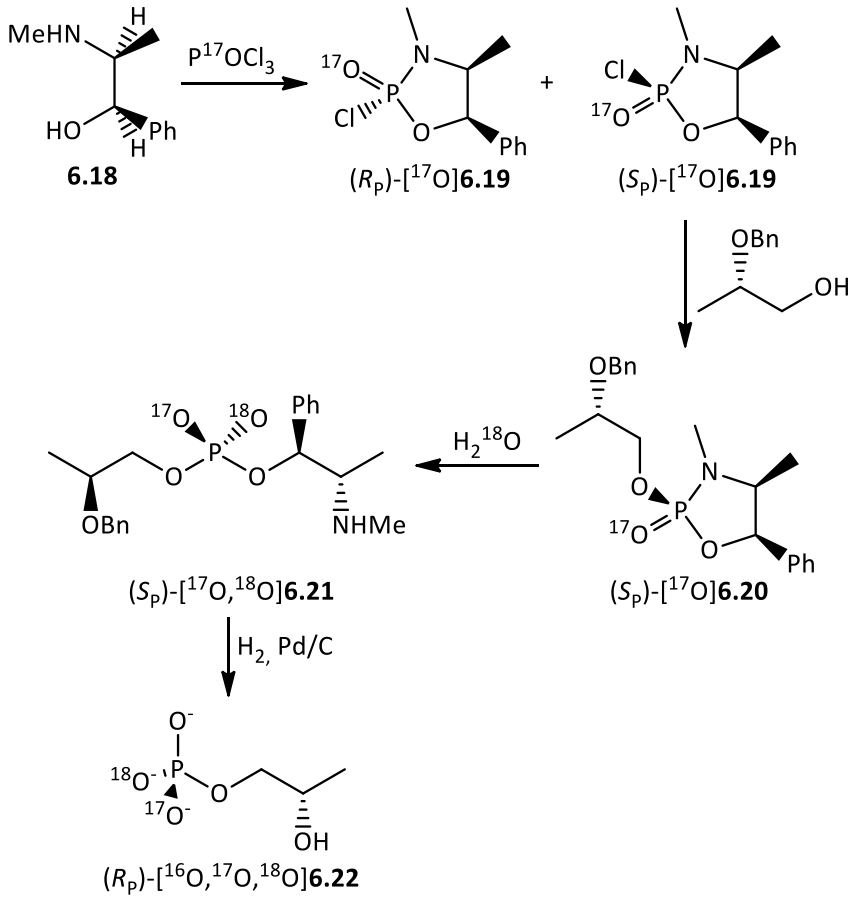
Lowe et al. based his synthesis of methyl (S_P)-[^{16}O,^{17}O,^{18}O]phosphate {(S_P)-[^{16}O,^{17}O,^{18}O]**6.17**} on enantiomerically pure (*S*)-mandelic acid [(*S*)-**6.12**] that was reacted with phenyllithium to yield (*S*)-benzoin [(*S*)-**6.13**] (Scheme 6.7).



Scheme 6.7. Synthesis of enantiomerically pure methyl (S_P)-[^{16}O,^{17}O,^{18}O]phosphate {(S_P)-[^{16}O,^{17}O,^{18}O]**6.17**}.

Its carbonyl ^{16}O atom was replaced by an ^{18}O atom by ketalisation with ethylene glycol and deketalisation in the presence of $H_2{}^{18}O$. Reduction of (*S*)-[^{18}O]benzoin {(*S*)-[^{18}O]**6.13**} with LAH furnished (1*R*,2*S*)-1,2-diphenylethane-1,2-[1-^{18}O]diol {(*S*)-[^{18}O]**6.15**}, which was reacted at first with $P^{17}OCl_3$ and then with methanol. Catalytic hydrogenolysis of the cyclic phosphate (S_P)-[^{17}O,^{18}O]**6.16** yielded enantiomerically pure methyl (S_P)-[^{16}O,^{17}O,^{18}O]phosphate {(S_P)-[^{16}O,^{17}O,^{18}O]**6.17**}. Its absolute configuration was deduced from the configuration of the starting mandelic acid and the stereochemistry of the ensuing steps.[135]

Knowles et al. published another synthesis of chirally labeled phosphate esters.[136] He started from $P^{17}OCl_3$ that reacted with (-)-ephedrine (**6.18**) to yield diastereomers (R_P)- and (S_P)-[^{17}O]**6.19** separable by chromatography (Scheme 6.8).



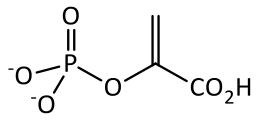
Scheme 6.8. Synthesis of [(R_P)-^{16}O,^{17}O,^{18}O]phospho-(*S*)-propane-1,2-diol {(R_P)-[^{16}O,^{17}O,^{18}O]**6.22**}.

The synthesis was continued with each diastereomer separately. The cyclic phosphorylchloride {(S_P)-[^{17}O]**6.19**} was converted with an alcohol to a phosphoramidate {(S_P)-[^{17}O]**6.20**}. Hydrolytic cleavage of the cyclic phosphoramidate in the presence of $H_2{}^{18}O$ and finally reductive removal of

the benzyl group yielded the (R_P)-[^{16}O,^{17}O,^{18}O]phosphate ester {(R_P)-[^{16}O,^{17}O,^{18}O]**6.22**}. The addition of alcohol is not stereospecific and the product is thus not enantiomerically pure.

6.5 Phosphoenolpyruvic acid

Phosphoenolpyruvates (**6.23**), the salts of phosphoenolpyruvic acid are very important compounds in living cells (Figure 6.2).



6.23

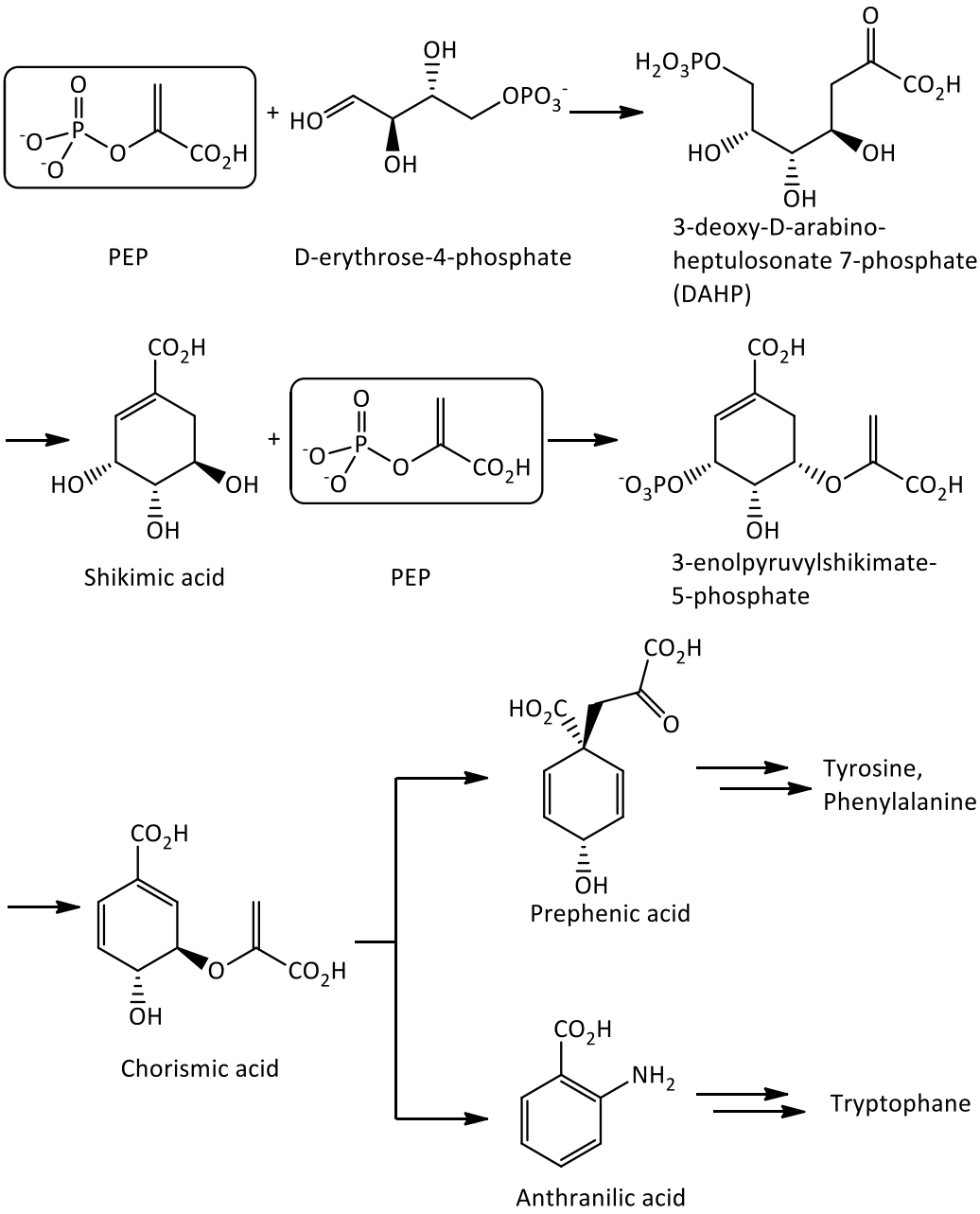
Figure 6.2. Phosphoenolpyruvate (PEP, **6.23**).

They contains the highest energy phosphate bond (-61.9 kJ/mol, -14.8 kcal/mol) and are one of the compounds (along with e.g. carbamoyl phosphate - -51.5 kJ/mol and acetylphosphate - -43.1 kJ/mol) that can be used for the preparation of adenosyltriphosphate (ATP, -30.5 kJ/mol) and for the transfer of a phosphate group to various acceptors. It is an important intermediate in a number of metabolic pathways.[137]

During glycolysis, PEP is formed from 2-phosphoglycerate by enolase through elimination of water. PEP is used to regenerate ATP from ADP by pyruvate kinase. Phosphoenolpyruvate carboxykinase an enzyme important for gluconeogensis that converts oxaloacetate to PEP and carbon dioxide, whereby one equivalent of ATP is consumed.[137]

The shikimic acid pathway is crucial for the biosynthesis of the amino acids phenylalanine, tyrosine and tryptophan from carbohydrates, taking place in plants, algae, fungi and bacteria, but not in man (Scheme 6.9).

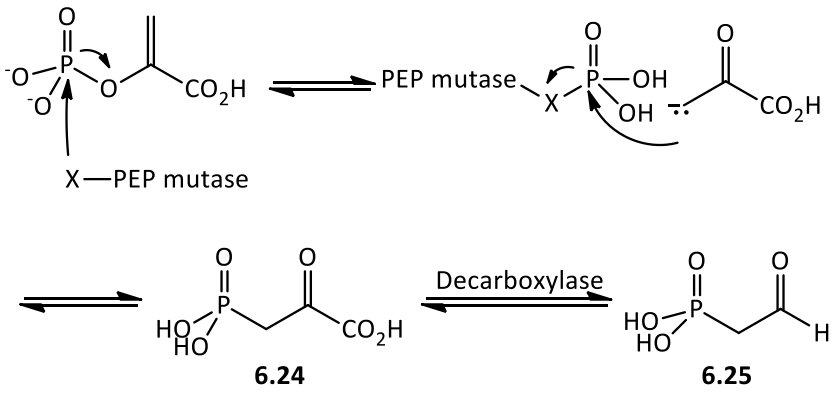
These amino acids are therefore essential ones for man.[138] The sequence consists of a couple of steps which start with the condensation of phosphoenolpyruvate and erythrose-4-phosphate and the release of phosphate.[137]



Scheme 6.9. Shikimic acid pathway with highlighted role of PEP.

6.6 Biosynthesis of natural products with a P-C bond

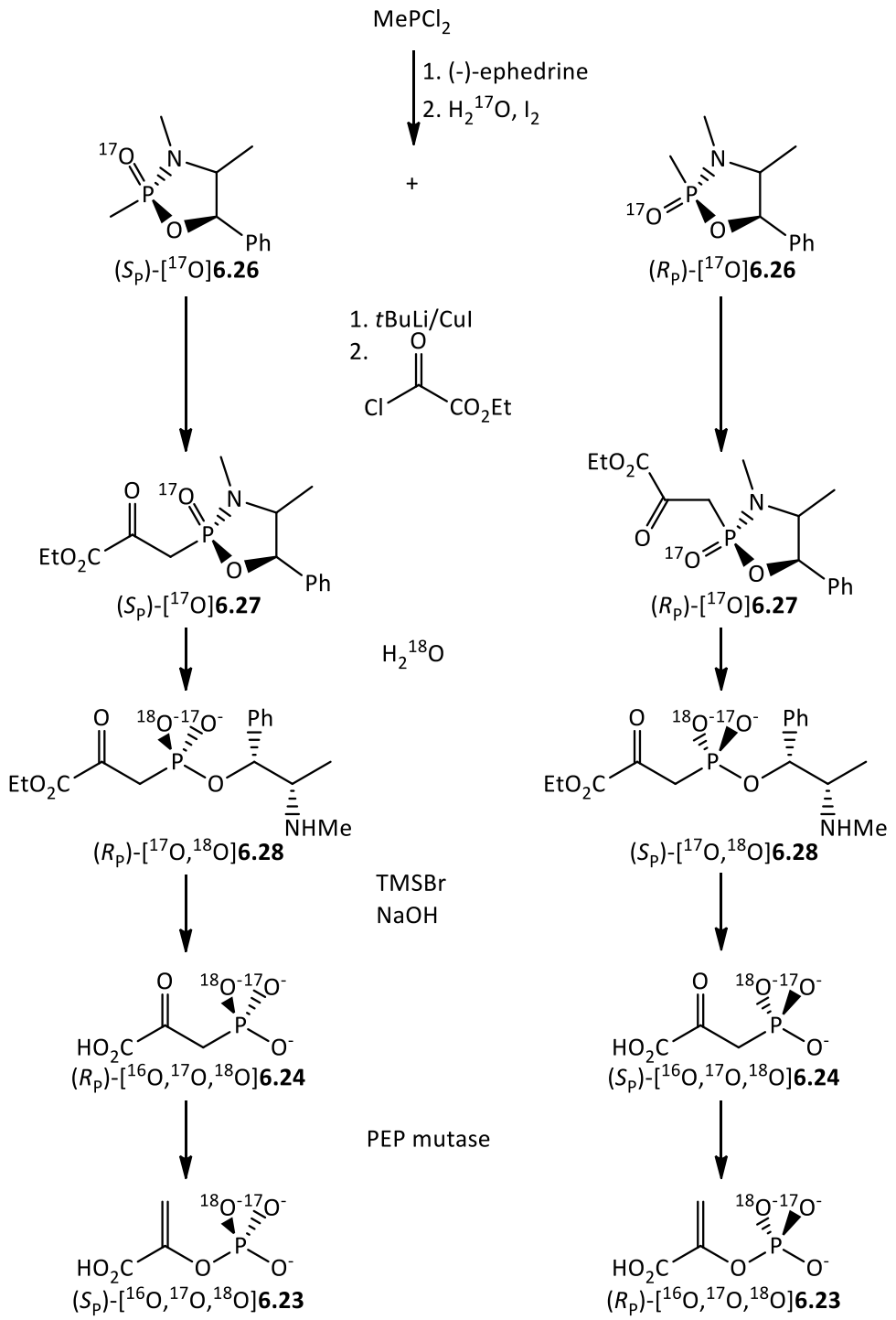
Compounds containing the C-P bond like phosphonates and C-P-C bonds like phosphinates are known in the nature. The biosynthesis of these compounds starts from phosphoenolpyruvate that is converted by PEP mutase to phosphonopyruvate (**6.24**), the starting material for all natural phosphonates and phosphinates (Scheme 6.10).[139]



Scheme 6.10. Biosynthesis of natural products containing a C-P bond.

6.7 [$^{16}O_1$,^{17}O,$^{18}O_1$]Phosphoenolpyruvate

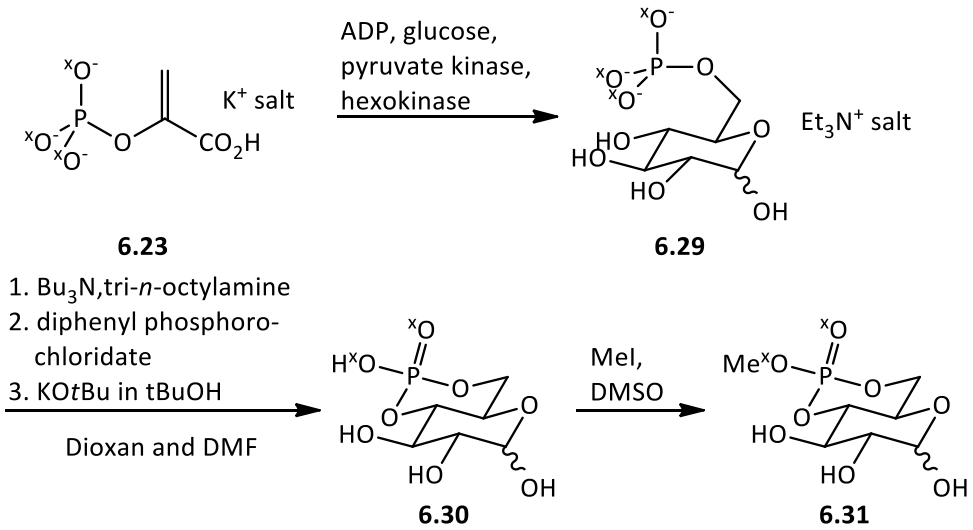
No purely chemical synthesis of [^{16}O,^{17}O,^{18}O]phosphoenolpyruvate was known until now. Knowles et al. developed a chemoenzymatic synthesis based on their general method for the preparation of [^{16}O,^{17}O,^{18}O]phosphate monoesters (Scheme 6.11).[136,140] (From now for the sake of simplification I will refer to [$^{16}O_1$,^{17}O,$^{18}O_1$] as [^{16}O,^{17}O,^{18}O].) They reacted methyldichlorophosphine with (-)-ephedrine. The 1,3,2-oxazaphospholidines formed were immediately oxidized with iodine in $H_2{}^{17}O$. The resulting diastereomeric methylphosphonamides (*R*)- and (*S*)-[^{17}O]**6.26** were separated by flash chromatography. Each methylphosphonamide was metalated with *t*BuLi and acylated with CuI/Cl(O)CCO_2Et to deliver phosphonamides (R_P)- and (S_P)-[^{17}O]**6.27**, which were ringopened with $H_2{}^{18}O/H^+$. TMSBr was used to remove the benzylic protecting group from phosphorus and NaOH to saponify the carboxylic ester. The (R_P)- and (S_P)-[^{16}O,^{17}O,^{18}O]phosphonopyruvate {(R_P)- and (S_P)-[^{16}O,^{17}O,^{18}O]**6.24**} were rearranged by PEP mutase to (S_P)- and (R_P)-[^{16}O,^{17}O,^{18}O]phosphoenolpyruvate, {(S_P)- and (R_P)-[^{16}O,^{17}O,^{18}O]**6.23**} respectively.



Scheme 6.11. Synthesis of [^{16}O,^{17}O,^{18}O]phosphoenolpyruvate ([^{16}O,^{17}O,^{18}O]**6.23**).

A method for the determination of the enantiomeric excess and absolute configuration of chiral [^{16}O,^{17}O,^{18}O]phosphate esters also applicable to chiral [^{16}O,^{17}O,^{18}O]phosphoenolpyruvate was developed by Potter et al.[141] The chiral phosphate group of PEP was transferred to the C-6 hydroxyl group of D-glucose using ADP/glucose/pyruvate kinase and hexokinase. The glucose-6-phosphate **6.29** was purified by ion exchange chromatography, activated at phosphorus with

diphenyl phosphorochloridate and treated with potassium *t*-butoxide in DMF to form cyclic phosphates **6.30**. Methylation with MeI in DMSO to yielded D-glucose 4,6-phosphate methyl esters **6.31** which were analysed by ^{31}P NMR spectroscopy to determine the configuration at phosphorus (Scheme 6.12).



Scheme 6.12. Determination of absolute configuration and ee of labeled phosphate esters. ''x'' stands for different isotopes of oxygen.

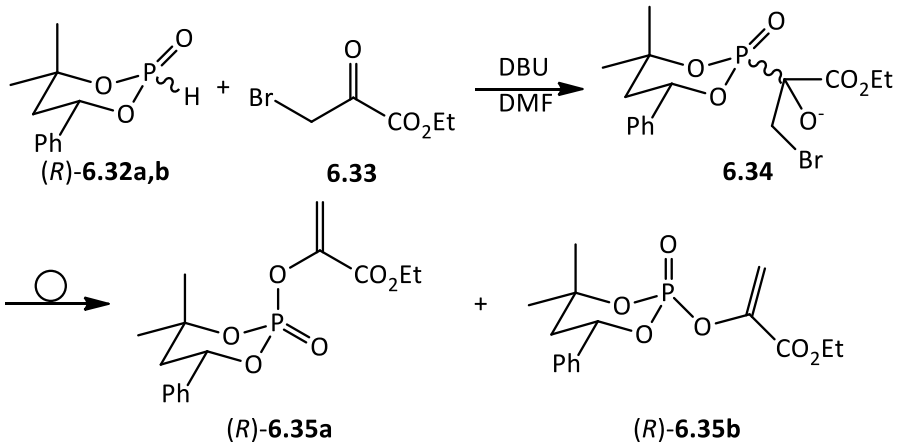
This analysis results in the net inversion of configuration on phosphorus because the transfer of a phosphate group from PEP to ADP proceeds with the inversion of configuration as does the transfer from ATP to glucose to form G-6-P. The last cyclization step was also found to proceed with inversion of configuration.[141]

6.8 Chemical synthesis of (*R*)- and (*S*)-[^{16}O,^{17}O,^{18}O]phospho-enolpyruvate

The synthesis had to fulfill two important conditions. Firstly, ^{17}O and ^{18}O had to be introduced through labeled water as late as possible and at some point, diastereomers separable by flash chromatography had to be formed. ^{18}O labelled water is commercially available in 99% enrichment and the ^{17}O labelled one at 70%.

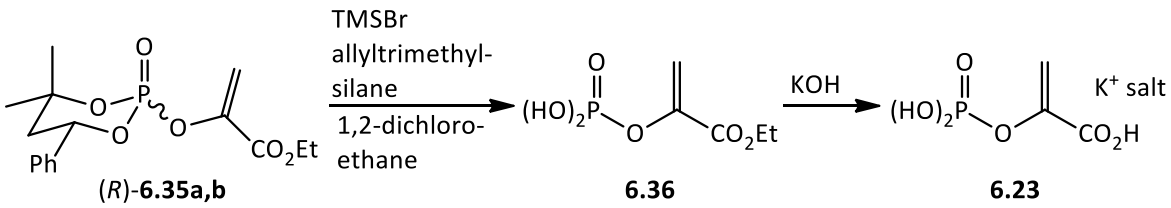
6.8.1 Synthesis design

The synthesis was based on a discovery by Pisljagic.[142] She found that the phosphonates formed during the reaction of cyclic phosphites (*R*)-**6.32a,b** with bromopyruvate **6.33** immediately undergo a phosphonate-phosphate rearrangement to diastereomeric enolphosphates (*R*)-**6.35a,b** in 30% yield that can be separated by flash chromatography (Scheme 6.13). (From now on, when ''*R*'' or ''*S*'' is used, they mean the configuration at C-6. When ''R_P'' and ''S_P'' are used, they mean the configuration on phosphorus.)



Scheme 6.13. Preparation of diastereomeric enolphosphates (*R*)-**6.35a,b**.

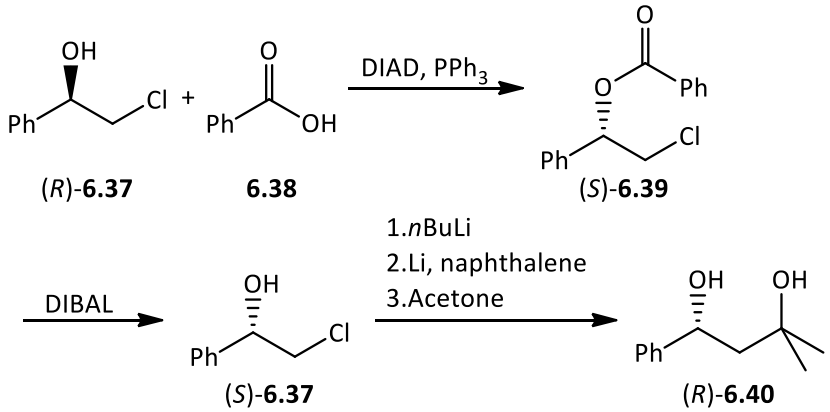
I found that the enolphosphates (*R*)-**6.35a,b** can be transformed into a salt of phosphoenolpyruvic acid quite easily. The hydroxy groups on phosphorus can be deprotected with TMSBr and allyltrimethylsilane to obtain ester **6.36**. The carboxylic ester group can be saponified with NaOH and the sodium salt could be converted to the potassium salt **6.23** needed for the enzymatic analysis of the ee (Scheme 6.14).[143]



Scheme 6.14. Conversion of enolphosphates (*R*)-**6.35a,b** to the potassium salt of phosphoenolpyruvic acid (**6.23**).

Although the synthetic approach for the phosphoenolpyruvate was in principle viable, individual steps had to be improved. The low yield of the enolphosphates had to be increased and the labelling of precursors had to be solved. The sequence was tested in the racemic and optically active series first. The ^{17}O had to be introduced as late and as efficiently as possible, because $H_2{}^{17}O$ is very expensive.

I took advantage of the fact that Pisljagic developed a synthesis for enantiomerically pure diol **6.40** derived from chlorohydrin **6.37** and acetone.[142] A preliminary experiment of the Mitsunobu reaction showed that it could be used to label the chlorohydrin with ^{18}O. Commericially available (*R*)-chlorohydrin **6.37** of 97% ee yielded with Ph_3P/DIAD/benzoic acid (**6.38**) (*S*)-benzoate **6.39** of unknown ee. The ester was deprotected with DIBAH and the ee of the isolated (*S*)-chlorohydrin **6.37** was determined with HPLC on a chiral stationary phase. The ee was found to be 99%, virtually identical to that of the starting material, although it is known that substitution reactions at benzylic position are prone to partial racemization (Scheme 6.15).



Scheme 6.15. Proposed synthesis of diol **6.40** with steps needed for the labeling.

Therefore the Mitsunobu reaction with labeled benzoic acid seemed to be the best step for introducing ^{18}O. Doubly ^{18}O-labeled benzoic acid ([$^{18}O_2$]**6.38**) was prepared according to a known

procedure from benzonitrile and trichloromethylbenzene and $H_2{}^{18}O$.[53] Although this reaction was in the beginning of the synthesis, it was performed because $H_2{}^{18}O$ is much cheaper than $H_2{}^{17}O$. The Mitsunobu reaction was repeated with the labeled benzoic acid (98% ^{18}O) with 92% yield and the reduction with 84% yield.

The coupling of chlorohydrin with acetone is the worst reaction in the sequence. It is described in the literature[144] but the yields were unfortunately not reproducible. First naphthalene was reacted with lithium to give lithium naphthalenide and the intensely colored reaction mixture was slowly added to the chlorohydrin converted to the lithium alkoxide with *n*BuLi at low temperature. There are a couple of things that can go wrong and thus decrease the yield and also problems that prevented me from fixing them:

1. Lithium is easily oxidized by air during its storage which can hinder the lithiation.
2. It is impossible to test whether the lithiation is completed or whether the lithium naphthalenide or LiDTBB [or di(*tert*-butyl)biphenyl = DTBB] decomposed – the titration of the solution only gives the information on how much LiOH is formed when the reaction is quenched with water, but none on whether it comes from lithium naphthalenide (or LiDTBB) or a decomposition product.
3. There may be some decomposition when the chlorohydrin is deprotonated by *n*BuLi at the hydroxyl group.
4. The solution of lithium naphthalenide or LiDTBB should be slowly added to the lithium alcoxide derived from chlorohydrin at very low temperature, but even addition over 30 minutes at -95 to -78°C does not guarantee that the solution does not temporarily get warmer and that intermediates decompose.
5. There is no way to check whether the double lithiation of chlorohydrin is completed or the product decomposed already.
6. It is impossible to tell when the coupling with acetone is finished or whether it has been stirred for too long and decomposition takes place.

The results of my optimization experiments with racemic and enantiomerically pure chlorohydrin can be seen in Table 6.1.

It is obvious, that the results are all over the place. For the sake of clarity experiments performed with lithium naphthalenide will be compared first. As can be seen from the results, using 3.5 eq. of lithium naphthalenide was worse than using 2.5 eq. (entries 1 and 2 vs. especially entries 3-4).

Entry	Lithium[1]	Arene (eq)[2]	Arene lithiation (h)[3]	Time of chlorohydrin lithitation (h)[4]	Coupling with acetone (h)[5]	SM:P:BP[6]	Yield (%)[7]
1	ribbon, old	Naphthalene (3.5)	3	0.5	1	N/A	18
2	ribbon, old	Naphthalene (3.5)	2.5	0.5 [(-78)-(-95°C)]	1	0.64:1:1.42	23
3	ribbon, old	Naphthalene (2.5)	2	4 [(-78)-(-95°C)]	1	0.29:1:0.20	48
4	ribbon, old	Naphthalene (2.5)	2	2 [(-78)-(-95°C)]	1	1.15:1:0.42	39
5	ribbon, old	DTBB (2.5)	3	2.5 [(-78)-(-95°C)]	1	N/A	57
6	ribbon, old	DTBB (2.5)	2.5	2.5 [(-78)-(-95°C)]	18	N/A	28
7	ribbon, old	DTBB (2.5)	2.5	2.5 [(-78)-(-95°C)]	1	N/A	53
8	ribbon, old	DTBB (2.5)	2.5	2.5 [(-78)-(-95°C)]	1	N/A	18
9	ribbon, old	Naphthalene (2.5)	17	2.5 [(-78)-(-95°C)]	2.5	N/A	14
10	ribbon, old	DTBB (2.5)	2	1.5 [(-78)-(-95°C)]	1	N/A	11
11	granular, new	DTBB (2.5)	2	2 [(-78)-(-95°C)]	1.5	N/A	36
12	granular, new	DTBB (2.5)	3	2 [(-78)-(-95°C)]	1	N/A	10
13	granular, now old	Naphthalene (2.5)	5	1.5	1	N/A	36
14	granular, now old	Naphthalene (2.5)	4.5	1.5	1.5	N/A	23
15	granular, now old	Naphthalene (2.5)	4.5	4	0.5	1.12:1:0.10	18
16	granular, now old	Naphthalene (2.5)	4	4	0.5	0.64:1:0.50	36
17	granular, now old	Naphthalene (2.5)	4	4	18 (-78°C)	14:1:2	N/A
18	granular, now old	Naphthalene (2.5)	4	4	18 (-78°C)	1:0:0.2	N/A
19	granular, now old	DTBB (2.5)	4 (0°C)	4	18 (-78°C)	0.92:1:0.32	37
20	granular, now old	DTBB (2.5)	16 (0°C)	4	18 (-78°C)	3.93:1:0	N/A
21	granular, now old	DTBB (2.5)	4	4	18 (-78°C)	4.53:1:0.46	N/A
22	granular, now old	DTBB (2.5)	19 (0°C)	4	18 (-78°C)	4.39:1:0	N/A
23	granular, now old	DTBB (2.5)	4	4	18 (-78°C)	0.96:1:0.49	N/A
24	granular, new	DTBB (3)	4	4	18 (-78°C)	0:1:0.48	57
25[8]	granular, new	DTBB (3)	4	4	18 (-78°C)	0:1:0.32	53
26[8]	granular, new	DTBB (3)	4	4	18 (-78°C)	0.55:1:0.11	50
27[8]	granular, new	DTBB (3)	4	4	18 (-78°C)	0.45:1:0.15	47

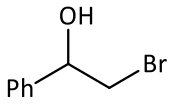
Table 6.1. Optimization of the coupling conditions. All experiments are given in chronological order. [1]At first, old (~1 year) lithium ribbon was used, but it was already rather oxidized at the surface, so granular lithium was bought which also became oxidized during the course of this project. For the last four experiments, brand new granular lithium was bought and used. [2]The same amount of lithium and arene was used, eq. are with respect to the chlorohydrin. [3]Performed at RT unless otherwise specified. [4]Performed at -78°C unless otherwise specified. [5]Performed at RT unless otherwise specified.[6]SM is starting material **6.37**, P is product **6.40**, BP (byproduct) is 1-phenylethanol, ratio calculated from ^{1}H NMR of the crude mixture. N/A (not available) means no ^{1}H NMR spectrum was taken. [7]Yield after flash chromatography, N/A means that the product was not purified. [8]Performed with ^{18}O-labeled (*S*)-chlorohydrin (*S*)-[^{18}O]**6.37**.

There was virtually no difference between using new granular lithium (entries 13-18 with the exception of entry 16) and old lithium in the form of a ribbon (that cannot be weighed as precisely, entries 3-4). The yields were not reproducible even when almost same reaction conditions were used (entry 15 vs. 16). In none of the cases where ^{1}H NMR spectrum of the crude product was recorded it was possible to get all of the starting material lithiated (entries 2-4, 15-18). I argued that the problem might lie in a slow reaction between lithium and naphthalene so it was reacted overnight, but again with a poor yield, probably due to decomposition of the complex (entry 9). A reaction time for the addition of the dilithiated chlorohydrin to acetone for 18 hours at -78°C brought no increase in the yield (entries 17, 18). 1-phenylethanol was detected as byproduct, which was probably formed by protonation of the dilithiated chlorohydrin by acetone and subsequent work-up (entries 2-4, 15-18).

Then it was decided to use 4,4'-di-*tert*-butyl-biphenyl (DTBB) as a different arene instead of naphthalene.[145] The first experiments were promising, even though the results were not reproducible (entries 5,7 vs. 6,8, 10-12). In order to start the reaction between lithium and DTBB, the reaction mixture had to be sonicated for around 45 minutes (the solution became progressively warmer) until it started turning blue and then the reaction mixture was stirred at RT. The desired dark blue/green color was gradually turning brown which could signalize decomposition. When formation of the LiDTBB was tried at 0°C with sonication for only 3 minutes to see whether the yield would be better, the results were even worse. Probably, the reaction does not proceed very quickly at this temperature and longer reaction times do not help (entries 19, 20, 22). The last parameter which could be changed at that point were the conditions for the coupling of the dilithiated intermediate with acetone. Therefore, this last part of the reaction was performed at -78°C overnight (entry 17 and up). The first results were not encouraging (entries 19-23), but now it seemed that the problem was lithium, not the reaction itself. This was confirmed when coupling was performed with brand new lithium, even though it was evident that the more often the lithium was opened, the poorer the yield (entries 24-27).

The last three experiments were repeated with ^{18}O-labeled chlorohydrin (*S*)-[^{18}O]**6.37** and fortunately resulted in ^{18}O-labeled diol (*R*)-[^{18}O]**6.40** needed for the synthesis in over 50% yield.

Later, the condensation with acetone was tried again to see whether its yield could be improved by using bromohydrin **6.41** (Figure 6.3) instead of chlorohydrin.



6.41

Figure 6.3. Bromohydrin **6.41**.

Since these were just preliminary experiments, they were performed with racemic bromohydrin **6.41** obtained by the reduction of 2-bromoacetophenone with $NaBH_4$ in THF in 85% yield. The results of these experiments are summarized in Table 6.2.

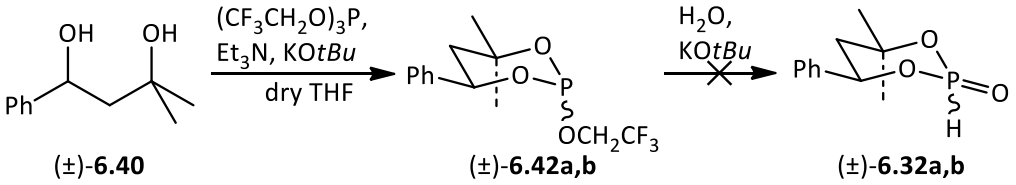
Entry	Lithium[1]	Arene (eq)[2]	Arene lithiation (h)[3]	Time of chlorohydrin lithitation (h)[4]	Coupling with acetone (h)[5]	SM:P:BP[6]	Yield (%)[7]
1	granular, now old	Naphthalene (2.5)	4	2.5	0.5	4:1:4	N/A
2	granular, now old	Naphthalene (2.5)	4	2	18 (-78°C)	only BP	N/A
3	granular, now old	Naphthalene (2.5)	4	2	18 (-78°C)	0:1:0.40	56
4	granular, now old	Naphthalene (2.5)	5	2	18 (-78°C)	2.7:1:2.5	N/A
5	granular, now old	Naphthalene (2.5)	4	2.5	18 (-78°C)	0.6:1:0.5	N/A
6	granular, now old	Naphthalene (2.5)	3.5	4	18 (-78°C)	0:1:0.5	42

Table 6.2. Optimization of the coupling conditions. All experiments are given in chronological order. [1]Only granular, already old lithium was used. [2]The same amount of lithium and arene was used, eq. are with respect to the bromohydrin **6.41**. [3]Performed at RT unless otherwise specified. [4]Performed at -78°C unless otherwise specified. [5]Performed at RT unless otherwise specified.[6]SM is starting material **6.41**, P is product **6.40**, BP is the byproduct 1-phenylethanol, ratio calculated from ^{1}H NMR spectrum of the crude mixture. N/A means no ^{1}H NMR spectrum was taken. [7]Yield after flash chromatography, N/A means that the crude product was not purified.

The results suggest, that the yield is the same or a little better than that of the reaction with chlorohydrin **6.37** (entries 3 and 6), but not significantly. So it was not worth to prepare enantiomerically pure bromohydrin **6.41** and this alternative for the preparation of the diol was abandoned.

In order to synthesize cyclic phosphites (±)-**6.32a,b**, a couple of approaches were investigated. Racemic diol (±)-**6.40** was first coupled with tris(2,2,2-trifluoroethyl) phosphite to form cyclic phosphites (±)-**6.42a,b** which was achieved with Et_3N and KO*t*Bu as bases and stirring for 18 h

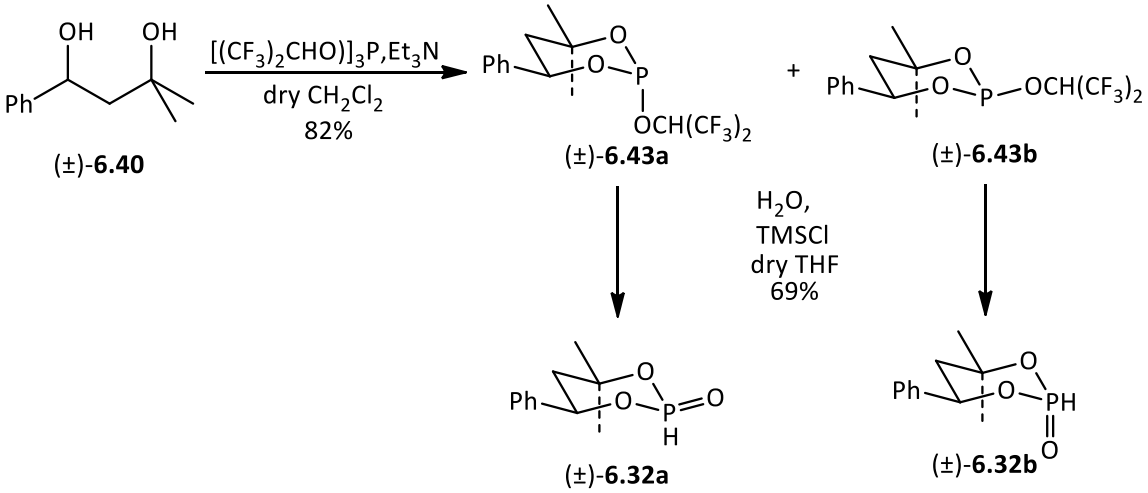
(complete conversion was determined by ^{1}H NMR spectroscopy) (Scheme 6.16). Unfortunately, base catalysed hydrolysis of phosphites (±)-**6.42a,b** to cyclic phosphites (±)-**6.32a,b** by addition of water, more KO*t*Bu and warming to 60°C was not successful. CF_3CH_2OH seemed to be a bad leaving group at phosphorus.



(±)-**6.40** (±)-**6.42a,b** (±)-**6.32a,b**

Scheme 6.16. Unsuccesful attempt to prepare cyclic phosphites (±)-**6.32a,b** using tris (2,2,2-trifluoroethyl)phosphite.

To use a better leaving group, hexafluoroisopropanol, the diol was transesterified with tris(1,1,1,3,3,3-hexafluoro-2-propyl) phosphite prepared according to literature (Scheme 6.17).[146]



(±)-**6.40** (±)-**6.43a** (±)-**6.43b** (±)-**6.32a** (±)-**6.32b**

Scheme 6.17. Preparation of cyclic phosphites (±)-**6.32a** and (±)-**6.32b** using tris(1,1,1,3,3,3-hexafluoro-2-propyl) phosphite.

The racemic diastereomeric phosphites (±)-**6.43a** and (±)-**6.43b** could be separated by HPLC on a Nucleosil 50-5 column. The base-catalyzed hydrolysis of the mixture of phosphites **6.43** (ratio by NMR: 1:0.51) to cyclic phosphites (±)-**6.32a,b** was unsuccessful again. Reversing the order of reactions and performing the hydrolysis first did not bring any success either. However, acid-catalyzed hydrolysis of phosphites (±)-**6.43a,b** with excess H_2O and catalytic TMSCl to produce HCl in situ worked well.

Initially, the two diastereomeric cyclic phosphites (±)-**6.32a** and (±)-**6.32b** produced in a 2:1 ratio could not be separated by flash chromatography, but by HPLC on an achiral column. Letters **a** and **b** denote the less polar and more polar diastereomer (by TLC), respectively. In addition, diastereomer (±)-**6.43a** is a crystalline compound. A single crystal X-ray structure analysis revealed its configuration given in Figure 6.4. (±)-**6.43a** was found to be the *trans* isomer and consequently (±)-**6.43b** had to be the *cis* isomer [*trans* and *cis* refer to the relative arrangement of equatorial Ph and axial and equatorial $(CF_3)_2CHO$, respectively]. Similarly, the sequence with the racemic diol was repeated with the (*R*)-diol and the respective products were fully characterized.

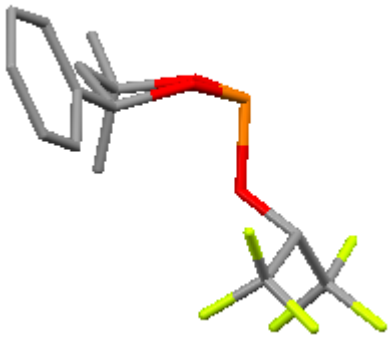
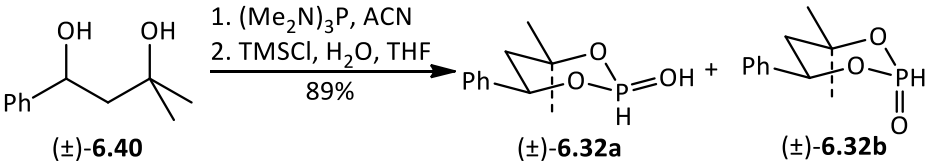


Figure 6.4. X-ray structure of (±)-**6.43a**.

Each homogeneous diastereomer of (±)-**6.43** was hydrolyzed separately to see whether epimerization occurs at phosphorus. It was indeed found that both diastereomers (±)-**6.43a** and (±)-**6.43b** partially epimerised (5.7% and 10%, respectively). When a mixture of the diastereomeric phosphites (±)-**6.43** (**a**:**b** = 2:1) was hydrolyzed under acidic conditions, the ratio of the resulting cyclic phosphites was 1:0.40 [(±)-**6.32a**: (±)-**6.32b**]. (±)-**6.32a** was found to be the *cis* isomer and (±)-**6.32b** was found to be the *trans* isomer based on their ^{1}H NMR spectra. This finding was corroborated by a single crystal structure analysis by Pallitsch and Roller.

A 1:1 (or as close as possible) ratio of diastereomeric cyclic phosphites **6.32** was desirable to obtain the enolphosphates **6.35** in a 1:1 ratio as well. That seemed to be achievable by hydrolysis of a mixture of cyclic phosphites **6.43** in a 1:1 ratio. The best conditions which actually made this conversion easier and the use of tris(1,1,1,3,3,3-hexafluoro-2-propyl) phosphite unnecessary were stirring of the racemic diol (±)-**6.40** with tris(dimethylamino)phosphine in dry ACN in a microwave oven at 110°C for 1 h and the subsequent rapid hydrolysis of the crude product after removal of

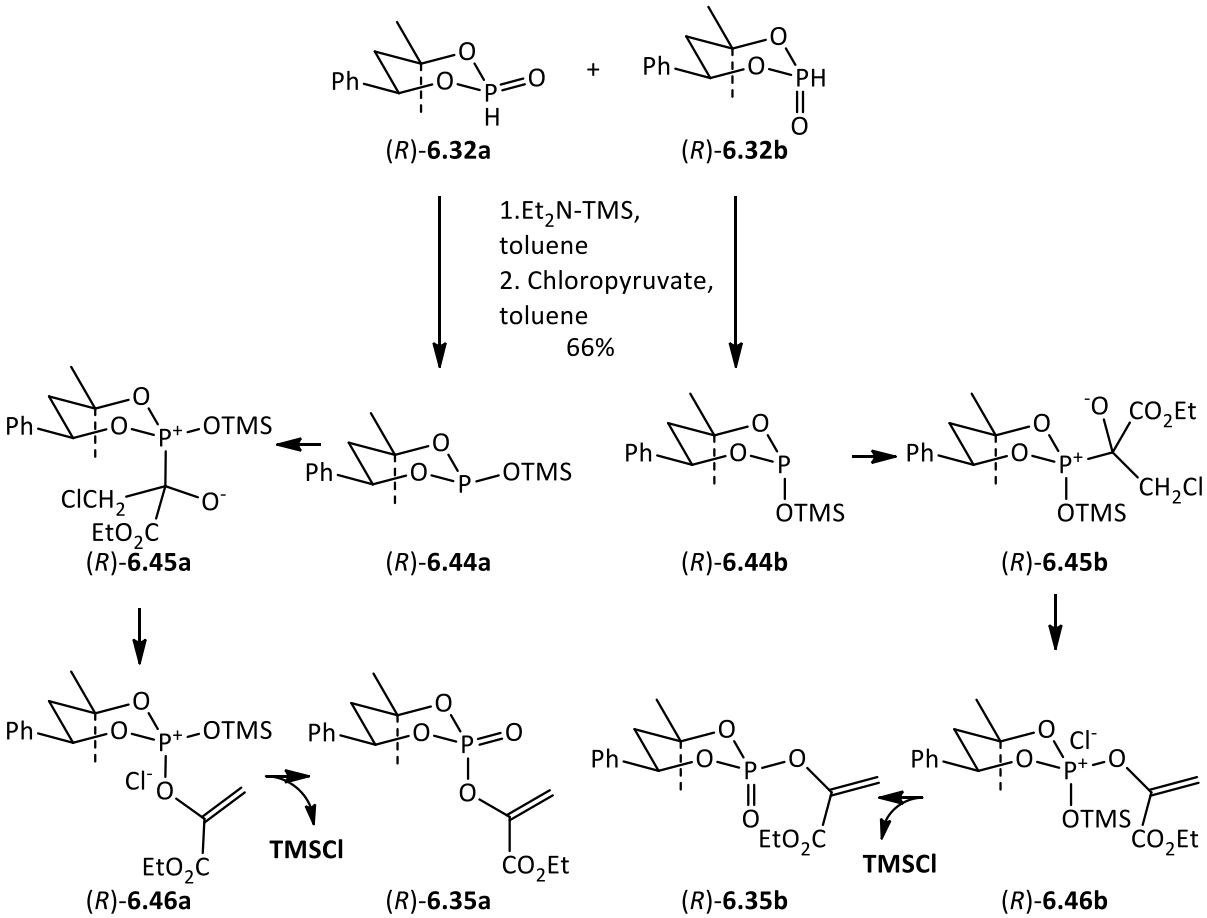
volatile components with catalytic TMSCl and H_2O. The mixture [(±)-**6.32a**: (±)-**6.32b** = 0.68:1] of cyclic phosphites resulted in 89% yield (Scheme 6.18).



(±)-**6.40** (±)-**6.32a** (±)-**6.32b**

Scheme 6.18. Improved synthesis of cyclic phosphites (±)-**6.32a,b**.

The next and critical step was the conversion of cyclic phosphites **6.32a** and **6.32b** to diastereomeric enolphosphates **6.35a** and **6.35b** (Scheme 6.19)



Scheme 6.19. Synthesis of diastereomers (*R*)-**6.35a** and (*R*)-**6.35b**.

This was achieved easily by silylating the mixture of the enantiomerically pure cyclic phosphites (*R*)-**6.32a** and (*R*)-**6.32b** derived from the (*R*)-diol (*R*)-**6.40** with *N,N*-diethyl-1,1,1-trimethylsilylamine. The progress of the reaction was monitored by ^{31}P NMR spectroscopy. The subsequent Perkow reaction of the silylated cyclic phosphites (*R*)-**6.44a** and (*R*)-**6.44b** with

chloropyruvate furnished enolphosphates (*R*)-**6.35a** and (*R*)-**6.35b** easily separable by flash column chromatography in a combined yield of 66%.[147] It is assumed that the silyl phosphates (*R*)-**6.44a** and (*R*)-**6.44b** are added to the carbon atom of the more electrophilic carbonyl group to form betains (*R*)-**6.45a** and (*R*)-**6.45b**. Migration of the substituted phosphorus group from the carbon atom to the oxyanion generates vinyloxyphosphonium salts (*R*)-**6.46a** and (*R*)-**6.46b**, which give enolphosphates (*R*)-**6.35a** and (*R*)-**6.35b** with the release of TMSCl.

It is noteworthy that the silylation had to be monitored for completion, because it took different reaction times every time this experiment was performed. Also a small amount of starting material does not interfere with the coupling as it also seems to react with the chloropyruvate, possibly after silylation with TMSCl formed during the Perkow reaction. The ratio of diastereomeric enolphosphates (*R*)-**6.35a** and (*R*)-**6.35b** was 0.62:1 [ratio of starting cyclic phosphites (*R*)-**6.32a**: (*R*)-**6.32b** = 0.73:1] with the yield of 66%, which is much better than Pisljagic´s yield of 30%. Both diastereomers were crystalline compounds. A single-crystal X-ray structure analysis allowed the assignement of *trans* configuration to enolphosphate (*R*)-**6.35a** and consequently *cis* to isomer (*R*)-**6.35b** (Figure 6.5).

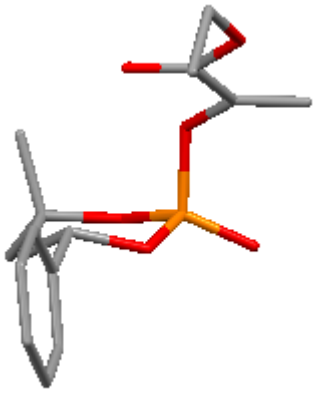


Figure 6.5. X-ray structure of enolphosphate (*R*)-**6.35a**.

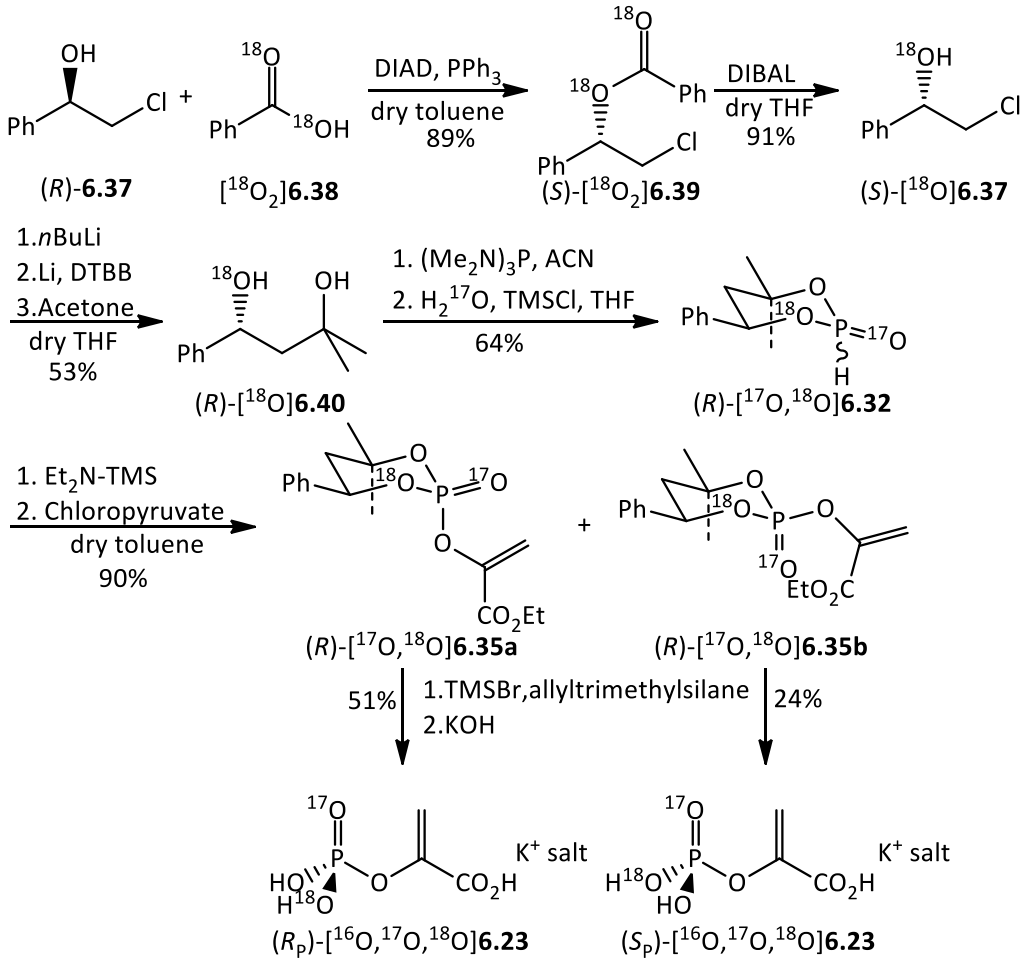
In order to investigate the epimerization at phosphorus during the reaction, cyclic phosphites (*R*)-**6.32a** and (*R*)-**6.32b** were separated by flash chromatography and each diastereomer was transformed into an enolphosphate (*R*)-**6.35** separately. Cyclic phosphite (*R*)-**6.32a** did not epimerize at phosphorus neither during silylation nor the Perkow reation. However, cyclic phosphite (*R*)-**6.32b** did (7%) when it was silylated with *N,N*-diethyltrimethylsilane in toluene. Epimerization was negligible (1%) when dimethyltrimethylsilylamine was used both for the silylation and as the solvent. Nifant´ev and Borisenko found that the cyclic H-phosphonate trans-4-

methyl-2-oxo-2H-1,3,2-dioxaphosphorinane was converted to the *cis* isomer by inversion of configuration at the phosphorus atom on heating.[148]

The last step in the synthesis of phosphoenolpyruvate was the global deprotection of enolphosphates (*R*)-**6.35a** and (*R*)-**6.35b**. This was achieved according to the procedure already mentioned earlier with around 50% yield (Scheme 6.14).

6.8.2 Synthesis and analysis of fully labeled compound

Scheme 6.20 shows the complete synthesis of (*R*)- and (*S*)-[^{16}O,^{17}O,^{18}O]phosphoenolpyruvate {(*R*)- and (*S*)-[^{16}O,^{17}O,^{18}O]**6.23**} where ^{18}O was introduced into chlorohydrin (*R*)-**6.37** and ^{17}O was introduced into cyclic phosphites (*R*)-[^{17}O,^{18}O]**6.32** on hydrolysis of the intermediate cyclic phosphoramidites with $H_2{}^{17}O$ (70% ^{17}O) formed from diol and tris(dimethylamino)phosphine.



Scheme 6.20. Synthesis of (R_P)- and (S_P)-[^{16}O,^{17}O,^{18}O]phosphoenolpyruvate {(R_P)- and (S_P)-[^{16}O,^{17}O,^{18}O]**6.23**}.

The synthesis of the enantiomers of chirally labeled phosphoenolpyruvates was straightforward and the reaction steps were performed in analogy to the experiments in the non-labeled series. The ee of (*S*)-chlorohydrin and (*R*)-diol was determined by HPLC on a chiral stationary phase and the labeling grade by MS. [^{18}O]-Labeled diol (*R*)-[^{18}O]**6.40** had an ee >99.2% and contained 98.2% ^{18}O. [^{17}O,^{18}O]-labeled cyclic phosphites (*R*)-[^{17}O,^{18}O]**6.32** contained 64.3% ^{17}O and 98.6% ^{18}O. Both [^{17}O,^{18}O]-labeled phosphates (*R*)-[^{17}O,^{18}O]**6.35** contained 64.5% ^{17}O and 98.6% ^{18}O.

The chemoenzymatic analysis of the chiral phosphoenolpyruvate was performed according to the method developed by Lowe et al. and already used by Knowles et al.[134] It was performed with (R_P)-[^{16}O,^{17}O,^{18}O]**6.23** formed through the old route through cyclic phosphite (*R*)-[^{18}O]**6.43** and the less polar (*R*)-[^{17}O,^{18}O]**6.35a**. The first two enzymatic reactions were generally straightforward (Scheme 6.12). It was always monitored by ^{31}P NMR spectroscopy and showed a peak to peak conversion. It seems that the transfer of phosphate from ATP to glucose was the rate determining step, because ATP, not ADP was always present in the spectrum. The only tricky part was the purification of glucose-6-phosphate ([^{16}O,^{17}O,^{18}O]**6.29**). It was performed by an AG1-X8 ion exchanger in the HCO_3^- form but the uncomfortable part was its visualization – it had to be done by first spraying the TLC plate with perchloric acid to free the phosphate and then dying it with malachite green.[149] The next sequence was the cyclization itself and methylation. Even when I started from 0.5 mmol of labeled G-6-P [^{16}O,^{17}O,^{18}O]**6.29**, I only got traces of product that was purified by flash chromatography, but fortunately it was enough for the ^{31}P NMR analysis.

Before I will start talking about the actual analyses, I would like to explain the calculations and general logic of the catalysis. Assuming the substance is labeled with 100% ^{17}Oand ^{18}O, 6 esters will be formed from each (R_P)- and (S_P)-[^{16}O,^{17}O,^{18}O]**6.23** (Figure 6.6).

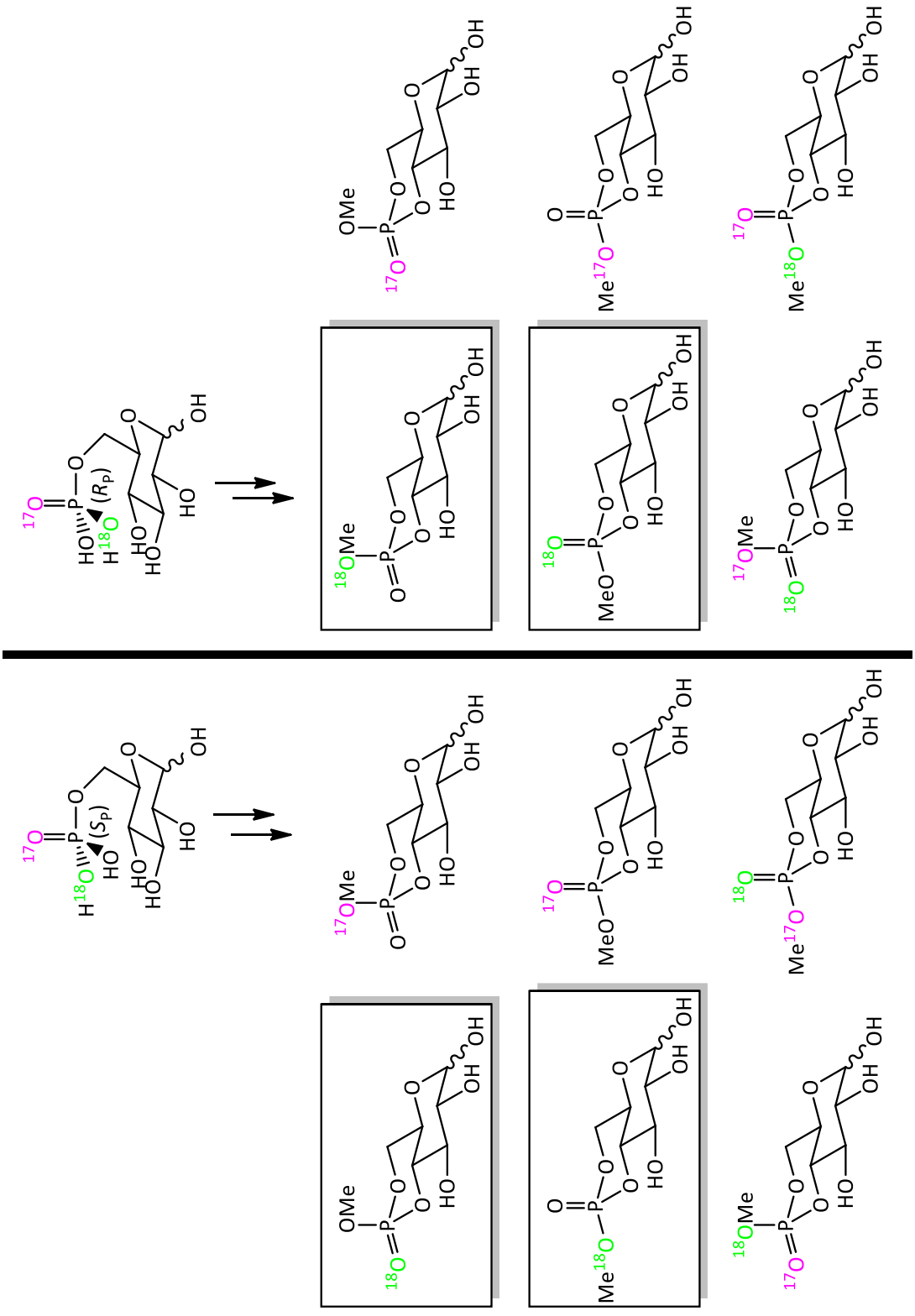


Figure 6.6. 6 possible esters derived from (R_P)- and (S_P)-[^{16}O,^{17}O,^{18}O]**6.23**. The esters in brackets are the only ones visible in ^{31}P NMR.

When ^{17}O is attached to the phosphorus, its signal in ^{31}P NMR becomes very broad and thus invisible, so the only esters visible in the NMR spectrum are the ones without ^{17}O (2 out of 6 for each diastereomer). Things of course get more complicated when the labeling grade is not 100%,

because in place of ^{17}O we now have ^{16}O or ^{18}O which makes those esters visible in the NMR spectrum. We assume the content of ^{18}O is practically 100% based on MS analysis of [^{17}O,^{18}O]**6.35** which gave the content of 98.6% but the approximation will affect the result somewhat (Figure 6.7).

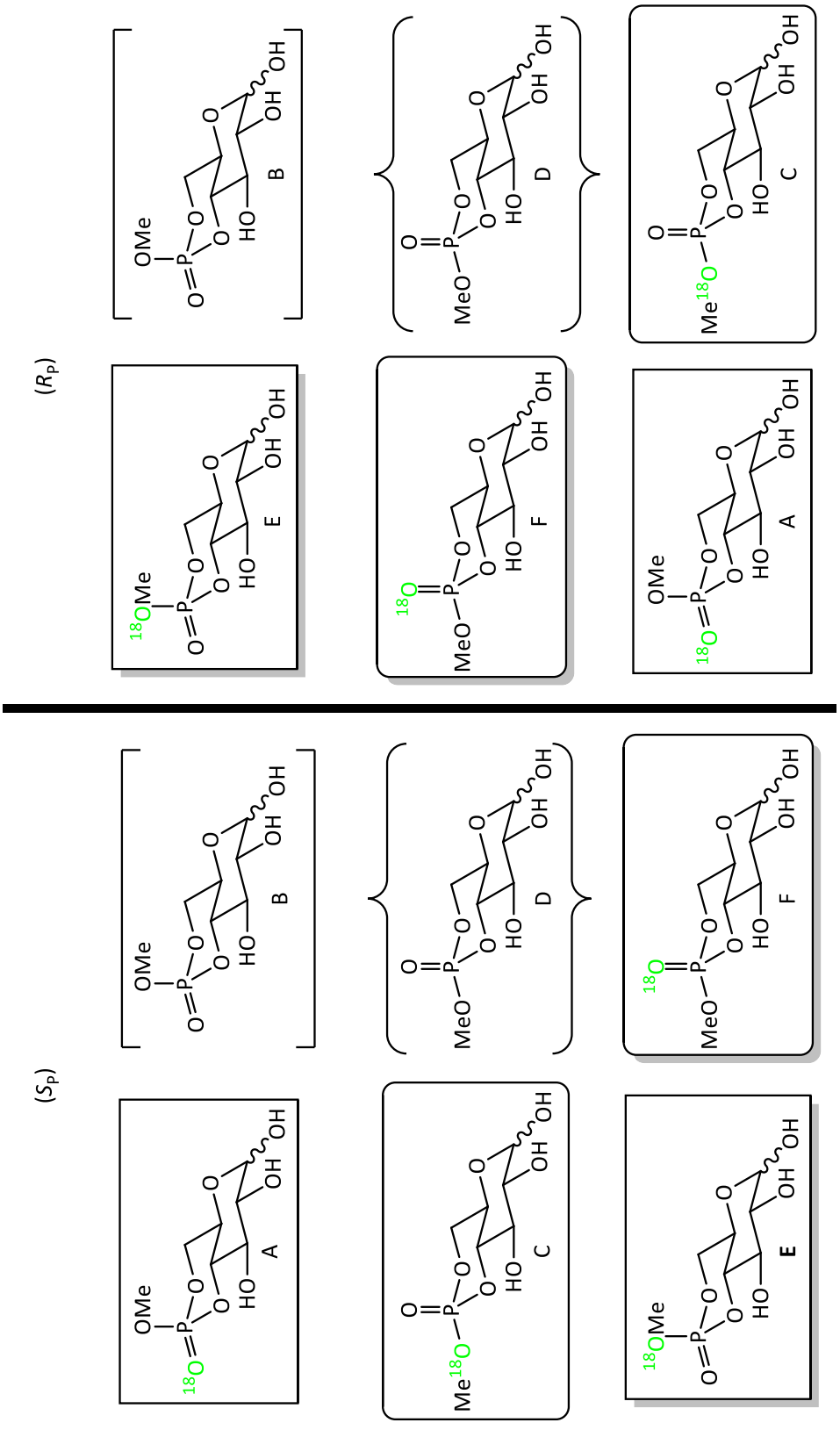


Figure 6.7. Esters formed when the labeling grade of ^{17}O is not 100%.

Esters in the same type of brackets are identical. As can be seen, all structures result from both (R_P)- and (S_P)-[^{16}O,^{17}O,^{18}O]**6.23**.

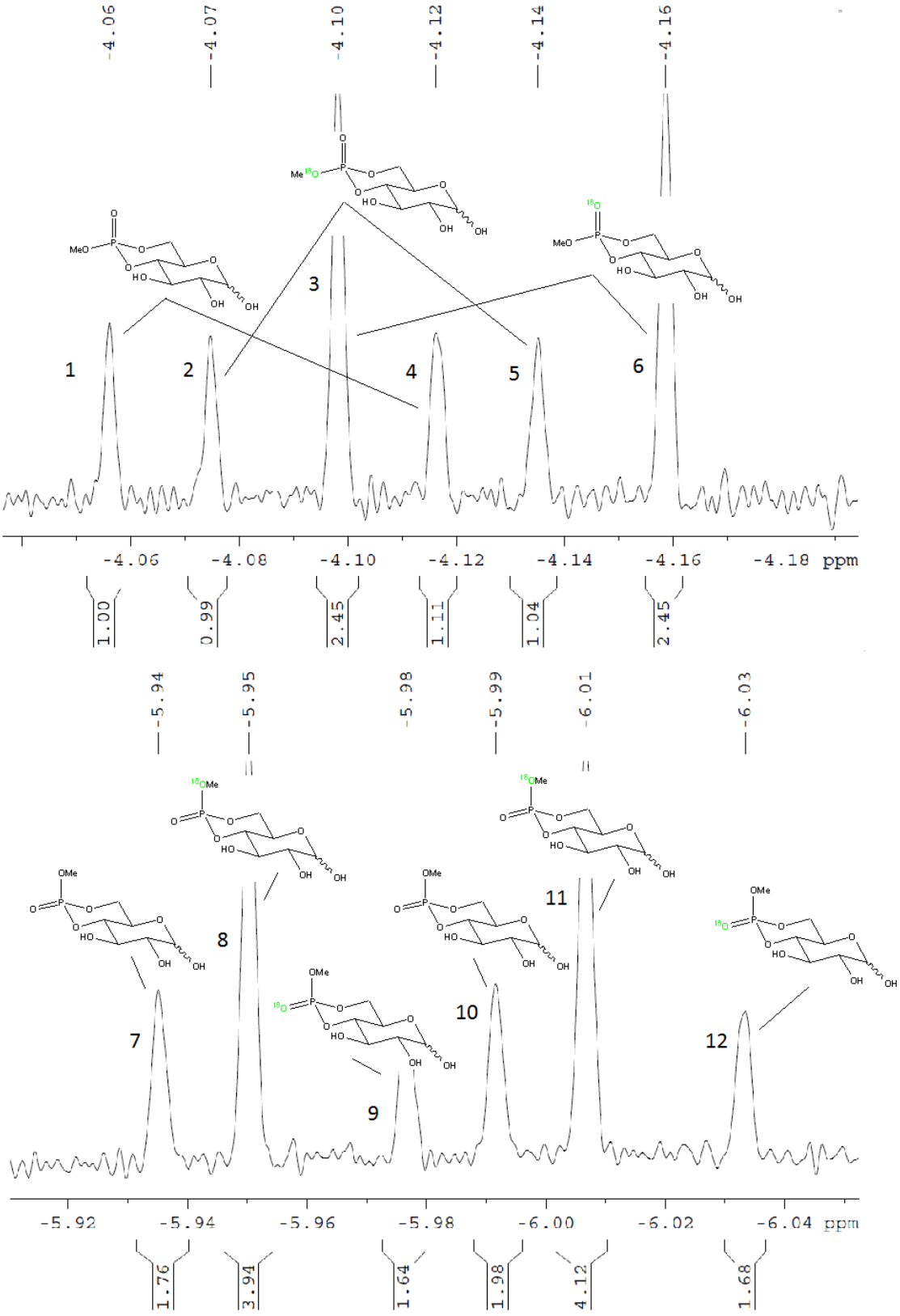


Figure 6.8. Segments of ^{31}P NMR spectrum containing the desired peaks with their assignment.

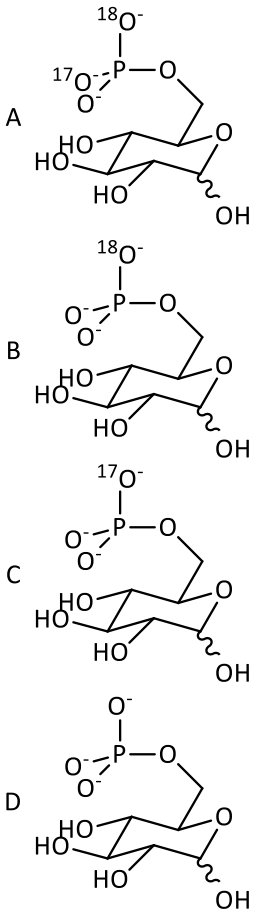
Structures, where ^{17}O was replaced by ^{18}O are practically nonexistent because there was almost none (<1%) of ^{18}O in our $H_2{}^{17}O$. When I performed the analysis with fully labeled (R_P)-[^{16}O,^{17}O,^{18}O]**6.23**, the following peaks were visible in the NMR spectrum (Figure 6.8).

As I assigned the peaks based on literature,[141] I noticed that they apparently made a mistake. They assumed that the peaks belonging to α/β pairs were 1/2, 3/4 and 5/6, but I noticed that it was impossible, because the ratio must be the same across all couples, so I paired peaks 1/4, 2/5 and 3/6. The mistake probably comes from the fact that their labeling grade was smaller and all peaks had pretty much the same area. The calculation itself is easy once one figures it out. Basically one has to solve 4 equations with 3 unknowns. The first thing to do is to ''divide'' peaks into ''r'' (relative size of peaks representing esters from only from (R_P)-[^{16}O,^{17}O,^{18}O]**6.23** if the content of ^{17}O was 100%, 3, 6, 8, 11), ''s'' (relative size of peaks representing esters from only from (S_P)-[^{16}O,^{17}O,^{18}O]**6.23** if the content of ^{17}O was 100%, peaks 2, 5, 9, 12), ''unlabeled'' (relative size of peaks from esters containing no labeled oxygen, peaks 1, 4, 7, 10) and ''invisible'' (stands for the relative size of all peaks that are invisible) and define their relationship with the help of unknown ''a'' which represents the relative amount attributed to the visible peaks and ''1-a'' represents all the rest. As an example I will simply use my results (Figure 6.9).

$$r = 12.96 = 53.64\%$$
$$s = 5.35 = 22.14\%$$
$$unlabeled = 5.85 = 24.21\%$$
$$\downarrow$$
$$r = 0.5364a$$
$$s = 0.2214a$$
$$unlabeled = 0.2421a$$
$$invisible = 1 - a$$

Figure 6.9. Defining one side of the equations where ''a'' is the amount of visible peaks.

In order to define the other side of the equation, we have to think about what all is present in the solution before the cyclization (now ignoring the configuration) and to what amount, which can be calculated based on the last known labeling grade and the assumption, that if labeling is lost, it is lost for each isomer equally (Figure 6.10).



$A = {}^{17}O*{}^{18}O = (0.674-x)*(0.963-x) = 0.649 - 1.637x + x^2$

$B = (1-{}^{17}O)*{}^{18}O = (0.326+x)*(0.963-x) = 0.314 + 0.637x - x^2$

$C = {}^{17}O*(1-{}^{18}O) = (0.674-x)*(0.037+x) = 0.025 + 0.637x - x^2$

$D = (1-{}^{17}O)*(1-{}^{18}O) = (0.326+x)*(0.037+x) = 0.012 + 0.363x + x^2$

Figure 6.10. Amount of every species calculated based on the known labeling grade with taking into account the possibility of labeling defined by ''x''.

Now that this is done, we have to realize which esters will be formed from each of these species (Figure 6.11).

At last we can start piecing together the other side of the equation. We assume that the probability of losing each oxygen is 1/3, meaning there is no isotope effect, but this is where it gets tricky. The ''r'' peaks are formed by 2 out of 6 esters derived from species A with (*R*) configuration (the other 4 are invisible due to ^{17}O) and from 2 out of 6 (1/3) esters formed from species B (the other esters form other peaks). The ''s'' peaks are formed by 2 out of the 6 (1/3) esters formed from species A with (*S*) configuration (could also be written as 1-R, other 4 are invisible) and from 2 out of 6 (1/3) esters formed from species B (the other esters form other peaks). ''Unlabeled'' peaks are formed from 2 out of 6 esters formed from species B, from 2 out of 6 esters formed from species C and from all of the esters formed from species D. The invisible peaks are formed from 8 out of 12 (2/3) esters formed from species A [both from (*R*)- and (*S*)-configured] and from 4 out of 6 esters formed from species C.

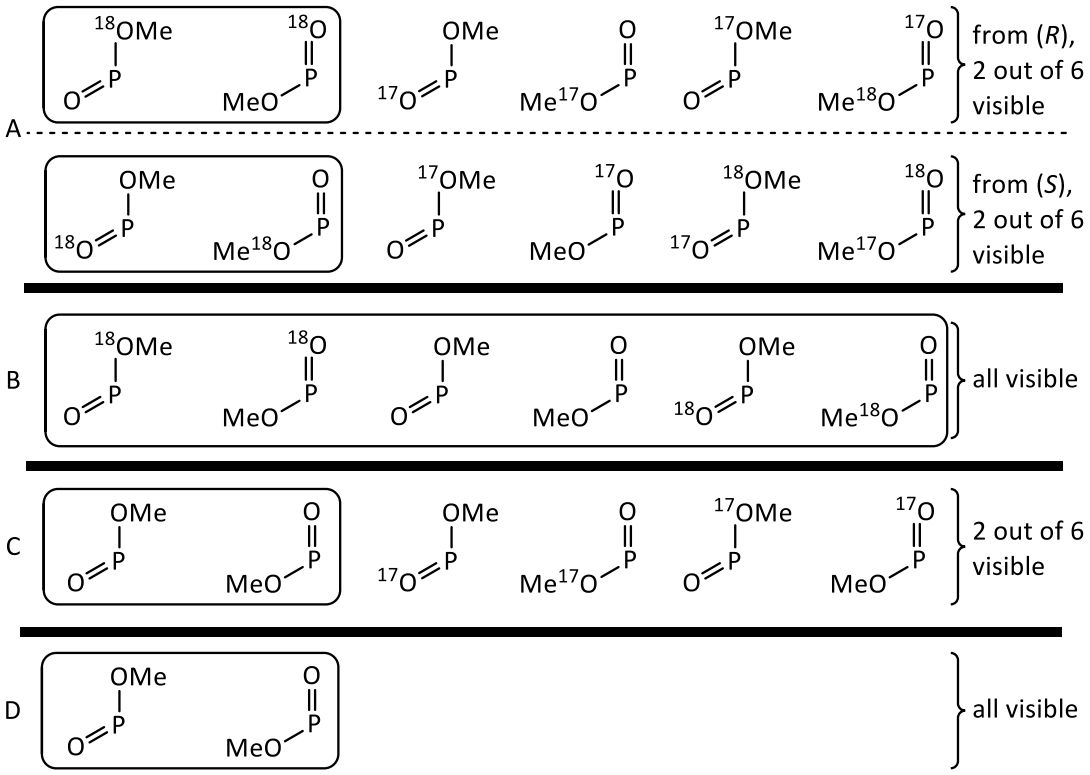


Figure 6.11. All species (schematically drawn, position facing up represents the axial position and position facing down represents equatorial position) present in the solution after cyclization. The structures in brackets are esters visible in ^{31}P NMR, the others are invisible.

The following equations are a general formula, later I will substitute my own number to show an example (Figure 6.12).

$$r = \frac{1}{3}R * A + \frac{1}{3}B$$

$$s = \frac{1}{3}(1 - R) * A + \frac{1}{3}B$$

$$unlabeled = \frac{1}{3}B + \frac{1}{3}C + D$$

$$invisible = \frac{2}{3}A + \frac{2}{3}C$$

Figure 6.12. Schematic representation of the other side of the equations. ''A'' is the total amount resulting from the species labeled with both ^{17}O and ^{18}O, ''B'' is the total amount from the species containing only ^{18}O, ''C'' is the total amount from the species only containing ^{17}O and ''D'' is the total amount from the unlabeled species. ''R'' represents the part derived from (R_P)-[^{16}O,^{17}O,^{18}O]**6.23** and ''(1-R)'' represents the part derived from (S_P)-[^{16}O,^{17}O,^{18}O]**6.23**.

We are now ready to put the two sides together (Figure 6.13).

$$0.5364a = \frac{1}{3}R * A + \frac{1}{3}B$$

$$0.2214a = \frac{1}{3}(1 - R) * A + \frac{1}{3}B$$

$$0.2421a = \frac{1}{3}B + \frac{1}{3}C + D$$

$$1 - a = \frac{2}{3}A + \frac{2}{3}C$$

$$\downarrow$$

$$0.5364a = \frac{1}{3}R * [0.649 - 1.637x + x^2] + \frac{1}{3}[0.314 + 0.637x - x^2]$$

$$0.2214a = \frac{1}{3}(1 - R) * [0.649 - 1.637x + x^2] + \frac{1}{3}[0.314 + 0.637x - x^2]$$

$$0.2421a = \frac{1}{3}[0.314 + 0.637x - x^2] + \frac{1}{3}[0.025 + 0.637x - x^2] + [0.012 + 0.363x + x^2]$$

$$1 - a = \frac{2}{3}[0.649 - 1.637x + x^2] + \frac{2}{3}[0.025 + 0.637x - x^2]$$

Figure 6.13. Four equations with three unknowns. ''a'' stands for the amount of all visible peaks, ''R'' stands for the amount of esters derived from (*R*)-[^{16}O,^{17}O,^{18}O]**6.23** and ''x'' represents the loss of labeling grade.

It is also assumed that the systematic error of integration of the peaks in NMR spectrum is 5%. Its influence on the ee is quantifiable so it was calculated. What is not quantifiable is the effect of the underlying very broad peaks representing species contatining ^{17}O. Other publications containing the synthesis of the chiral phosphate group did not mention anything about the determination and calculation of ee.

When we solve for these three unknowns, we come to following values: ''a'' = 0.5597, ''x'' = 0.01316 = 1.32% loss of each labeling and ''R'' = 0.9216 = 92.16 ± 7.22%. The ''R'' value was used to determine the ee, which was found to be 84.32 ± 14.44%.

I successfully synthesized (R_P)- and (S_P)-[^{16}O,^{17}O,^{18}O]**6.23** with the combined yield of 12.6% starting from chlorohydrin (*R*)-**6.37** and with the ee of 84 ± 15%. I assume that the ee is rather 98% because the diastereomerically homogeneous and protected [^{16}O,^{17}O,^{18}O]**6.35** were stereospecifically converted to [^{16}O,^{17}O,^{18}O]phosphoenolpyruvates and one enantiomer was used to prepare glucose-6-[^{16}O,^{17}O,^{18}O]phosphate involving two enzymes of known stereospecificity.

7 Experimental

7.1 General remarks

$^{1}H/^{13}C$ NMR spectra were measured at 300 K on Bruker Avance DRX 400 (^{1}H: 400.13 MHz, ^{13}C: 100.61 MHz, ^{31}P: 161.98 MHz), AV 400 (^{1}H: 400.27 MHz, ^{13}C: 100.65 MHz, ^{31}P: 162.03 MHz) and DRX 600 (^{1}H: 600.13 MHz, ^{13}C: 150. 92 MHz, ^{31}P: 242.94 MHz). All chemical shifts (δ) are given in ppm, solvent and the specific calibration are written in front of every spectrum.

HPLC was performed either on a Jasco System with PU-980 pump, UV 975 and RI 930 (in case of analytical determination using a Chiracel OD-H column, Ø 0.46 cm x 25 cm) or on a Dynamix Model SD-1 with a UV-1 absorbance detector (in case of semipreparative separation using Nucleosil 50-5 column, Ø 4.6 cm x 25 cm).

GC was performed on Agilent Technologies 7890A instrument with a Lipodex A 25 m x 0.25 mm column.

IR spectra were recorded using ATR on a Perkin-Elmer Spectrum 2000 FT-IR.

High resolution mass spectra (HRMS) were obtained on a MAT 59 using the EI ionization method.

Optical rotations were measured at 20 ˚C (unless otherwise specified) on a Perkin-Elmer 141 polarimeter in a 1 dm cell and all $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}.

Melting points were measured with a Leica Galen III Reichert Thermovar instrument and are uncorrected.

Reactions and flash (column) chromatography were monitored by TLC carried out on 0.25 mm thick, silica gel 60, F_{254} Merck plates. Unless otherwise specified, the spots were visualized by UV and dipping the plate into a solution of $(NH_4)_6Mo_7O_{24}\cdot 4\ H_2O$ (23.0 g) and $Ce(SO_4)_2\cdot 4\ H_2O$ (1.0 g) in 10% aqueous H_2SO_4 (500 mL) and heating with a heat gun. Flash chromatography was performed with Merck silica gel 60 (230-400 mesh).

THF was dried over K, Et_2O over $LiAlH_4$ and they were used right after distillation. TMEDA was refluxed over CaH_2, distilled and stored over molecular sieves (4 Å).

All of the other chemicals were used as supplied from ABCR, Acros, Alfa Aesar, Carbosynth, Fluka, Merck, Molekula or Sigma Aldrich.

Small quantities of reagents (µL) were measured with appropriate syringes (Hamilton).

General Procedure A - preparation of (*R*)-Mosher esters:

A solution of alcohol (0.1 mmol), dry pyridine (0.25 mL) and (*S*)-MTPACl (0.3 mL, 0.5 M solution in dry CH_2Cl_2, 0.15 mmol) in dry CH_2Cl_2 (2 mL) was stirred for 18 h at room temperature. Afterwards, CH_2Cl_2 (10 mL) and 1 M HCl (10 mL) were added. The organic layer was separated, washed with a saturated aqueous solution of $NaHCO_3$ and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was purified by flash chromatography.

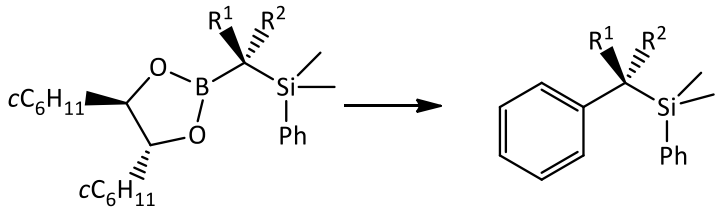
General Procedure B - preparation of diastereomeric boronates derived from various diols:

Butyllithium (1.2 eq.) was added to a solution of thiocarbamate or thioester (1 eq.) and TMEDA (1.2 eq.) in dry THF (1 mL/mmol) under argon at -95 or -78°C. After stirring for a certain time, borate[56,83] (1 eq.; formed from enantiomerically pure diol and trialkyl borate) dissolved in dry THF (1 mL/mmol) was added and stirring was continued a certain time. TFA (1.5 eq. in 1 mL/mmol dry THF) and a saturated aqueous solution of $NaHCO_3$ (10 mL) were added and it was extracted with Et_2O (3x15 mL). The combined organic phases were dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by flash chromatography (boronates were unstable on silica gel and could not be separated) to yield diastereomeric boronates as an oil. As the oil contained some impurities, only the ^1H NMR spectrum is given, but no other spectra, no combustion analysis and no specific optical rotation.

7.2 Suzuki-Miyaura coupling of bromobenzene with (dimethylphenylsilyl)methylboronates

These experiments were already published (with the exception of the last two procedures) and are copied from the supporting information almost without changes.[150]

Dimethyl-phenyl-(phenylmethyl)- and (*S*)-dimethyl-phenyl-(phenyl-[D_1]methyl)silane {2.22 and (*S*)-[D_1]2.22}



2.20: $R^1 = R^2 = H$ **2.22**: $R^1 = R^2 = H$

(*S*)-[D_1]**2.20**: $R^1 = H, R^2 = D$ (*S*)-[D_1]**2.22**: $R^1 = H, R^2 = D$

Boronate **2.20** (0.354 g, 0.91 mmol)[20] and 2M NaOH (3.64 mL) were added to a mixture of bromobenzene (0.429 g, 2.73 mmol, 0.287 mL) and $Pd(PPh_3)_4$ (0.052 g, 0.046 mmol) in dry dioxane (3 mL) under Ar that was stirred for 20 min at RT before heating at 90°C.[25] After stirring for 18 h, water was added and it was extracted three times with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by two flash chromatographies (first one: hexanes: CH_2Cl_2 = 2:1, R_f = 0.44; second: hexanes) to give silane[151] **2.22** (0.15 g, 59%) as colorless liquid and biphenyl (0.05 g, 15%) as colorless crystals.

4dec1010, 290: ^{1}H NMR (400.27 MHz, $CDCl_3$, 7.24): δ = 7.47-7.42 (m, 2H, H_{Ar}), 7.38-7.30 (m, 3H, H_{Ar}), 7.19-7.13 (m, 2H, H_{Ar}), 7.08-7.02 (m, 1H, H_{Ar}), 6.94-6.90 (m, 2H, H_{Ar}), 2.30 (s, 2H, CH_2), 0.24 (s, 6H, 2xCH_3).

Biphenyl (spectra are identical to those in the literature):[152]

4jan2611, 390: ^{1}H NMR (400.27 MHz, $CDCl_3$, 7.24): δ = 7.60-7.56 (m, 4H, H_{Ar}), 7.45-7.40 (m, 4H, H_{Ar}), 7.36-7.31 (m, 2H, H_{Ar}).

4jan2611, 390: ^{13}C NMR (100.65 MHz, $CDCl_3$, 77.0): δ = 141.3 (2x$C_{q,Ar}$), 128.7 (4xCH_{Ar}), 127.24 (2xCH_{Ar}), 127.16 (4xCH_{Ar}).

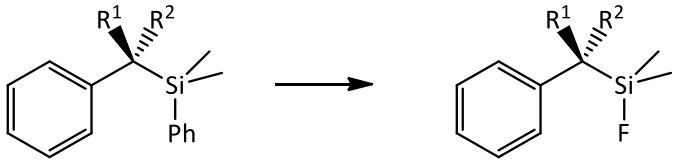
HRMS (EI): calcd. for $C_{12}O_{10}$ (M^+) 154.0783, found 154.0781.

Similarly, (*S*)-dimethyl-phenyl-[D_1]methylboronate {(*S*)-[D_1]**2.20**, 0.88 g, 2.27 mmol} was converted to (*S*)-dimethyl-phenyl-(phenyl-[D_1]methyl)silane {(*S*)-[D_1]**2.22**, 0.28 g, 54%}.

4jan2611, 340: ^{1}H NMR (400.27 MHz, $CDCl_3$, 7.24): δ = 7.49-7.44 (m, 2H, H_{Ar}), 7.40-7.31 (m, 3H, H_{Ar}), 7.21-7.15 (m, 2H, H_{Ar}), 7.09-7.04 (m, 1H, H_{Ar}), 6.96-6.92 (m, 2H, H_{Ar}), 2.29 (broadened s, 1H, CHD), 0.25 (s, 6H, 2xCH_3).

4jan2611, 341: ^{13}C NMR (100.65 MHz, $CDCl_3$, 77.0): δ = 139.6 ($C_{q,Ar}$), 138.5 ($C_{q,Ar}$), 133.7 (2xCH_{Ar}), 129.0 (CH_{Ar}), 128.3 (2xCH_{Ar}), 128.1 (2xCH_{Ar}), 127.7 (2xCH_{Ar}), 124.1 (CH_{Ar}), 25.8 (t, *J* = 18.3 Hz, CHD), –3.5 (2C).

Fluorodimethyl(phenylmethyl)- and (*S*)-fluorodimethyl(phenyl-[D_1]methyl)silane {2.29 and (*S*)-[D_1]2.29}



2.22: $R^1 = R^2 = H$ **2.29**: $R^1 = R^2 = H$

(*S*)-[D_1]**2.22**: $R^1 = H, R^2 = D$ (*S*)-[D_1]**2.29**: $R^1 = H, R^2 = D$

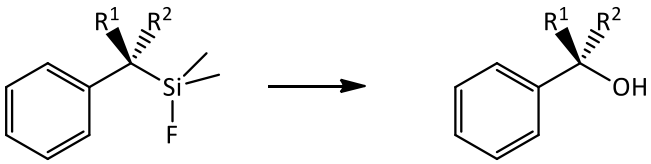
$HBF_4 \cdot Et_2O$ (0.72 g, 4.4 mmol, 0.60 mL) was added to a solution of silane **2.22** (0.45 g, 2 mmol) in dry CH_2Cl_2 (11 mL) at 0°C.[22] After stirring for 1 h at 0°C and 1 h at RT water was added. The mixture was extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The crude fluorosilane **2.29** (0.32 g, 95%) was immediately used in the following reaction.

4jan1411, 140: ^{1}H NMR (400.27 MHz, $CDCl_3$, 7.24): δ = 7.15-7.10 (m, 2H, CH_{Ar}), 7.02-6.94 (m, 3H, CH_{Ar}), 2.14 (d, J_{HF} = 5.8 Hz, 2H, CH_2), 0.08 (d, J_{HF} = 7.4 Hz, 6H, 2xCH_3).

Similarly, (*S*)-dimethyl-phenyl(phenyl-[D_1]methyl)silane {(*S*)-[D_1]**2.22**, 0.30 g, 1.3 mmol} was converted to (*S*)-fluorodimethyl(phenyl-[D_1]methyl)silane {(*S*)-[D_1]**2.29**, 0.20 g, 92%}.

4jan1911, 490: ^{1}H NMR (400.27 MHz, $CDCl_3$, 7.24): δ = 7.14-7.09 (m, 2H, H_{Ar}), 7.02-6.93 (m, 3H, H_{Ar}), 2.12 (td, J_{HF} = 5.9 Hz, J_{HD} = 1.9 H, 1H, CHD), 0.08 (d, *J* = 7.4 Hz, 6H, 2xCH_3).

Phenylmethanol and (*S*)-phenyl-[D_1]methanol {2.30 and (*S*)-[D_1]2.30}



2.29: $R^1 = R^2 = H$ **2.30**: $R^1 = R^2 = H$

(*S*)-[D_1]**2.29**: $R^1 = H, R^2 = D$ (*S*)-[D_1]**2.30**: $R^1 = H, R^2 = D$

A mixture of fluorosilane **2.29** (0.36 g, 2.1 mmol), KF (0.37 g, 6.3 mmol), $NaHCO_3$ (0.18 g, 2.1 mmol) and 30% H_2O_2 (21 mmol, 2.44 mL) in dry methanol (8 mL) and dry THF (8 mL) was refluxed for 2 h.[153] A saturated aqueous solution of $NaHCO_3$ was added and it was extracted three times with Et_2O. The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash chromatography (hexanes: ethyl acetate = 5:1, R_f = 0.22) to give phenylmethanol (**2.30**, 0.15 g, 67%) as a colorless liquid.

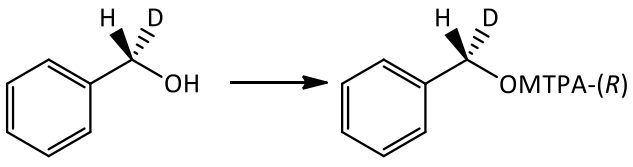
4jan1711, 230: ^{1}H NMR (400.27 MHz, $CDCl_3$, 7.24): δ = 7.36-7.34 (m, 4H, H_{Ar}), 7.31-7.26 (m, 1H, H_{Ar}), 4.68 (s, 2H, CH_2), 1.69 (broad s, 1H, OH).

Similarly, (*S*)-fluorodimethyl(phenyl-[D_1]methyl)silane {(*S*)-[D_1]**2.29**, 0.20 g, 1.19 mmol} was converted to (*S*)-phenyl-[D_1]methanol {(*S*)-[D_1]**2.30**, 0.057 g, 44%}.

4jan2011, 170: ^{1}H NMR (400.27 MHz, $CDCl_3$, 7.24): δ = 7.36-7.34 (m, 4H, H_{Ar}), 7.32-7.26 (m, 1H, H_{Ar}), 4.66 (t, J_{HD} = 1.9 H, 1H, CHD), 1.68 (broad s, 1H, OH).

4jan2011, 171: ^{13}C NMR (100.65 MHz, $CDCl_3$, 77.0): δ = 140.8 ($C_{q,Ar}$), 128.6 (2xCH_{Ar}), 127.7 (CH_{Ar}), 127.0 (2xCH_{Ar}), 65.0 (t, J = 21.7 Hz, CHD).

(*R*)-Mosher ester of (*S*)-phenyl-[D_1]methanol {(*S*)-[D_1]31}



(*S*)-[D_1]**2.30** (*S*)-[D_1]**2.31**

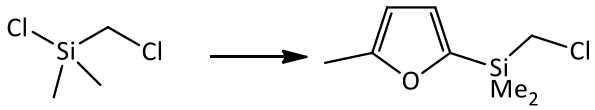
(*S*)-[D_1]**2.30** (0.012 g, 0.11 mmol) was converted to its Mosher ester (*S*)-[D_1]**2.31** (0.033 g, 90%, ee ≥ 99%) according to general procedure A.

4jan2811, 200: ^{1}H NMR (400.27 MHz, $CDCl_3$): δ 7.46-7.41 (m, 2H), 7.40-7.30 (m, 8H), 5.29 (broadened s, 1H, CHD), 3.50 (q, J = 1.3 Hz, 3H).

Similarly, (*R*)-phenyl-[D_1]methanol obtained by horse-liver alcohol dehydrogenase catalysed reduction of [formyl-D_1]benzaldehyde was converted to its (*R*)-Mosher ester.

^{1}H NMR (400.27 MHz, $CDCl_3$): δ 7.45-7.31 (m, 10H), 5.33 (t, J_{HD} = 1.5 Hz, 1H, CHD), 3.50 (q, J_{HF} = 1.1 Hz, 3H).

(Chloromethyl)dimethyl(2-methylfuryl) silane (2.35)



2.34 **2.35**

A mixture of 2-methylfuran (1.64 g, 20 mmol, 1.77 mL), *n*BuLi (2.5 M in hexane, 18 mmol, 7.20 mL) and 2,2'-bipyridin (10 mg) in dry THF (35 mL) was stirred at 0°C for 2 h and the solution turned dark red/brown. (Chloromethyl)dimethylchlorosilane (**2.**34, 2.86 g, 20 mmol) was added upon which the solution turned light yellow and it was stirred at 0°C for 1 h and at RT for 30 min. Saturated solution of $NaHCO_3$ (30 mL) was added and the mixture was extracted with Et_2O (3x30 mL), the combined organic phases were dried with $MgSO_4$ and concentrated under reduced pressure. The product was purified by bulb to bulb distillation (95-110°C/20 mm Hg) to yield silane **2.35** (2.422 g, 71%) as a colorless oil. Unfortunately it was impossible to purify the product so that it contained no unidentified contaminant.

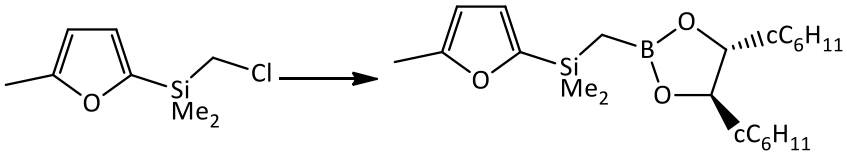
IR (ATR): ν = 2962, 2926, 2855, 1496, 1394, 1306, 1275, 1254, 1216, 1188, 1019 cm^{-1}.

4apr2011, 160: ^{1}H NMR (400.27 MHz, $CDCl_3$, 7.24): δ = 6.61 (d, J = 3.0 Hz, 1H, H_{Ar}), 5.96 (qd, J = 3.0, 1.0 Hz, 1H, H_{Ar}), 2.92 (s, 2H, $SiCH_2$), 2.31 (br. s, 3H, CH_3 on furan), 0.36 (s, 6H, 2xCH_3).

4apr2011, 161: ^{13}C NMR (100.65 MHz, $CDCl_3$, 77.0): δ = 157.3 ($C_{q,Ar}$), 154.3 ($C_{q,Ar}$), 122.7 (CH_{Ar}), 106.0 (CH_{Ar}), 29.8 ($SiCH_2$), 13.7 (CH_3 on furan), -4.9 (2x $SiCH_3$).

Anal. Calcd for $C_8H_{13}ClOSi$ (188.73): C, 50.91; H, 6.94. Found: C, 50.43; H, 4.70.

Boronate ester 2.36



2.35 **2.36**

A mixture of silane **2.35** (1.45 g, 8.3 mmol), Mg (0.486 g, 20 mmol) and 1,2-dibromoethane (0.1 mL) in dry THF (5 mL) was sonicated for 1 h and then stirred for 20 min at RT.[154] Borate **2.27**[56] [2.08 g, 7.82 mmol; formed from (*R*,*R*)-1,2-dicyclohexyl-1,2-ethanediol and tri(*tert*-butyl) borate] in dry THF (2 mL) was added at 0°C and it was stirred for 1 h at RT after which water (10 mL) and citric acid (0.5 g) were added and the whole mixture was extracted with CH_2Cl_2 (3x10 mL). The combined organic phases were dried with Na_2SO_4 and concentrated under reduced pressure. The product was purified with flash chromatography (hexanes: CH_2Cl_2 = 2:1, R_f = 0.55) to yield the product (**2.36**, 1.27 g, 41%) as colorless oil. Unfortunately it was impossible to get a sample of homogeneous boronate for the collection of analytical data, because the product decomposes slightly on silica gel.

IR (ATR): ν = 2926, 2854, 1450, 1390, 1328, 1302, 1276, 1228, 1056 cm^{-1}.

4apr0611, 450: ^{1}H NMR (400.27 MHz, $CDCl_3$, 7.24): δ = 6.52 (d, *J* = 3.0 Hz, 1H, H_{Ar}), 5.91 (qd, *J* = 3.0, 1.0 Hz, 1H, H_{Ar}), 3.79-3.73 (m, 2H, 2xBOCH), 2.29 (br. s, 3H, CH_3 on furan), 1.76-1.69 (m, 6H, cyclohexane), 1.67-1.61 (m, 2H, cyclohexane), 1.58-1.52 (m, 2H, cyclohexane), 1.30-1.08 (m, 8H, cyclohexane), 1.06-0.85 (m, 4H, cyclohexane), 0.32 (broad s, 2H, BCH_2), 0.27 (s, 3H, $SiCH_3$), 0.26 (s, 3H, $SiCH_3$).

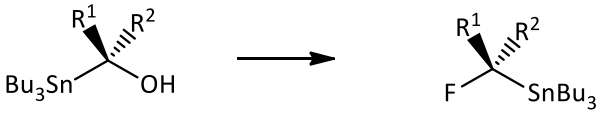
4apr0611, 451: ^{13}C NMR (100.65 MHz, $CDCl_3$, 77.0): δ = 158.1 ($C_{q,Ar}$), 156.3 ($C_{q,Ar}$), 120.9 (CH_{Ar}), 105.6 (CH_{Ar}), 83.4 (2xOCH), 43.1 (2xCH), 28.5 (CH_2), 27.5 (CH_2), 36.5 (CH_2), 26.1 (CH_2), 25.9 (CH_2), 13.7 (CH_3 on furan), -1.1 ($SiCH_3$), -1.4 ($SiCH_3$).

Anal. Calcd for $C_{22}H_{37}BO_3Si$ (388.42): C, 68.03; H, 9.60. Found: C, 67.92; H, 9.40.

7.3 Configurational stability of fluoromethyllithium

These experiments were already published (with the exception of the last two procedures) and are copied from the supporting information almost without changes.[62]

Tributyl-(fluoromethyl)stannane (3.34), (*S*)- and (*R*)-tributyl-(fluoro-[D_1]methyl)stannane {(*R*)- and (*S*)-[D_1]3.34}:



3.40: $R^1 = R^2 = H$
(*R*)-[D_1]**3.40**: $R^1 = H$, $R^2 = D$
(*S*)-[D_1]**3.40**: $R^1 = D$, $R^2 = H$

3.34: $R^1 = R^2 = H$
(*S*)-[D_1]**3.34**: $R^1 = H$, $R^2 = D$
(*R*)-[D_1]**3.34**: $R^1 = D$, $R^2 = H$

a) Using Deoxo-Fluor: Deoxo-Fluor® (264 µL, 50% solution in THF, 0.62 mmol) was added to a solution of tributylstannylmethanol (**3.40**)[56] in dry THF (2 mL). The mixture was stirred for 1 h at RT before the reaction was quenched with methanol (100 µL) and triethylamine (100 µL). The solvent was removed under reduced pressure and the residue purified by flash chromatography (hexanes, R_f = 0.80) to yield fluoromethylstannane **3.34** (68 mg, 68%) as colorless oil.

4apr2110, 230: ^{1}H NMR (400.13 MHz, $CDCl_3$, 7.24): δ = 5.07 (d, $J(^{19}F)$ = 47.2 Hz, 2H, FCH_2), 1.55-1.46 (m, 6H, 3x$SnCCH_2$), 1.29 (sext, J = 7.3 Hz, 6H, 3xSnC_2CH_2), 0.97-0.91 (m, 6H, 3x$SnCH_2$), 0.88 (t, J = 7.3 Hz, 9H, 3xSnC_3CH_3).

Similarly, (*R*)-tributylstannyl-[D_1]methanol {(*R*)-[D_1]**3.40**, 99% ee} was converted to (*S*)-[D_1]**3.34** in similar yield with an ee of 90%.

b) Using *N,N*-diethyl-trimethylsilylamine and Deoxo-Fluor®: A solution of (*S*)-tributylstannyl-[D_1]methanol[56] {(*S*)-[D_1]**3.40**, 0.87 g, 2.71 mmol, 99% ee} and *N,N*-diethyl-trimethylsilylamine (1.18 g, 8.1 mmol, 1.54 mL, 3. equiv.) in dry toluene (5 mL) was stirred for 1 h at room temperature and at 40°C until the reaction was complete (1 h, progress checked by TLC, hexanes). The solution was concentrated under reduced pressure and dried for 30 min at 40°C/0.3 mbar to yield the silyl ether (1.06 g, quantitative yield) as colorless oil, which was used immediately for the next step. Dry toluene (5 mL) and Deoxo Fluor® (5.37 mmol, 1.73 mL were added, ~50% in toluene) at 0°C and the mixture was stirred for 30 min at 0°C and 1 h at room temperature. After the addition of a

saturated aqueous solution of $NaHCO_3$ (5 mL), the mixture was extracted with CH_2Cl_2 (3x5 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was flash chromatographed (hexanes, R_f = 0.84) to yield fluoro-[D_1]methylstannane (*R*)-[D_1]**3.34** (0.64 g, 73%, 98% ee, containing 5% unlabeled **3.34**) as colorless oil.

Analogously, (*R*)-tributylstannyl-[D_1]methanol {(*R*)-[D_1]**3.40**, 99% ee} was converted to (*S*)-[D_1]**3.34** in similar yield and an ee of 98%.

(*R*)-[D_1]3 and (*S*)-[D_1]3.34:

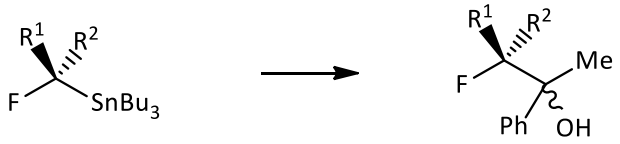
The spectroscopic data were identical to those of the unlabelled species except for:

4nov3011, 500: ^{1}H NMR (400.13 MHz, $CDCl_3$, 7.24): δ = 5.05 (td, $J(^{19}F)$ = 47.3 Hz, J = 1.5 Hz, 1H, CHD) and ^{13}C NMR (100.61 MHz, $CDCl_3$, 77.0): δ = 80.69 (td, $J(^{19}F)$ = 179.7 Hz, J = 22.2 Hz, CHD).

Determination of ee of (*R*)- and (*S*)-tributyl-(fluoro-[D_1]methyl)stannane 3.46:[58] *n*BuLi (0.2 mmol, 0.125 mL, 1.6 M in hexanes) was added to a stirred solution of (*R*)-1-(2-naphthyl)ethanethiol (0.038 g, 0.2 mmol) in dry THF (3 mL) under argon at 0˚C. After stirring for 5 min, (*R*)-tributyl-(fluoro-[D_1]methyl)stannane {(*R*)-[D_1]**3.40**, 0.043 g, 0.133 mmol} was added and stirring was continued for 18 h at RT. The solution was concentrated under reduced pressure and water was added. The mixture was extracted three times with Et_2O and the combined organic layers were washed with water, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes: CH_2Cl_2 = 10:1), R_f = 0.42) to give (*S*)-tributylstannyl-[D_1]methyl sulfide {(*S*)-[D_1]**3.46**, 0.023 g, 37%, 98% ee} as colorless oil. The ^{1}H NMR spectrum was identical to the spectrum reported in the literature.

Similarly, the ee of (*S*)-tributyl-(fluoro-[D_1]methyl)stannane {(*S*)-[D_1]**3.40**} was determined. I assume that both enantiomers of tributyl-(fluoro-[D_1]methyl)stannane reacted with the lithium thiolate with equal rates.

General procedure for the generation and addition of fluoromethyl- (3.33) and (*R*)- and (*S*)-fluoro-[D_1]methyllithium {(*R*)- and (*S*)-[D_1]3.33} to acetophenone – (1*R,2R/S*)- and (1*S,2R/S*)-1-fluoro-2-phenyl-2-[1-D_1]propanol {(*R*)- and (*S*)-[D_1]3.42a}:



3.34: $R^1 = R^2 = H$ — **3.42a**: $R^1 = R^2 = H$

(*R*)-[D_1]**3.34**: $R^1 = D$, $R^2 = H$ — (*S*)-[D_1]**3.42a**: $R^1 = D$, $R^2 = H$

(*S*)-[D_1]**3.34**: $R^1 = H$, $R^2 = D$ — (*R*)-[D_1]**3.42a**: $R^1 = H$, $R^2 = D$

Experiment performed with fluoromethyllithium (3.33)

1) Methyllithium (0.92 mmol, 0.92 mL, 1 M, prepared by mixing a 3 M solution in diethoxymethane with dry THF) was added dropwise (1 drop every 5 s) to a solution of acetophenone (**3.41a**, 0.92 mmol, 0.46 mL, 2 M in dry THF) and (fluoromethyl)stannane **3.34** (0.149 g, 0.46 mmol) in dry THF (3 mL) under argon at -95 ˚C. After stirring for 5 min CF_3CO_2H (1.02 mmol, 0.51 mL, 2 M in CH_2Cl_2) and water were added. The mixture was extracted three times with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes: ethyl acetate = 15:1, R_f = 0.19 for **3.42a** and **3.43a**) to give a mixture of the fluorohydrin [**3.42a**][155] and 1-phenyl-2-propanol (**3.43a**)[156] (0.059 g, molar ratio: 1.0:0.8, contained 34.6 mg of **3.42a**, corresponding to a yield of 49%) as a colorless oil.

4dec2011, 280: ^{1}H NMR (400.27 MHz, $CDCl_3$, 7.24): δ = 7.50-7.20 (m, 5H, H_{ar}), 4.43 (AB-system coupling with F, J_{AB} = 9.2 Hz, $J_{AF} = J_{BF}$ = 48.1 Hz, 2H, FCH_2), 1.59 (d, J_{FH} = 2.1 Hz, 3H, CH_3), 1.90 (br. s, 1H, OH).

Experiments performed with chiral, nonracemic fluoro-[D_1]methyllithiums

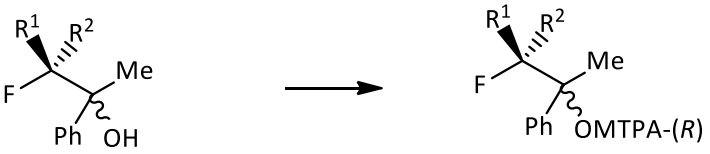
2) Similarly, (*S*)-fluoro-[D_1]methylstannane (*S*)-[D_1]**3.34** (0.238 g,0.74 mmol, ee ≥90%) at -30°C gave a mixture of (*R*)-[D_1]**3.42a** and **3.43a** (11 mg, molar ratio 1:0.4, contained 8.2 mg of (*R*)-[D_1]**3.42a**, corresponding to a yield of 7%) as a colorless oil. Esterification with (*S*)-MTPACl gave a mixture of (*R*)-Mosher esters (10.2 mg, ee 90%) (see Figure 7.1, spectrum B and C).

3) Similarly, at -78°C fluoro-[D_1]methylstannane (*R*)-[D_1]**3.34** (0.304 g,0.94 mmol, ee 98%, D_1 95%) gave (*S*)-[D_1]**3.42a** (35 mg, 24%, containing only a small amount of **3.43a**). Esterification with (*S*)-MTPACl gave a mixture of (*R*)-Mosher esters (6.5 mg, ee 98%).

4) Similarly, at -30°C fluoro-[D_1]methylstannane (*R*)-[D_1]**3.34** (0.314 g, 0.97 mmol, ee 98%, D_1 95%) gave a mixture of (*S*)-[D_1]**3.42a** and **3.43a** (16 mg, 24%, molar ratio: 1.0:0.3, contained 12.6 mg of (*S*)-[D_1]**3.42a**, corresponding to a yield of 8%) as a colorless oil. Esterification with (*S*)-MTPACl gave a mixture of (*R*)-Mosher esters (4.6 mg, ee 98%).

5) Similarly, at 0°C fluoro-[D_1]methylstannane (*R*)-[D_1]**3.34** (74 mg, 0.23 mmol, ee 98%, D_1 95%) gave a mixture of (*S*)-[D_1]**3.42a** and **3.43a** (30 mg, molar ratio: 1.0:17, contained 1 mg of (*S*)-[D_1]**3.42a**, corresponding to a yield of 3%) as a colorless oil. Esterification with (*S*)-MTPACl gave a mixture of (*R*)-Mosher esters (1 mg, ee 98%).

Preparation of (*R*)-Mosher esters of 1-fluoro-2-phenyl-2-propanols {3.45a and [D_1]3.45a}:



3.42a: $R^1 = R^2 = H$
(*R*)-[D_1]**3.42a**: $R^1 = H$, $R^2 = D$
(*S*)-[D_1]**3.42a**: $R^1 = D$, $R^2 = H$

3.45a: $R^1 = R^2 = H$·
(*R*)-[D_1]**3.45a**: $R^1 = H$, $R^2 = D$
(*S*)-[D_1]**3.45a**: $R^1 = D$, $R^2 = H$

A solution of (*S*)-MTPACl (0.18 mmol, 0.342 mL, 0.53 M in dry 1,4-dioxane), the mixture of fluorohydrin **3.42a** and **3.43a** [14 mg, 0.09 mmol calculated as pure fluorohydrin], DMAP (0.044 g, 0.36 mmol) and dry dioxane (2 mL) was stirred under argon for 9 h at 50 ˚C. HCl (2 M) was added and the mixture was extracted three times with CH_2Cl_2. The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$, dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified first by flash chromatography (hexanes: ethyl acetate = 15:1, R_f = 0.35), then preparative TLC (hexanes: CH_2Cl_2 = 2:1) and finally again by flash chromatography (hexanes: ethyl acetate =15:1, R_f = 0.35, p. A. solvents were used for the PTLC and for the 2nd chromatography) to give a mixture of diastereomeric (*R*)-Mosher esters **3.45a** [14.6 mg, 44%; ratio of diastereomers: 3.0:1.9 (by ^{1}H NMR of signals for OCH_3 at 3.59 and 3.53 ppm)] as a colorless oil.

4jan1812, 240: ^{1}H NMR (400.27 MHz, $CDCl_3$, 7.24): δ = 7.70-7.10 (m, H_{Ar}), 4.71 (AB-system coupling with F, J_{AB} = 9.8 Hz, J_{HF} = 47.7 Hz, 2H, FCH_2, minor diasteromer B), 4.56 (AB-system coupling with F, J_{AB} = 9.9 Hz, J_{HF} = 45.6 Hz, 2H, FCH_2, major diastereomer A), 3.59 (q, J = 1.2 Hz, 3H, OCH_3, A), 3.53 (q, J = 1.0 Hz, 3H, OCH_3, B), 2.04 (d, J_{HF} = 2.3 Hz, 3H, CH_3, A), 1.94 (d, J_{HF} = 2.3 Hz, 3H, CH_3, B).

6jan1812, 10: ^{1}H NMR (600.13 MHz, $CDCl_3$, 7.24): δ = 7.54-7.49 (m, 4H, H_{Ar}), 7.43-7.37 (m, 6H, H_{Ar}), 7.36-7.30 (m, 6H, H_{Ar}), 7.27-7.25 (m, 2H, H_{Ar}), 7.23-7.20 (m, 2H, H_{Ar}), 4.71 (AB-system coupling with F, J_{AB} = 9.8 Hz, J_{HF} = 47.7 Hz, 2H, FCH_2, minor diastereomer B), 4.56 (AB-system coupling with F, J_{AB} = 9.9 Hz, J_{HF} = 45.6 Hz, 2H, FCH_2, major diastereomer A), 3.59 (q, J = 1.3 Hz, 3H, OCH_3, A), 3.53 (q, J = 1.0 Hz, 3H, OCH_3, B), 2.04 (d, J_{HF} = 2.4 Hz, 3H, CH_3, A), 1.94 (d, J_{HF} = 2.3 Hz, 3H, CH_3, B).

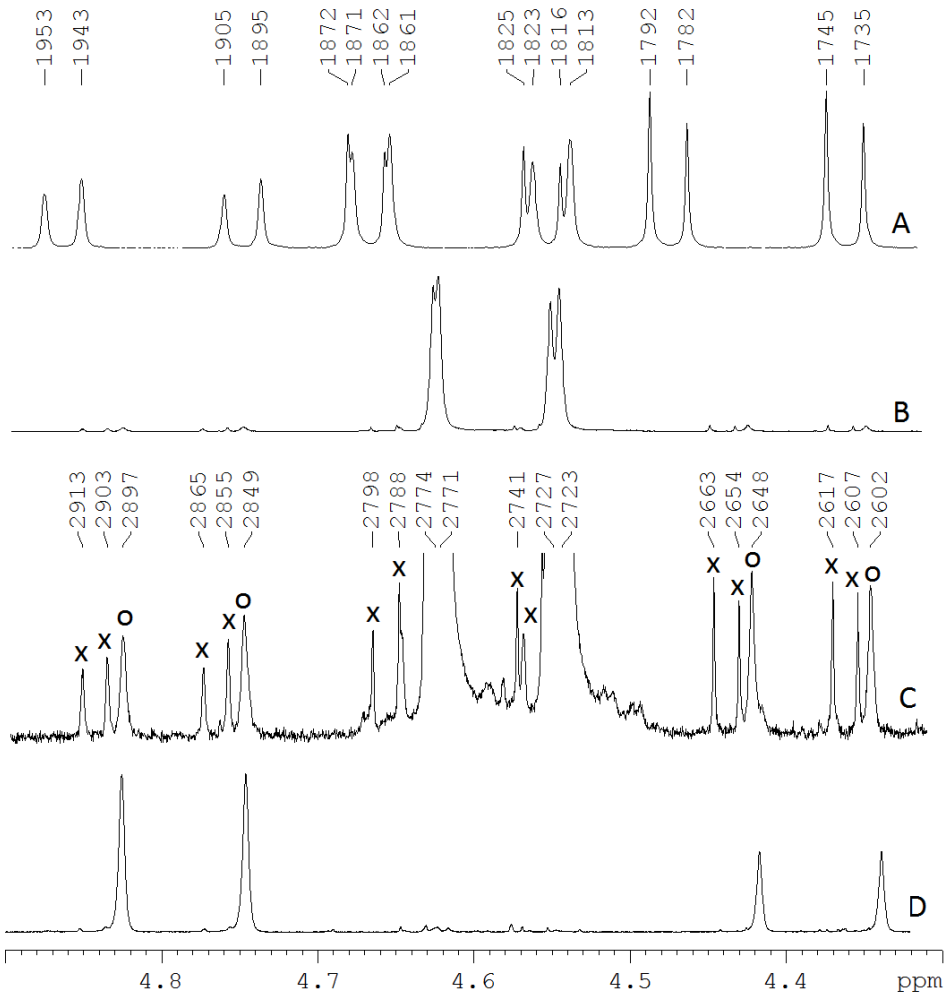
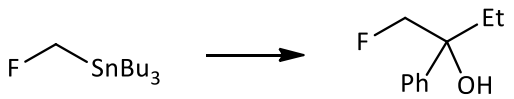


Figure 7.1. Signals of CH_2F and CHDF groups in the ^{1}H NMR spectra (400 MHz in case of A, 600 MHz in case of B, C and D, $CDCl_3$) of (*R*)-Mosher esters derived from A) **3.42a**, B) (*R*)-[D_1]**3.42a** of 90% ee; C) zoom of spectrum shown in B to show the peaks of the unlabeled species marked with "o" and those of the two (*S*)-[D_1]diastereomers marked with "x"; D) (*S*)-[D_1]**3.42a** of 98% ee.

General procedure for the generation and addition of fluoromethyllithium (3.33) to propiophenone (3.41b) - (±)-1-fluoro-3,3-dimethyl-2-butanol 3.42b:



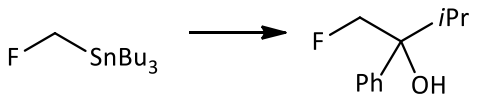
3.34 **3.42b**

This reaction was performed in the same way as the generation and addition of fluoromethyllithium (**3.33**) to acetophenone (**3.41a**). At -95°C fluoromethylstannane **3.34** (0.199 g, 0.61 mmol) gave with propiophenone (**3.41b**) a crude product which was flash chromatographed [hexanes: ethyl acetate = 10:1, fluoroalcohol **3.42b**: R_f = 0.38; 2-phenyl-2-butanol (**3.43b**):[157] R_f = 0.30] to yield **3.42b** (30 mg, 29%) as a colorless oil.

Similarly, at -78°C (fluoromethyl)stannane **3.34** (0.199 g, 0.61 mmol) gave with propiophenone a crude product which was flash chromatographed to yield **3.42b** (9 mg, 9 %) as a colorless oil.

4aug0411, 250: ^{1}H NMR (400.27 MHz, $CDCl_3$, 7.24): δ = 7.43-7.39 (m, 2H, H_{Ar}), 7.38-7.33 (m, 2H, H_{Ar}), 7.29-7.25 (m, 1H, H_{Ar}), 4.49 (AB-system coupling with F, J_{AB} = 9.3 Hz, J_{AF} = J_{BF} = 47.9 Hz, 2H, FCH_2), 2.25 (s, 1H, OH), 2.00-1.81 (m, 2H, CH_2), 0.78 (t, J = 7.5 Hz, 3H, CH_3).

General procedure for the generation and addition of fluoromethyllithium (3.33) to isobutyrophenone (3.41c) - (±)-1-fluoro-3,3-dimethyl-2-butanol 3.42c:



3.34 **3.42c**

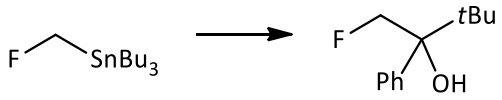
This reaction was performed in the same way as the generation and addition of fluoromethyl-lithium (**3.33**) to acetophenone (**3.41a**). At -95°C fluoromethyl)stannane **3.34** (0.199 g, 0.61 mmol) gave with isobutyrophenone (**3.41c**) a crude product which was flash chromatographed (hexanes: ethyl acetate = 10:1, fluoroalcohol **3.42c** and **3.43c**: R_f = 0.55) to yield a mixture of **3.42c** and (±)-3-methyl-2-phenylbutan-2-ol (**3.43c**)[158] (97 mg, molar ratio 1.22:1, contained 55 mg of **3.42c**, corresponding to a yield of 50%) as a colorless oil.

Similarly, at -78°C (fluoromethyl)stannane **3.34** (0.199 g, 0.61 mmol) gave with isobutyrophenone a crude product which was flash chromatographed to yield a mixture of **3.42c** and (±)-3-methyl-2-

phenylbutan-2-ol (**3.43c**) (120 mg, molar ratio 1:3.21, contained 31 mg of **3.42c**, corresponding to a yield of 28 %) as a colorless oil.

4aug0311, 220: ^{1}H NMR (400.27 MHz, $CDCl_3$, 7.24): δ = 7.43-7.39 (m, 2H, H_{Ar}), 7.37-7.32 (m, 2H, H_{Ar}), 7.29-7.24 (m, 1H, H_{Ar}), 4.68 (AB-system coupling with F, J_{AB} = 9.3 Hz, J_{AF} = J_{BF} = 47.3 Hz, 2H, FCH_2), 2.29 (s, 1H, OH), 2.13 (sept, J = 6.8 Hz, 1H, CH), 0.93 (d, J = 6.8 Hz, 3H, CH_3), 0.78 (d, J = 6.8 Hz, 3H, CH_3).

General procedure for the generation and addition of fluoromethyllithium (3.33) to *t*-butyl phenyl ketone - (±)-1-fluoro-3,3-dimethyl-2-butanol 3.42d:



3.34 **3.42d**

This reaction was performed in the same way as the generation and addition of fluoromethyl-lithium (**3.33**) to acetophenone (**3.41a**). At -95°C fluoromethyl)stannane **3.34** (0.161 g, 0.50 mmol) gave with *t*-butyl phenyl ketone a crude product which was flash chromatographed (hexanes: ethyl acetate = 10:1, fluoroalcohol **3.42d**: R_f = 0.39; **3.43d**: R_f = 0.34) to yield a mixture of **3.42d** and **3.43d** (87 mg, molar ratio 1:1, contained 46 mg of **3.42d**, corresponding to a yield of 46%) as a colorless oil.

Similarly, at -78°C (fluoromethyl)stannane **3.34** (0.170 g, 0.53 mmol) gave with *t*-butyl phenyl ketone a crude product which was flash chromatographed to yield a mixture of **3.42d** and (±)-3,3-dimethyl-2-phenylbutan-2-ol (**3.43d**)[159] (117 mg, molar ratio 1:3.4, contained 29 mg of **3.42d**, corresponding to a yield of 28%) as a colorless oil.

4aug1911, 310: ^{1}H NMR (400.27 MHz, $CDCl_3$, 7.24): δ = 7.47-7.18 (m, 5H, H_{Ar}), 4.92 (AB-system coupling with F, J_{AB} = 9.4 Hz, J_{AF} = J_{BF} = 47.0 Hz, 2H, FCH_2), 1.34 (s, 1H, OH), 0.93 (d, J_{FH} = 0.6 Hz, 9H, 3xCH_3).

7.4 Boronic esters

Experiments performed to optimize conditions for metalation/deuteration of thiocarbamate or thioesters:

*s*BuLi (1.4 M in cyclohexane, 1.2 eq.) was added to a solution of thiocarbamate (1 eq.), TMEDA (1.2 eq.) in THF (2 mL/mmol) under argon at a certain temperature. After some time, D_2O (10 eq.) in THF (1 mL) was added, followed by water and the mixture was extracted with ethyl acetate (3x10 mL). The combined organic phases were washed with water (15 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The labeling grade was determined from ^1H NMR spectrum of the crude product which was not further purified. The results are given in Table 7.1.

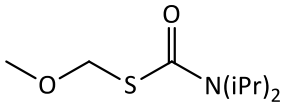
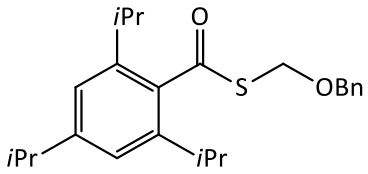
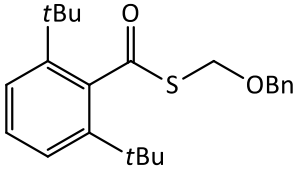
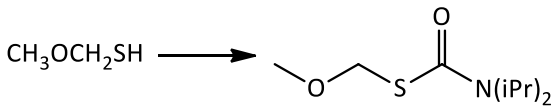
Entry	Thiocarbamate or thioester	T (°C)	Time (min)	D-content (%)
1	 **4.50**	-78	30	45
2		-78	60	27
3		-78	120	40
4	 **4.54**	-78	30	15
5		-95	90	100
6	 **4.66**	-95	30	50

Table 7.1. Metalation/deuteration experiments.

***S*-(Methoxymethyl) diisopropylthiocarbamate (4.50)**



4.49 **4.50**

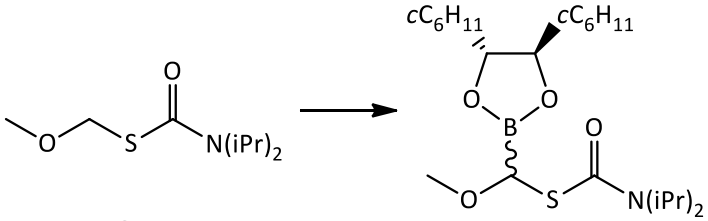
Diisopropylcarbamoyl chloride (0.82 g, 5 mmol) in dry THF (3 mL) was added to a solution of methoxymethanethiol (**4.49**) (7 mmol, 6.20 mL, 1.125 M in toluene) and KO*t*Bu (0.79 g, 7 mmol) in

dry THF (10 mL) stirred under argon at -78°C for 5 min.[82] After stirring at -78°C for 10 min and at RT for 22 h the reaction mixture was concentrated under reduced pressure to about a third of its volume, water (20 mL) was added and it was extracted with ethyl acetate (3x20 mL). The combined organic phases were washed with water (20 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by flash chromatography twice (hexanes: ethyl acetate = 15:1, R_f = 0.44) to yield thiocarbamate **4.50** (0.60 g, 59%) as an oil that still contained some impurities even after distillation (95-100°C/1 mbar). A correct combustion analysis could not be obtained.

IR (Si): v = 2973, 1655, 1421, 1275, 1210, 1185 cm^{-1}.

6feb2510, 61 ^{1}H NMR (600.13 MHz, $CDCl_3$, 7.24): δ = 5.05 (s, 2H, CH_2), 4.40-3.90 (broad s, 1H, CH), 3.70-3.30 (broad s, 1H, CH), 3.32 (s, 3H, OCH_3), 1.55-1.00 (m, 12H, 4xCH_3).
6feb2510, 60: ^{13}C NMR (150.92 MHz, $CDCl_3$, 77.0): δ = 163.6 (C=O), 73.0 (CH_2), 56.7 (OCH_3), 49.4 (CH), 47.3 (CH), 20.6 (4xCH_3).

Diastereomeric boronates 4.51 derived from (*R*,*R*)-1,2-dicyclohexyl-1,2-ethanediol



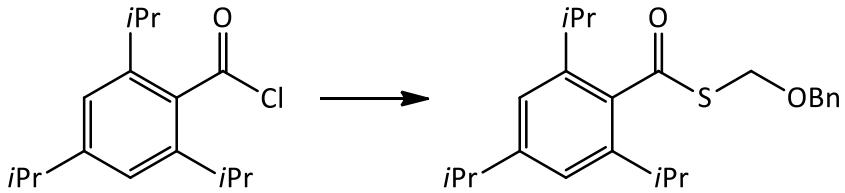
4.50 **4.51**

Thiocarbamate **4.50** (0.30 g, 1.44 mmol) dissolved in dry THF (2 mL) was added to a solution of 2,2,6,6-tetramethylpiperidine (0.25 g, 1. 73 mmol, 0.29 mL, 1.2 equiv.) and *n*BuLi (1.73 mmol, 1.08 mL, 1.6M in hexane) in dry THF (3 mL) under argon, that has been previously stirred for 15 min at -30°C, at -78°C and the solution was stirred at this temperature for 30 min. Borate **2.27**[56] [0.53 g, 1. 73 mmol; formed from (*R*,*R*)-1,2-dicyclohexyl-1,2-ethanediol and tri(*tert*-butyl) borate] was dissolved in dry THF (2 mL) and added. The reaction mixture was stirred for anadditional 1 h. A saturated aqueous solution of NH_4Cl:H_2O (1:1, 10 mL) was added and the aqueous phase was extracted with Et_2O (3x10 mL). The combined organic phases were dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by flash chromatography (hexanes: ethyl acetate = 2:1, R_f = 0.44, diastereomeric boronates partly decomposed on silica gel

and eluted together with impurities) to yield impure mixture of diastereomers **4.51** (0.27 g, 43%; 1:1.1) as an oil.

4mar0510, 130: ^{1}H NMR (400.27 MHz, $CDCl_3$, 7.24): δ = 4.60 (s, 1H, BCH), 4.58 (s, 1H. BCH), 4.20-4.10 (m, 2H, 2xNCH), 3.75-3.65 (m, 2H, 2xNCH), 3.65-3.60 (m, 4H, 4xOCH), 3.35 (s, 3H, OCH_3), 3.33 (s, 3H, OCH_3), 2.00-0.91 (m, 68H).

***S*-(Benzyloxy)methyl 2,4,6-triisopropylbenzothioate (4.54)**



4.53 **4.54**

A mixture of 2,4,6-triisopropylbenzoyl chloride (**4.53**, 2.67 g, 10 mmol) and Na_2S (0.86 g, 11 mmol) in dry THF (50 mL) under argon was stirred for 18 h, sonicated for 1 h and stirred again for 5 h at RT. Benzyl chloromethyl ether (1.72 g, 11 mmol) in dry THF (5 mL) was added at -30°C and the reaction mixture was warmed to RT over 17 h. After the addition of a saturated aqueous solution of $NaHCO_3$ (5 mL) the mixture was concentrated under reduced pressure, water (10 mL) was added and it was extracted with CH_2Cl_2 (3x15 mL). The combined organic phases were dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by flash chromatography (hexanes: CH_2Cl_2 = 1:1, R_f = 0.54) to yield benzothioate **4.54** (2.61 g, 68%) as colorless crystals that were recrystallized from hexanes, mp. 58-60°C.

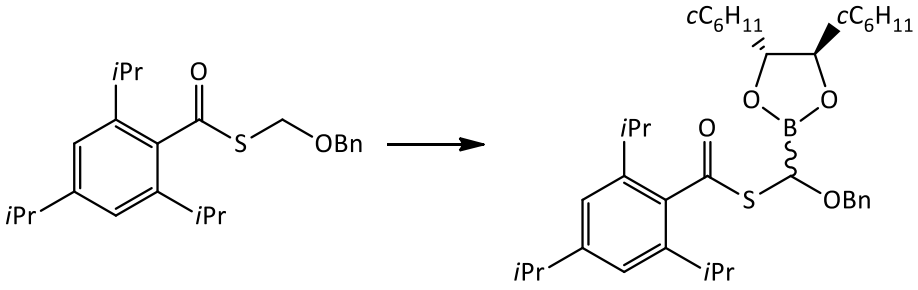
IR (Si): v = 2962, 2929, 1685, 1460, 1275, 1261, 1207, 1093 cm^{-1}.

4jan2811, 330: ^{1}H NMR (400.27 MHz, $CDCl_3$, 7.24): δ = 7.37-7.27 (m, 5H, H_{Ar}), 7.00 (s, 2H, H_{Ar}), 5.31 (s, 2H, SCH_2O), 4.63 (s, 2H, OCH_2), 3.00 (hept, J = 6.8 Hz, 2H, 2xCH), 2.88 (hept, J = 6.9 Hz, 1H, CH), 1.24 (d, J = 6.9 Hz, 6H, 2xCH_3), 1.23 (d, J = 6.8 Hz, 12H, 4xCH_3).

4feb0111, 381: ^{13}C NMR (100.65 MHz, $CDCl_3$, 77.0): δ = 197.0 (C=O), 150.7 ($C_{q,Ar}$), 144.3 (2x$C_{q,Ar}$), 137.1 ($C_{q,Ar}$), 135.6 ($C_{q,Ar}$), 128.5 (2xCH_{Ar}), 128.1 (2xCH_{Ar}), 128.0 (CH_{Ar}), 121.2 (2xCH_{Ar}), 71.5 (SCH_2O), 70.2 (OCH_2), 34.4 (CH), 30.8 (2xCH), 24.4 (4xCH_3), 23.9 (2xCH_3).

Anal. calcd. for $C_{24}H_{32}O_2S$: C, 74.95%, H, 8.39%, 0, 8.32%; Found: C, 74.86%, H, 8.26%, O, 8.41%.

Diastereomeric boronates 4.55 derived from (*R*,*R*)-1,2-dicyclohexyl-1,2-ethanediol

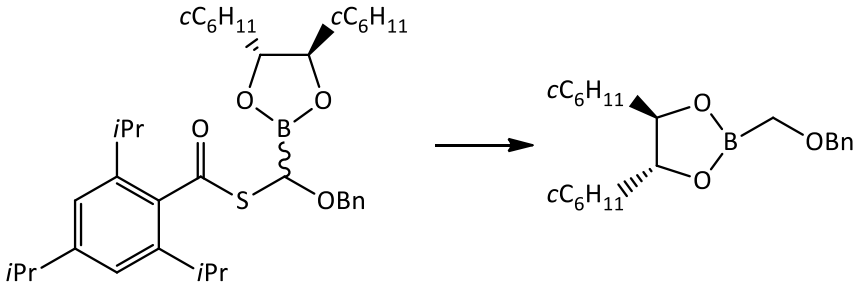


4.54 **4.55**

Boronates **4.55** were formed according to general procedure B from borate **2.27**[56] [0.53 g, 1. 99 mmol; formed from (*R*,*R*)-1,2-dicyclohexyl-1,2-ethanediol and trimethyl borate], benzothioate **4.54** (0.77 g, 2.00 mmol), TMEDA (2.4 mmol, 0.36 mL) and *s*BuLi (2.4 mmol, 1.71 mL, 1.4M in cyclohexane). The depronotation took 30 min at -95°C and the mixture was then stirred for 1 h. The crude product was purified by flash chromatography (hexanes: ethyl acetate = 7:1, R_f = 0.30, 0.15, boronates were unstable on silica gel and could not be separated) to yield diastereomeric boronates **4.55** in 1:1.12 ratio (0.80 g, 65%) as an oil that still contained some impurities.

4feb1011, 270: ^{1}H NMR (400.27 MHz, $CDCl_3$, 7.24): δ = 7.39-7.26 (m, 10H, H_{Ar}, A+B), 6.99 (s, 4H, H_{Ar}, A+B), 4.97 (s, 1H, BCH, A), 4.96 (s, 1H, BCH, B), 4.83 (d, *J* = 12.0 Hz, 1H, OCH_2, A), 4.82 (d, *J* = 12.5 Hz, 1H, OCH_2, 5), 4.55 (d, *J* = 12.0 Hz, 1H, OCH_2, A), 4.51 (d, *J* = 12.5 Hz, 1H, OCH_2, B), 4.01-3.96 (m, 2H, 2xOCH, B), 3.94-3.89 (m, 2H, 2xOCH, A), 3.13-2.95 (m, 4H, 4xCH, A+B), 2.95-2.81 (m, 2H, 2xCH, A+B), 1.91-0.95 (m, 80H, A+B).

Reduction of benzoylthiomethylboronates 4.55 to benzyloxymethylboronate 4.56



4.55 **4.56**

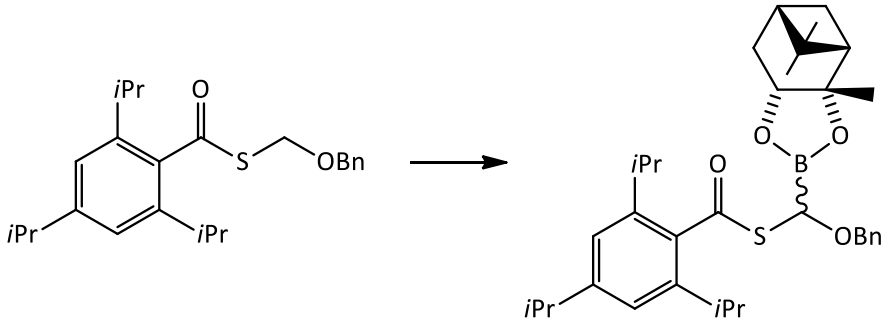
A mixture of impure boronates **4.55** (0.72 g, 1.16 mmol) from the previous experiment and $LiAlH_4$ (0.07 g, 1.74 mmol) in dry THF (10 mL) was stirred under argon at RT for 90 min. Acetone (1 mL) and HCl (2M, 10 mL) were added and the mixture was extracted with Et_2O (3x15 mL). The

combined organic phases were washed with a saturated aqueous solution of $NaHCO_3$ (10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by flash chromatography (hexanes: ethyl acetate = 10:1, R_f = 0.44) to yield benzyloxymethylboronate **4.56** (0.21 g, 50%) as a colorless solid that still contained some impurities.

^{1}H NMR is identical to that in the literature.[160]

4feb1111, 430: ^{1}H NMR (400.27 MHz, $CDCl_3$, 7.24): δ = 7.35-7.23 (m, 5H, H_{Ar}), 4.50 (AB System, J = 12.1 Hz, 2H, OCH_2Ph), 3.92-3.87 (m, 2H, 2xOCH), 3.33 (AB System, J = 16.1 Hz, 2H, $BOCH_2$), 1.80-0.82 (m, 22H)

Diastereomeric boronates 4.58 derived from (+)-pinane-2,3-diol



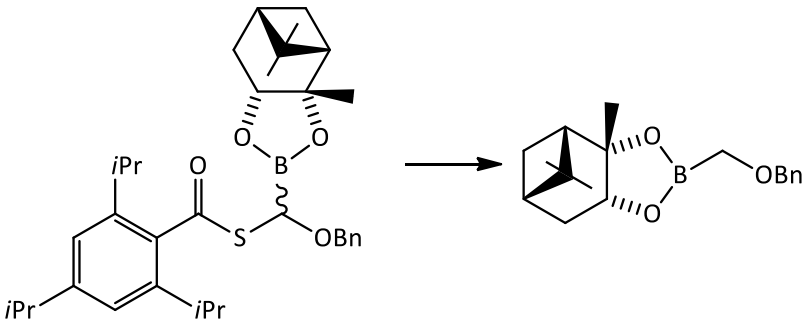
4.54 **4.58**

Boronates **4.58** were formed according to general procedure B from borate **4.57**[83] [0.52 g, 2.48 mmol, formed from (+)-pinane-2,3-diol and trimethyl borate] dissolved in dry THF (3.5 mL), benzothioate **4.54** (0.91 g, 2.36 mmol), TMEDA (0.33 g, 2.83 mmol, 0.42 mL) and *s*BuLi (2.83 mmol, 2.02 mL, 1.4M in cyclohexane) in dry THF (11 mL). The deprotonation took 30 min at -95°C and the reaction mixture was stirred for another 30 min. The crude product was purified by flash chromatography (hexanes: ethyl acetate = 7:1, R_f = 0.30, 0.15, the boronates partly decomposed on silica gel and were not separated) to yield diastereomeric boronates **4.58** (0.77 g, 58%, 1:1.10) as an oil that still contained some impurities.

4feb2111, 490: ^{1}H NMR (400.27 MHz, $CDCl_3$, 7.24): δ = 7.37-7.24 (m, 10H, H_{Ar}, A+B), 6.98 (s, 2H, H_{Ar}, A), 6.97 (s, 2H, H_{Ar}, B), 4.91 (s, 1H, BCH, A), 4.84 (d, J = 12.2 Hz, 1H, OCH_2), 4.83 (d, J = 12.3 Hz, 1H, OCH_2), 4.80 (s. 1H, BCH, B), 4.55 (d, J = 12.3 Hz, 1H, OCH_2), 4.52 (d, J = 12.2 Hz, 1H, OCH_2), 4.49 (dd, J = 8.8; 2.0 Hz, 1H, OCH, B), 4.33 (dd, J = 8.8; 2.0 Hz, 1H, OCH, A), 3.06 (hept, J = 6.8 Hz, 4H, 4xCH, A+B), 2.86 (hept, J = 6.8 Hz, 2H, 2xCH, A+B), 2.39-2.27 (m, 2H, A+B), 2.23-2.14 (m, 2H, A+B),

2.13-2.05 (m, 2H, A+B), 2.00-1.84 (m, 4H, A+B), 1.28 (s, 6H, 2xCH_3, A+B), 1.27 (s, 6H, 2xCH_3, A+B), 1.24-1.16 (two broad overlapping d, 36H, 12xCH_3, A+B), 0.84 (s, 6H, 2xCH_3, A+B).

Reduction of (2,4,6-triisopropylbenzoylthio)methylboronates 4.58 to benzyloxymethylboronates 4.59



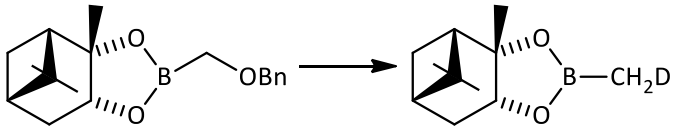
4.58 **4.59**

A mixture of impure boronates **4.58** (0.77 g, 1.36 mmol) from the above experiment and $LiBEt_3H$ (2.04 mmol, 2.04 mL, 1M in THF) in dry THF (13 mL) was stirred under argon at 60°C for 90 min. Acetone (2 mL) and HCl (2M, 10 mL) were added and the mixture was extracted with Et_2O (3x10 mL). The combined organic phases were washed with a saturated aqueous solution of $NaHCO_3$ (10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by flash chromatography (hexanes: ethyl acetate = 7:1, R_f = 0.40) to yield benzyloxymethylboronate **4.59** (0.19 g, 47%) as a colorless oil that still contained some impurities.

The ^{1}H NMR spectrum was identical to that in the literature.[161]

4feb2211, 380: ^{1}H NMR (400.27 MHz, $CDCl_3$, 7.24): δ = 7.35-7.25 (m, 5H, H_{Ar}), 4.51 (AB System, J = 12.2 Hz, 2H, OCH_2Ph), 4.31 (dd, J = 8.7, 1.8 Hz, 1H, OCH), 3.32 (AB System, J = 16.1 Hz, 2H, $BOCH_2$), 2.35-2.27 (m, 1H, CH_x), 2.24-2.17 (m, 1H, CH_x), 2.07-2.03 (m, 1H, CH_x), 1.92-1.86 (m, 2H, CH_2), 1.39 (s, 3H, CH_3), 1.27 (s, 3H, CH_3), 1.14 (d, J = 10.9 Hz, 1H, CH), 0.82 (s, 3H, CH_3).

Deuterated methylboronate [D_1]4.60 derived from benzyloxymethyl boronate 4.59



4.59 [D_1]**4.60**

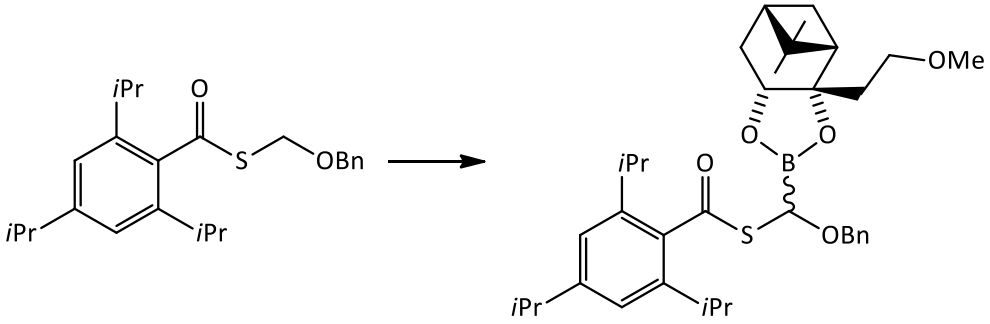
The impure boronate **4.59** (0.10 g, 0.34 mmol) and $LiAlD_4$ (0.02 g, 0.5 mmol) in dry THF (4 mL) was stirred under argon at RT for 1h and at 60°C for 2 h. Acetone (1 mL) and HCl (2M, 6 mL) and the

whole mixture was extracted with Et_2O (3x10 mL). The combined organic phases were washed with a saturated aqueous solution of $NaHCO_3$ (10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by flash chromatography (hexanes: ethyl acetate = 5:1, R_f = 0.45) to yield methylboronate [D_1]**4.60** (0.02 g, 34%) as a colorless oil that still contained some impurities.

^{1}H NMR spectrum was identical to that found in the literature with exception of the BCH_2D peak.[162]

4feb2411, 280: ^{1}H NMR (400.27 MHz, $CDCl_3$, 7.24): δ = 4.22 (dd, J = 8.7, 1.9 Hz, 1H, OCH), 2.35-2.27 (m, 1H, CH_x), 2.24-2.16 (m, 1H, CH_x), 2.04-2.00 (m, 1H, CH_x), 1.92-1.80 (m, 2H, CH_x), 1.37 (s, 3H, CH_3), 1.27 (s, 3H, CH_3), 1.11 (d, J = 10.9 Hz, 1H, CH), 0.83 (s, 3H, CH_3), 0.25 (t, J = 2.1 Hz, 1H, CH_2D).

Diastereomeric (2,4,6-triisopropylbenzoylthio)methylboronates 4.62 derived from (1*R*)-(-)-nop-2,3-diol



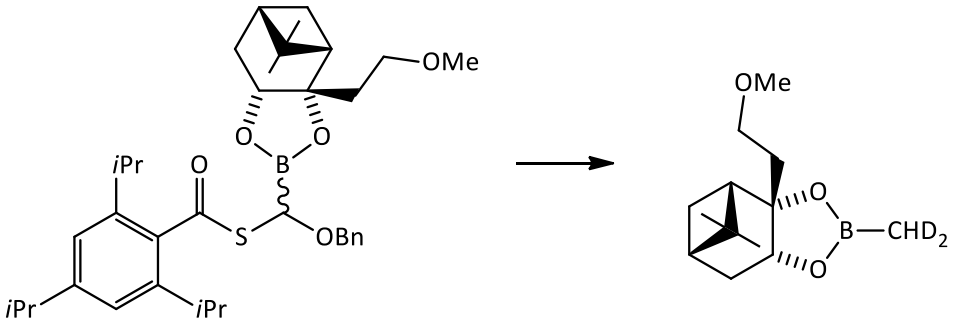
4.54 **4.62**

Boronates **4.62** were formed according to general procedure B from borate **4.61**[56] [0.56 g, 2.2 mmol; formed from trimethyl borate and the diol derived from the methyl ether of (1*R*)-(-)-nop-2,3-diol, benzothioate **4.54** (0.77 g, 2.0 mmol), TMEDA (2.4 mmol, 0.36 mL) and *s*BuLi (2.4 mmol, 1.71 mL, 1.4M in cyclohexane). The deprotonation took 30 min at -95°C and the mixture was stirred for 45 min. The crude product was purified by flash chromatography (hexanes: ethyl acetate = 5:1, R_f = 0.30, 0.15, the boronates partly decomposed on silica gel and were not separated) to yield diastereomeric boronates **4.62** (0.88 g, 68%, ratio: 1:1.10) as a colorless oil that still contained some impurities.

4feb2811, 180: ^{1}H NMR (400.27 MHz, $CDCl_3$, 7.24): δ = 7.39-7.24 (m, 10H, H_{Ar}, A+B), 6.99 (s, 4H, H_{Ar}, A+B), 5.01 (s, 1H, BCH, A), 4.88 (s, 1H, BCH, B), 4.84 (d, J = 12.1 Hz, 2H, 2xOCH_2Ph, A+B), 4.57 (dd, J = 8.9, 2.0 Hz, 1H, OCH, B), 4.56 (d, J = 12.1 Hz, 1H, OCH_2Ph, A), 4.53 (d, J = 12.1 Hz, 1H,

OCH_2Ph, B), 4.53 (dd, *J* = 8.9, 2.0 Hz, 1H, OCH, A), 3.59-3.46 (m, 4H, 2xOCH_2, A+B), 3.25 (s, 3H, OCH_3, A), 3.24 (s, 3H, OCH_3, B), 3.04 (sept, *J* = 6.9 Hz, 4H, 4xCH*i*Pr, A+B), 2.87 (sept, *J* = 6.9 Hz, 2H, 2xCH*i*Pr, A+B), 2.39-2.30 (m, 2H, A+B), 2.23-2.10 (m, 4H, A+B), 2.08-1.84 (m, 8H, A+B), 1.27 (s, 6H, 2xCH_3, A+B), 1.25-1.18 (m, 38H, A+B), 0.86 (s, 6H, 2xCH_3, A+B).

Dideuteromethylboronate [D_2]4.63 derived from (-)-nop-2,3-ol

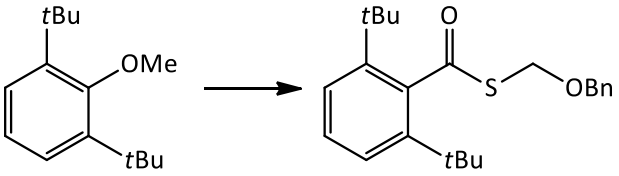


4.62 [D_2]**4.63**

A mixture of impure boronates **4.62** (0.51 g, 0.85 mmol) and $LiAlD_4$ (0.05 g, 1.27 mmol) in dry THF (9 mL) was stirred under argon at RT for 2 h and at 50°C for 3 h when acetone (1 mL) and HCl (2M, 10 mL) and the whole mixture was extracted with Et_2O (3x15 mL). The combined organic phases were washed with a saturated aqueous solution of $NaHCO_3$ (10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by flash chromatography (hexanes: ethyl acetate = 7:1, R_f = 0.45) to yield dideuteromethylboronate [D_2]**4.63** (0.12 g, 58%) as a colorless oil that still contained some impurities.

4mar1011, 400: ^{1}H NMR (400.27 MHz, $CDCl_3$, 7.24): δ = 4.40 (dd, *J* = 8.8, 1.9 Hz, 1H, OCH), 3.54-3.44 (m, 2H, OCH_2), 3.30 (s, 3H, OCH_3), 2.36-2.28 (m, 1H, CH_x), 2.24-2.15 (m, 1H, CH_x), 2.11-2.06 (m, 1H, CH_x), 1.94-1.80 (m, 2H, CH_x), 1.26 (s, 3H, CH_3), 1.23 (t, *J* = 6.7 Hz, 2H, CH_2), 1.11 (d, *J* = 10.9 Hz, 1H, CH), 0.85 (s, 3H, CH_3), 0.25 (quint, *J* = 2.1 Hz, 1H, CHD_2).

***S*-(Benzyloxy)methyl 2,6-di-*tert*-butyl-benzothioate (4.66)**



4.65 **4.66**

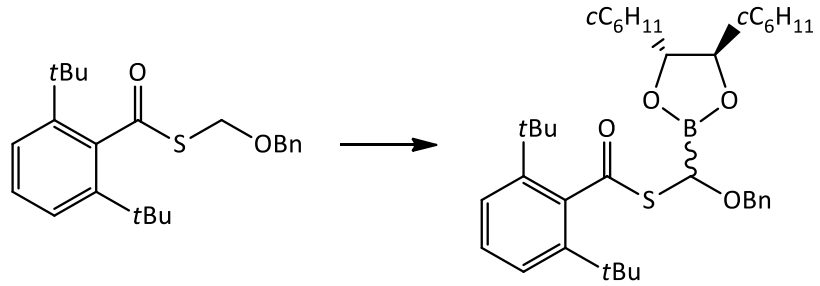
A mixture of 4,4'-di-*tert*-butylbiphenyl (3.44 g, 15.80 mmol) and lithium (0.68 g, 98.0 mmol) was stirred in dry THF (40 mL) under argon at RT for 2 h. A solution of di-tert.-butyl-methoxybenzene

4.65[84] (6.70g, 30.4 mmol) in dry THF (10 mL) was added and stirring was continued for 2.5 h at 15°C. Carbonyl sulfide[163] (~9.3 g) dissolved in dry toluene (14 mL) was added at -78°C and after stirring for 30 min, benzyl chloromethyl ether (7.83 g, 50 mL) was added and the reaction mixture was warmed to RT over 16 h and filtered. A saturated aqueous solution of $NaHCO_3$ (50 mL) was added and the mixture was extracted with CH_2Cl_2 (3x40 mL). The combined organic phases were washed with water (50 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash chromatography (hexanes: CH_2Cl_2 = 1:1, R_f = 0.53) to yield 2,6-di-*tert*-butylbenzothioate **4.66** (6.92 g, 62%) as a yellow oil that still contained some impurities.

IR (Si): v = 2967, 2911, 1699, 1454, 1365, 1187, 1074 cm^{-1}.

4nov2411, 340: ^{1}H NMR (400.27 MHz, $CDCl_3$, 7.24): δ = 7.37-7.23 (m, 8H, H_{Ar}), 5.20 (s, 2H, SCH_2O), 4.59 (s, 2H, OCH_2), 1.42 (s, 18H, 6xCH_3).

Diastereomeric boronates 4.67 derived from (*R*,*R*)-1,2-dicyclohexyl-1,2-ethanediol

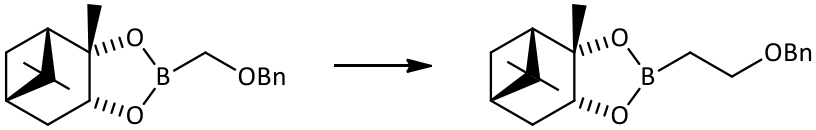


4.66 **4.67**

Boronates **4.67** were formed according to general procedure B from borate **2.27**[56] [0.27 g, 1.00 mmol; formed from (*R*,*R*)-1,2-dicyclohexyl-1,2-ethanediol and trimethyl borate], benzothioate **4.66** (0.32 g, 0.87 mmol), TMEDA (0.15 g, 1.31 mmol, 0.19 mL) and *s*BuLi (1.31 mmol, 0.93 mL, 1.4M in cyclohexane). The deprotonation took 45 min at -95°C and the mixture was allowed to warm up to -30°C over 2.5 h. The crude product (A:B = 1:0.71 in ^{1}H NMR spectrum) was purified by flash chromatography (hexanes: ethyl acetate = 5:1, R_f = 0.30, 0.15, the boronates partly decomposed on silica gel and were not separated) to yield diastereomeric boronates **4.67** (0.10 g, 18%) as a colorless solid that still contained some impurities.

4jul2711, 480: ^{1}H NMR (400.27 MHz, $CDCl_3$, 7.24): δ = 7.38-7.22 (m, 16H, H_{Ar}, A+B), 5.29 (s, 1H, BCH, A), 5.07 (s, 1H, BCH, B), 4.81 (d, *J* = 12.1 Hz, 1H, OCH_2, A), 4.80 (d, *J* = 12.1 Hz, 1H, OCH_2, B), 4.57 (d, *J* = 12.1 Hz, 1H, OCH_2, A), 4.52 (d, *J* = 12.1 Hz, 1H, OCH_2, B), 3.98-3.94 (m, 2H, 2xOCH, A), 3.94-3.89 (m, 2H, 2xOCH, B), 1.87-0.88 (m, 80H, A+B).

2-Benzyloxyethylboronate 4.74 derived from (+)-pinane-2,3-diol



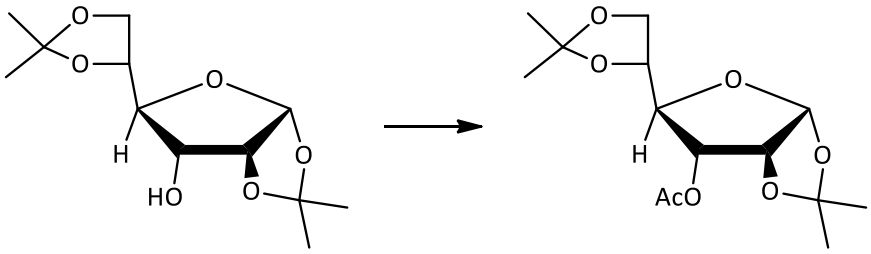
4.59 **4.74**

MeLi (1.20 mmol, 0.4 mL of 3M solution in diethoxymethane + 0.8 mL hexanes) was SLOWLY added to a mixture of boronate **4.59** (0.30 g, 1.0 mmol) and Bu_3SnCH_2Cl (0.41g, 1.2 mmol) in dry THF (6 mL) under argon at -78°C. The reaction mixture was allowed to warm up in the bath to 10°C over 16 h. A saturated aqueous solution of $NaHCO_3$ (5 mL) was added and the mixture was extracted with hexanes (3x5 mL). The combined organic phases were washed with a saturated aqueous solution of NH_4Cl (10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by flash chromatography (hexanes: ethyl acetate = 7:1, R_f = 0.49) to yield boronate **4.74** (0.09 g, 29%) as a colorless oil. This compound was prepared by Matteson et al. but he did not report complete spectroscopic data.[86]

4feb1213, 380: ^{1}H NMR (400.27 MHz, $CDCl_3$, 7.24): δ = 7.35-7.21 (m, 5H, H_{Ar}), 4.49 (s, 2H, OCH_2Ph), 4.24 (dd, J = 8.7, 1.9 Hz, 1H, OCH), 3.63 (t, J = 7.8 Hz, 2H, OCH_2), 2.35-2.26 (m, 1H, CH_x), 2.22-2.13 (m, 1H, CH_x), 2.02 (t, J = 5.5 Hz, 1H, CH), 1.92-1.79 (m, 2H, CH_2), 1.36 (s, 3H, CH_3), 1.26 (s, 3H, CH_3), 1.25 (t, J = 7.8 Hz, 2H, BCH_2), 1.12 (d, J = 10.9 Hz, 1H, CH), 0.82 (s, 3H, CH_3).

7.5 Synthesis of 1α- and 1-β-D-(2´,3´,5´-Tri-*O*-acetyl-6-*O*-p-toluenesulfonyl-allofuranosyl)-2-nitroimidazole (5.8)

3-*O*-Acetyl-1,2:5,6-di-*O*-isopropylidene-*α*-D-allofuranose (5.15)



5.10 **5.15**

A mixture of 1,2:5,6-di-*O*-isopropylidene-*α*-D-allofuranose (**5.10**, 13.01 g, 50 mmol) and Ac_2O (10.21 g, 9.45 mL, 100 mmol) in dry pyridine (11.87 g, 12.09 mL, 150 mmol) was stirred at 60°C until the starting material was consumed (1.5 h, TLC: hexanes: ethyl acetate, 2:1, R_f = 0.43 for product, 0.17 for starting material). Water (30 mL) was added and stirring was continued for 15 min. The mixture was extracted with CH_2Cl_2 (3x25 mL). The combined organic phases were washed with 2 M HCl (2x15 mL), water and saturated aqueous solution $NaHCO_3$, dried (Na_2SO_4) and concentrated under reduced pressure to give the crude product **5.15** (14.26 g, 94%) as a crystalline solid which was pure enough for the next step. The analytical sample was recrystallized from hexanes to yield colourless needles; mp. 75-76°C (lit.:[116] 77-78°C), $[\alpha]_D^{20}$ = +105.25 (*c* = 1.53, acetone) (lit.:[116] $[\alpha]_D^{20}$ = +116.20 (*c* = 1.59, $CHCl_3$).

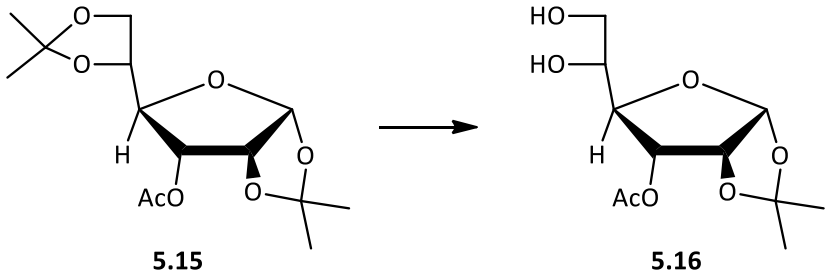
IR (Si): ν = 2989, 1745, 1374, 1245, 1070, 1024, 913 cm^{-1}.

The ^1H NMR spectrum is identical to the one in the literature.[117]

^1H NMR (400.27 MHz, $CDCl_3$, 7.24): *δ* = 5.80 (d, *J* = 3.8 Hz, 1H, 1-H), 4.86 (dd, *J* = 8.6, 5.0 Hz, 1H, 3-H), 4.79 (dd, *J* = 5.0, 3.8 Hz, 1H, 2-H), 4.27 (ddd, *J* = 6.8, 5.6, 4.5 Hz, 1H, 5-H), 4.14 (dd, *J* = 8.6, 4.5 Hz, 1H, 4-H), 4.05 (dd, *J* = 8.6, 6.8 Hz, 1H, 6-H), 3.89 (dd, *J* = 8.6, 5.6 Hz, 1H, 6-H), 2.10 (s, 3H, CH_3), 1.53 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 1.32 (s, 3H, CH_3). ^{13}C NMR (100.65 MHz, $CDCl_3$, 77.00): *δ* = 170.02 (C=O), 113.11 (C_q), 109.96 (C_q), 104.10 (C-1), 77.74 (CH), 77.57 (CH), 75.08 (CH), 72.56 (CH), 65.67 (C-6), 26.69 (CH_3), 26.65 (CH_3), 26.24 (CH_3), 24.99 (CH_3), 20.72 (CH_3CO).

Anal. Calcd for $C_{14}H_{22}O_7$ (302.32) C, 55.62; H, 7.33. Found: C, 55.44; H, 7.40.

3-*O*-Acetyl-1,2-*O*-isopropylidene-*α*-D-allofuranose (5.16)



5.15 **5.16**

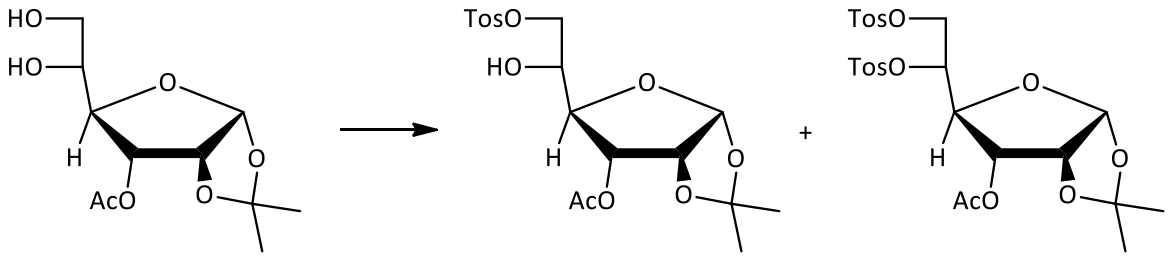
A mixture of 3-*O*-acetyl-1,2:5,6-di-*O*-isopropylidene-*α*-D-allofuranose (**5.15**, 8.34 g, prepared from 27.6 mmol of diacetonide, see above procedure) and 60% AcOH (75 mL) was stirred at RT for 23 h. The solution was then concentrated under reduced pressure (temperature of water bath should not be higher than 25°C) and coevaporated with toluene (2x10 mL). The crude product was purified by flash chromatography (hexanes: ethyl acetate = 1:2, R_f = 0.23) to yield diol **5.16** (6.12 g, 85% for both steps) as a colourless oil. Zsoldos-Mády and Zbiral obtained a "white solid material" on standing or treatment with $Et_2O/CHCl_3$; mp. 68-70°C.[116]

^{1}H NMR spectrum is identical to the one reported in the literature.[116]

^{1}H NMR (400.27 MHz, $CDCl_3$, 7.24): δ = 5.79 (d, J = 3.8 Hz, 1H, 1-H), 4.88 (dd, J = 8.8, 4.8 Hz, 1H, 3-H), 4.81 (dd, J = 4.8, 3.8 Hz, 1H, 2-H), 4.15 (dd, J = 8.8, 3.8 Hz, 1H, 4-H), 3.97 (td, J = 6.8, 3.8 Hz, 1H, 5-H), 3.66 (ABX sys., J_{AB} = 11.6 Hz, J_{AX} = 3.8 Hz, J_{BX} = 6.8 Hz, 2H, 6-H), 2.40 (br. s, 1H, OH), 2.11 (s, 3H, CH_3), 1.95 (br. s, 1H, OH), 1.54 (s, 3H, CH_3), 1.32 (s, 3H, CH_3).

^{13}C NMR (100.65 MHz, $CDCl_3$, 77.00): δ = 170.29 (C=O), 113.26 (C_q), 104.05 (C-1), 78.18 (CH), 77.74 (CH), 71.83 (CH), 71.16 (CH), 62.74 (C-6), 26.64 (2xCH_3), 20.73 (CH_3CO).

3-*O*-Acetyl-1,2-*O*-isopropylidene-6-*O*-p-toluenesulfonyl-*α*-D-allofuranose (5.18)



5.16 **5.18** **5.17**

A solution of 3-*O*-acetyl-1,2-*O*-isopropylidene-*α*-D-allofuranose (**5.16**, 5.25 g, 20 mmol) and *p*-toluenesulfonyl chloride (3.82 g, 20 mmol) in dry pyridine (23.73 g, 300 mmol, 15 equiv, 24.16 mL)

was kept at -25°C for 40 h.[164] Water (20 mL) was added and after stirring for 15 min the mixture was extracted with CH_2Cl_2 (3x20 mL). The combined organic phases were washed with 4 M HCl until the pyridine was gone (TLC checked), water and saturated aqueous solution of $NaHCO_3$, dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by flash chromatography (hexanes: ethyl acetate = 2:1, R_f = 0.18) to give the monotosylate **5.18** (6.15 g, 74%) as a crystalline solid; mp. 111-113°C (hexanes/$C_2H_4Cl_2$), $[\alpha]_D^{20}$ = +82.31 (*c* = 1.47, acetone). No ditosylate could be detected.

When the reaction mixture was kept at 4°C for 18 h, diol (0.481 g, 1.83 mmol) and tosyl chloride (0.420 g, 2.2 mmol, 1.2 equiv) was converted to monotosylate (0.503 g, 66%) and ditosylate (0.187 g, 18%) as colourless crystals; R_f = 0.30 (hexanes: ethyl acetate = 2:1); mp. 68-69°C (1,2-$C_2H_4Cl_2$/*i*Pr_2O); $[\alpha]_D^{20}$ = +60.0 (*c* = 1.01, acetone).

Monotosylate (**5.18**):

IR (Si): ν = 3491, 2988, 1744, 1372, 1243, 1177, 1028, 983, 913 cm^{-1}.

^{1}H NMR (400.27 MHz, $CDCl_3$, 7.24): δ = 7.80-7.75 (m, 2H, H_{ar}), 7.36-7.31 (m, 2H, H_{ar}), 5.74 (d, *J* = 3.7 Hz, 1H, 1-H), 4.83 (dd, *J* = 8.4, 4.9 Hz, 1H, 3-H), 4.79 (dd, *J* = 4.9, 3.7 Hz, 1H, 2-H), 4.16 (dd, *J* = 10.1, 3.4 Hz, 1H, 6-H), 4.10 (dd, *J* = 8.4, 4.6 Hz, 1H, 4-H) 4.07-4.02 (m, 1H, 5-H), 3.97 (dd, *J* = 10.1, 6.8 Hz, 1H, 6-H), 2.44 (s, 3H, CH_3-Ar), 2.34 (br. s, 1H, OH), 2.09 (s, 3H, CH_3), 1.52 (s, 3H, CH_3), 1.31 (s, 3H, CH_3CO).

^{13}C NMR (100.65 MHz, $CDCl_3$, 77.00): δ = 170.24 (C=O), 145.14 (C_q), 132.58 ($C_{q,ar}$), 129.95 (2xCH_{ar}), 128.02 (2xCH_{ar}), 113.37 ($C_{q,ar}$), 104.10 (C-1), 77.74 (CH), 77.10 (CH), 72.25 (CH), 70.11 (C-6), 69.41 (CH), 26.65 (2xCH_3), 21.66 (CH_3-Ar), 20.69 (CH_3CO).

Anal. calcd for $C_{18}H_{24}O_9S$ (416.44) C, 51.91; H, 5.81; S, 7.70. Found: C, 51.94; H, 5.84; S, 7.60.

3-*O*-Acetyl-1,2-*O*-isopropylidene-5,6-di-*O*-p-toluenesulfonyl-*α*-D-allofuranose (**5.17**):

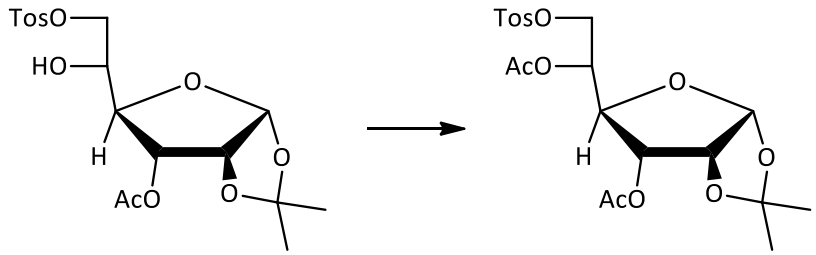
IR (ATR): ν = 2971, 1738, 1364, 1347, 1244, 1190, 1176, 1037, 1004, 921cm^{-1}.

^{1}H NMR (400.13 MHz, $CDCl_3$, 7.24): δ = 7.73-7.68 (m, 2H, H_{ar}), 7.66-7.61 (m, 2H, H_{ar}), 7.33-7.28 (m, 4H, H_{ar}), 5.51 (d, *J* = 3.4 Hz, 1H, 1-H), 4.80 (ddd, *J* = 6.2, 5.0, 4.2 Hz, 1H, 5-H); 4.77-4.70 (m, 2H, 2-H and 3-H), 4.21 (dd, *J* = 8.3, 5.0 Hz, 1H, 4-H), 4.07 (AB part of ABX system, J_{AB} = 11.1 Hz, J_{AX} = 4.2 Hz, J_{BX} = 6.2 Hz, 2H, 6-H), 2.43 (s, 6H, 2xCH_3Tos), 2.10 (s,3H, CH_3), 1.46 (s,. 3H, CH_3), 1.27 (s,. 3H, CH_3).

^{13}C NMR (100.62 MHz, $CDCl_3$, 77.00): δ = 170.03 (C=O), 145.24 (2xC_q), 133.28 (C_q), 132.09 (C_q), 129.93 (2CH_{ar}), 129.78 (2CH_{ar}), 128.02 (2CH_{ar}), 127.98 (2CH_{ar}), 113.51 (C_q), 104.05 (C-1), 77.42 (CH), 77.38 (CH), 75.55 (C-4), 73.02 (C-3), 66.95 (C-6), 26.66 (CH_3 isoprop), 26.61 (CH_3 isopropyl), 21.70 (CH_3 Tos?), 21.68 (CH_3 tos), 20.58 (CH_3CO).

Anal. calcd for $C_{25}H_{30}O_{11}S_2$ (570.63) C, 52.62; H, 5.30; S, 11.24. Found: C, 52.29; H, 5.15.

3,5-Di-*O*-acetyl-1,2-*O*-isopropylidene-6-*O*-p-toluenesulfonyl-*α*-D-allofuranose (5.13)



5.18 **5.13**

A mixture of 3-*O*-acetyl-1,2-*O*-isopropylidene-6-*O*-p-toluenesulfonyl-*α*-D-allofuranose (**5.18**, 6.15 g, 14.77 mmol), Ac_2O (3.02 g, 2.80 mL, 29.6 mmol, 2 equiv) and dry pyridine (3.50 g, 3.58 mL, 44.4 mmol, 3 equiv) in dry CH_2Cl_2 (7.5 mL) was stirred at 40°C for 2.5 h and then cooled to RT. Water (20 mL) was added and after stirring for 10 min the mixture was extracted with CH_2Cl_2 (3x20 mL). The combined organic phases were washed with 2 M HCl (2x20 mL), water and saturated aqueous solution of $NaHCO_3$, dried (Na_2SO_4) and concentrated under reduced pressure. The crude product **5.13** which was a very viscous oil (quantitative yield) was pure enough for the subsequent reaction. The analytical sample was crystallized from CH_2Cl_2/*i*Pr_2O to yield diacetate **5.13** as colourless crystals; mp. 76-77°C, $[\alpha]_D^{20}$ = +74.81 (*c* = 1.04, acetone).

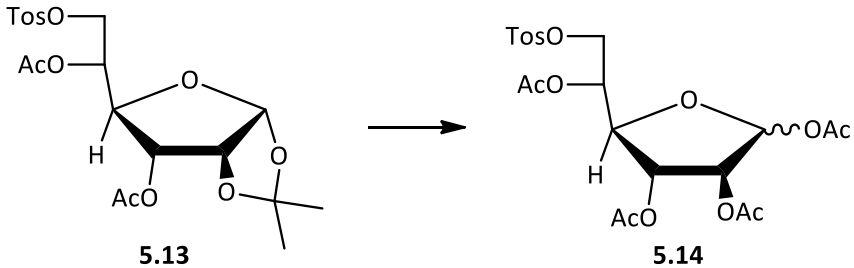
IR (Si): ν = 2990, 1750, 1374, 1243, 1178, 1025 cm^{-1}.

^{1}H NMR (400.27 MHz, $CDCl_3$, 7.24): δ = 7.77-7.74 (m, 2H, H_{ar}), 7.35-7.31 (m, 2H, H_{ar}), 5.70 (d, *J* = 3.6 Hz, 1H, 1-H), 5.12 (td, *J* = 5.8, 3.6 Hz, 1H, 5-H),4.77 (dd, *J* = 5.0, 3.6 Hz, 1H, 2-H), 4.73 (dd, *J* = 8.5, 5.0 Hz, 1H, 3-H), 4.20 (dd, *J* = 8.6, 5.8 Hz, 1H, 3-H), 4.18 (ABX sys, , J_{AB} = 11.0 Hz, J_{AX} = 3.6 Hz, J_{BX} = 5.8 Hz, 2H, 6-H), 2.43 (s, 3H, CH_3), 2.10 (s, 3H, CH_3), 1.99 (s, 3H, CH_3), 1.52 (s, 3H, CH_3), 1.30 (s, 3H, CH_3).

^{13}C NMR (100.65 MHz, $CDCl_3$, 77.0): δ = 169.79 (C=O), 169.56 (C=O), 145.00 (C_q), 132.68 ($C_{q,ar}$), 129.87 (CH_{ar}), 127.93 (CH_{ar}), 113.37 ($C_{q,ar}$), 104.02 (1-C), 77.41 (CH), 75.34 (CH), 73.45 (CH), 70.05 (CH), 67.39 (6-C), 26.59 (2xCH_3), 21.59 ($CH_{3,ar}$), 20.58 (CH_3), 20.48 (CH_3).

Anal. calcd for $C_{20}H_{26}O_{10}S$ (458.48): C, 52.39; H, 5.72. Found: C, 52.33; H, 5.69.

1,2,3,5-Tetra-*O*-acetyl-6-*O*-p-toluenesulfonyl-D-allofuranose (5.14)



5.13 **5.14**

A mixture of 3,5-di-*O*-acetyl-1,2-*O*-isopropylidene-6-*O*-p-toluenesulfonyl-α-D-allofuranose (**5.13**, 2.94 g, 6.4 mmol) and 60% TFA (12.84 mL) was stirred for 40 min at RT.[119] Water (20 mL) was added and the product was extracted with ethyl acetate (3x20 mL). The combined organic phases were washed with a saturated aqueous solution of $NaHCO_3$ until neutral, dried (Na_2SO_4) and concentrated under reduced pressure. After drying the gum at 1 mbar dry CH_2Cl_2 (13 mL), Ac_2O (2.62 g, 2.43 mL, 25.7 mmol), and dry pyridine (4.06 g, 4.12 mL, 51.3 mmol) were added. The mixture was stirred at 40°C for 2.5 h. Water (20 mL) was added and the mixture was extracted with CH_2Cl_2 (3x20 mL). The combined organic phases were washed with 2M HCl (20 mL), water and saturated aqueous solution of $NaHCO_3$, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes: ethyl acetate = 1:1, R_f = 0.53, 0.43 for anomers) to yield a mixture of anomers **5.14** (2.522 g, 78%) as a gum; α:β = 3:1 (by ^{1}H NMR); $[\alpha]_D^{20}$ = + 6.11 (*c* = 1.44, acetone).

A homogeneous sample of α-anomer (R_f = 0.53) was obtained by flash chromatography as a gum. Crystallisation from CH_2Cl_2/*i*P_2O gave crystals containing after drying at RT/1 mbar for an unknown time 0.41 mol of *i*Pr_2O (by ^{1}H NMR); melting range 48-55°C. $[\alpha]_D^{20}$ = -7.48 (*c* = 1.03, acetone).

α-anomer, gum, $[\alpha]_D^{20}$ –10.0 (c = 1.02, acetone):

IR (Si): ν = 3005, 2970, 1740, 1436, 1366, 1228, 1217 cm^{-1}.

^{1}H NMR (600.13 MHz, $CDCl_3$, 7.24): δ = 7.77-7.73 (m, 2H, H_{ar}), 7.35-7.32 (m, 2H, H_{ar}), 6.09 (d, *J* = 0.7 Hz, 1H, 1-H), 5.43 (dd, *J* = 6.7, 5.0 Hz, 1H, 3-H), 5.27 (dd, *J* = 5.0, 0.7 Hz,1H, 2-H), 5.00 (ddd, *J* = 7.0, 4.5, 3.2 Hz, 1H, 5-H), 4.31 (dd, *J* = 7.0, 6.7 Hz, 1H, 4-H), 4.24 (dd, *J* = 11.3, 3.2 Hz, 1-H, 6-H), 4.09 (dd, *J* = 11.3, 4.5 Hz, 1H, 6-H), 2.43 (s, 3H, CH_3), 2.11 (CH_3CO), 2.044 (CH_3CO), 2.042 (CH_3CO), 1.98 (CH_3CO).

^{13}C NMR (150.90 MHz, $CDCl_3$, 77.00): δ = 169.64 (C=O), 169.33 (C=O), 169.32 (C=O), 168.72 (C=O), 145.16 ($C_{q,ar}$), 132.54 ($C_{q,ar}$), 129.93 (2xCH_{ar}), 127.97 (2xCH_{ar}), 98.22 (C-1), 78.65 (C-4), 74.33 (C-2), 71.05 (C-5), 70.99 (C-3), 67.29 (C-6), 21.65 (CH_3tol), 20.96 (CH_3), 20.60 (CH_3), 20.45 (CH_3), 20.40 (CH_3).

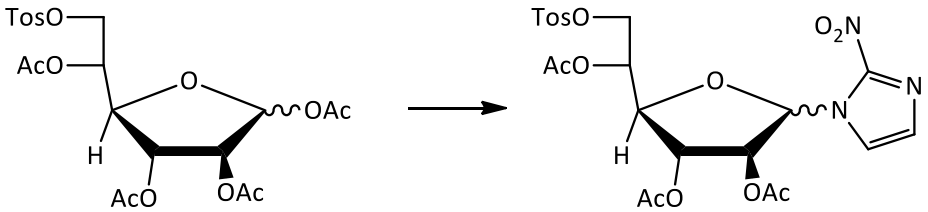
Mixture of anomers (α:β = 3:1), contained 5-10% of an impurity:

^{1}H NMR (400.27 MHz, $CDCl_3$, 7.24): only signals of β-anomer are given as those of the α-anomer are identical to those given data for the homogenous α-anomer above: δ = 7.78-7.71 (m, 2H, H_{ar}), 7.36-7.29 (m, 2H, H_{ar}), 6.30 (d, *J* = 4.5 Hz, 1H, 1-H), 5.37 (dd, *J* = 6.9, 3.1 Hz, 1H, 3-H), 5.08 (dd, *J* = 6.9, 4.5 Hz, 1H, 2-H), 5.03-4.97 (m, 1H, 5-H), 4.39 (dd, *J* = 4.5, 3.1 Hz, 1H, 4-H), 4.15 (AB part of ABX system, J_{AB} = 11.3 Hz, *J* = 4.4, 4.0 Hz, 2H, 6-H), 2.43 (s, 3H, CH_3tol), 2.10 (s, CH_3CO), 2.08 (s, CH_3CO), 2.02 (s, CH_3CO), 1.99 (s, CH_3CO).

^{13}C NMR (100.65 MHz, $CDCl_3$, 77.00); only signals of β-anomer are given, for those of α-anomer see above: δ = 169.67 (C=O), 169.63 (C=O), 169.46 (C=O), 169.16 (C=O), 145.22 ($C_{q,ar}$), 132.39 ($C_{q,ar}$), 129.95 (2xCH_{ar}), 127.98 (2xCH_{ar}), 93.38 (C-1), 81.37 (C-4), 69.71 (C-5), 69.59, 68.60, 67.06 (C-6), 21.61 (CH_3tol), 20.94 (CH_3), 20.63 (CH_3), 20.53 (CH_3), 21.20 (CH_3).

Anal. calcd for $C_{21}H_{26}O_{12}S$ (502.49): C, 50.19; H, 5.22. Found: C, 49.98; H, 5.25.

1α- and 1-β-D-(2´,3´,5´-tri-*O*-acetyl-6-*O*-p-toluenesulfonyl-allofuranosyl)-2-nitroimidazole (5.8)



5.14 **5.8**

A mixture of 2-nitroimidazole (0.134 g, 1.19 mmol, 1.1 equiv), hexaethyldisilazane (0.583 g, 2.38 mmol, 2.2 equiv) and dry pyridine (2.0 mL) were refluxed for 30 min. After cooling to room temperature volatiles were removed by bulb to bulb distillation at 0.7 mbar (final temperature 90°C). Acetonitrile (4.0 mL) and a solution of tetraacetate **5.14** (0.543 g, 1.08 mmol) in dry CH_3CN (6 mL) were added to the crystalline residue under argon atmosphere. The mixture was ultasonicated for 5 min before the addition of a solution of $TfOSiEt_3$ (1.296 mL, 1 M in dry 1,2-$C_2H_4Cl_2$, 1,2 equiv) at 0°C. After 1 h (TLC control, CH_2Cl_2: ethyl acetate = 7:1, R_f (α, less polar) =

0.43; R_f (β, more polar) = 0.33) the reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (10 mL). The mixture was extracted with EtOAc (3x10 mL). The combined organic layers were washed with a mixture of water and brine (5 mL each), dried (Na_2SO_4) and concentrated under reduced pressure. The residue (^{1}H NMR: α-product/β product/α starting material/β-starting material = 0.04:1.00:0.05:0.05) was flash chromatographed (CH_2Cl_2/EtOAc 7:1) to yield α- (0.029 g, 5%) and β-anomers **5.8** (0.266 g, 44%) as foams.

Similarly, tetraacetate **5.14** (1.79 g, 3.56 mmol, dissolved in 20 mL of dry CH_3CN) was reacted with silylated 2-nitroimidazole (in admixture with 13 mL of dry CH_3CN) prepared from 2-nitroimidazole (3.56 mmol) and TfOTES (4.27 mL, 4.27 mmol, 1.2 equiv, 1 M in dry 1,2-$C_2H_4Cl_2$) at room temperature for 1 h. The reaction was worked up and the crude product (^{1}H NMR: α-product/β product/α starting material/β-starting material = 1.00:1.09:1.14:0.32) was flash chromatographed to give anomers of starting material (0.518 g, 29%), α-anomer **5.8** (0.392 g, 20%) and β-anomer **5.8** (0.49 g, 25%).

α-Anomer: $[\alpha]_D^{20}$ = -43.14 (*c* = 1.02, acetone). α-Anomer could not be induced to crystallize.

IR (ATR): ν = 1752, 1540, 1480, 1365, 1219, 1177 cm^{-1}.

^{1}H NMR (400.13 MHz, $CDCl_3$, 7.24): δ = 7.79-7.74 (m, 2H, H_{ar}), 7.37 (d, *J* = 1.2 Hz, 1H, H_{im}), 7.36-7.32 (m, 2H, H_{ar}), 7.19 (d, *J* = 1.2 Hz, 1H, H_{im}), 6.79 (d, *J* = 5.3 Hz, 1H, 1-H), 5.76 (t, *J* = 5.3 Hz, 1H, 2-H), 5.49 (dd, *J* = 5.3, 4.0 Hz, 1H, 3-H), 5.08 (td, *J* = 6.1, 4.0 Hz, 1H, 5-H), 4.70 (dd, *J* = 6.1, 4.0 Hz, 1H, 4-H), 4.23 (AB part of ABX system, J_{AB} = 11.3 Hz, $J_{AX} \approx J_{BX}$ = 4.0 Hz, 2H, 6-H), 2.44 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 1.94 (s, 3H, CH_3), 1.85 (s, 3H, CH_3).

^{13}C NMR (150.90 MHz, $CDCl_3$, 77.00): δ = 169.49 (C=O), 168.94 (C=O), 168.14 (C=O), 145.53 (C_{ar}), 144.44 (C_{im}), 132.22 (C_{ar}), 130.07 (2xCH_{ar}), 127.99 (2xCH_{ar}), 127.94 (CH_{im}), 122. 54 (CH_{im}), 87.16 (C-1), 81.05 (C-4), 70.28 (C-2 or C-3), 70.23 (C-3 or C-2), 69.93 (C-5), 66.62 (C-6), 21.67 (CH_3), 20.66 (CH_3CO), 20.24 (CH_3CO), 19.76 (CH_3CO).

Anal. calcd for $C_{22}H_{25}N_3O_{12}S$ (555.51): C, 47.57; H, 4.54; N, 7.56. Found: C, 47.37; H, 4.48; N, 7.43.

β-Anomer: more polar than α-anomer. It was crystallized from EtOAc/*i*Pr_2O by slowly cooling from +25°C to –17°C to give light yellowish needles, which were dried for 1 h at RT/1 mbar, contained 0.50 mol of EtOAc (by ^{1}H NMR); when kept in vacuum (5 h/RT/0.8 mbar), the ratio changed from 1.00:0.50:0.01 to 1.00:0.45:0.01: mp. 71-72°C; $[\alpha]_D^{20}$ = +27.10 (*c* = 1.07, acetone).

IR (ATR, crystals): ν = 2914, 1755, 1739, 1548, 1484, 1358, 1230, 1178, 1075 cm^{-1}.

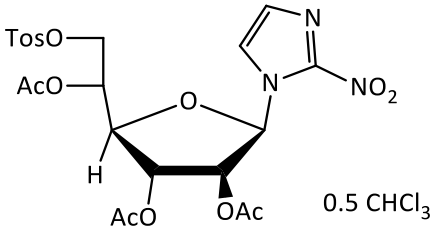
^{1}H NMR (400.13 MHz, $CDCl_3$, 7.24): δ = 7.77-7.72 (m, 2H, H_{Ar}), 7.36-7.30 (m, 2H, H_{Ar}), 7.24 (s, 1H, H_{im}), 7.17 (s, 1H, H_{im}), 6.54 (d, J = 4.2 Hz, 1H, 1-H), 5.40 (AB part of ABXY system, J_{AB} = 5.7 Hz, J = 5.6, 4.2 Hz, 2H, 2-H, 3-H), 5.22 (td, J = 5.6, 4.2 Hz, 1H, 5-H), 4.39 (t, J = 5.6 Hz, 1H, 4-H), 4.19 (AB part of ABX system, J_{AB} = 11.3 Hz, J_{AX} = J_{BX} = 4.2 Hz, 2H, 6-H), 2.43 (s, 3H, $CH_{3,Ar}$), 2.10 (s, 3H, CH_3), 2.09 (s, 3H, CH_3), 2.02 (s, 3H, CH_3). Signals of EtOAc: 4.09 (q, J = 7.0 Hz, 2H, CH_2), 2.02 (s, 3H, CH_3), 1.23 (t, J = 7.0 Hz, 3H, CH_3).

^{13}C NMR (100.65 MHz, $CDCl_3$, 77.00): δ = 169.54 (C=O), 169.16 (C=O), 169.04 (C=O), 145.45 (C_{Ar}), 144.39 (br. s, C_{Im}), 132.22 (C_{ar}), 130.00 (2xCH_{Ar}), 129.09 (CH_{Im}), 127.98 (2xCH_{Ar}), 121.05 (CH_{Im}), 88.70 (C-1), 79.49 (C-4), 74.39 (C-2), 69.70 (C-5), 69.28 (C-3), 66.61 (C-6), 21.65 (CH_3), 20.60 (CH_3CO), 20.35 (CH_3CO), 20.26 (CH_3CO). Signals for EtOAc not given.

Anal. calcd for $C_{22}H_{25}N_3O_{12}S$·x 0.50 EtOAc = $C_{24}H_{29}N_3O_{13}S$ (599.56): C, 48.08; H, 4.88; N, 7.01; O, 34.69; S, 5.35. Found: C, 48.04; H, 4.83; N, 7.10; S, 5.39.

Crystalline complexes of 1-β-D-(2´,3´,5´-tri-*O*-acetyl-6´-*O*-p-toluenesulfonyl-allofuranosyl)-2-nitroimidazoles with small halogenated molecules

With chloroform



By slow cooling of a solution of β-anomer in $CHCl_3$/*i*Pr_2O from RT to +4°C; very thin colourless needles containing 0.46 moles of $CHCl_3$ after drying for 1 h at RT/1 mbar (by ^{1}H NMR in acetone); mp. 67°C, $[\alpha]_D^{20}$ = +26.93 (*c* = 1.01, acetone).

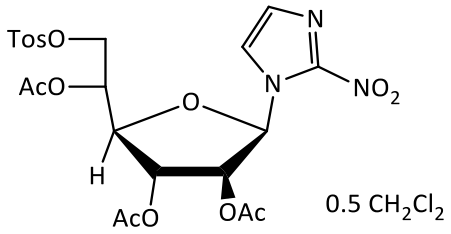
After heating at 50°C/1 mbar for 1 h: sample looked unchanged, still 0.4 moles of $CHCl_3$.

After heating at 70°C/1 mbar for 1 h, faint brownish, 0.23 $CHCl_3$, contained 20% of α-**5.8**.

After heating at 80°C/1 mbar for 1 h, melted, changed colour, sample discarded.

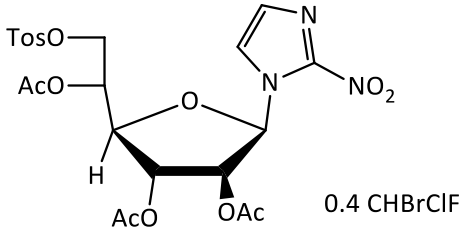
Anal. calcd for $C_{22}H_{25}N_3O_{12}S \cdot 0.50\ CHCl_3$ (615.21): C, 43.93; H, 4.18; N, 6.83; O, 31.21; S, 5.21, Cl, 8.64. Found: C, 44.14; H, 4.17; N, 6.89; O, 31.46; S, 5.11.

With CH_2Cl_2



When a solution of the nucleoside (1oo mg) in a mixture of CH_2Cl_2 (0.5 mL) and diisopropyl ether (0.7 mL) was allowed to cool from room temperature to 4°C very slowly (the flask with the solution was placed into a Dewar filled with water and covered with a styropor plate; the Dewar was placed into a refrigerator) crystals formed. They contained CH_2Cl_2 (ratio of nucleoside/CH_2Cl_2 1.0:0.3, by ^{1}H NMR spectroscopy, 400.27 MHz, $CDCl_3$; 4Feb2615/350) after drying (3 h, 20°C, 1 mbar). After drying for another 5 h, the amount of CH_2Cl_2 was somewhat lower (ratio of nucleoside/CH_2Cl_2 1.00:0.275 by ^{1}H NMR; 4Mar0415/60).

With CHBrClF (5.2)



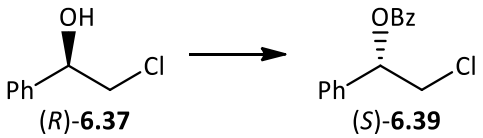
When a solution of the nucleoside (200 mg) in a mixure of (±)-**5.2** (1 mL; 92% CHBrClF, 8% $CHCl_2F$ by GC) and diisopropyl ether (1.2 mL) was allowed to cool in a sealed tube very slowly from room temperature to -78°C (the sealed tube with the solution was placed into a Dewar filled with water and covered with a styropor plate; the Dewar was placed into a freezer with -78° inside) colourless crystals. They were collected and dried (15 min, 20°C, 0.5 mbar; 0.188 g, 94%); ratio of nucleoside/CHBrClF (**5.2**)/$CHCl_2F$ 1:0.38:0.03 by ^{1}H NMR (400.27 MHz, $CDCl_3$; 4Mar1815/70); after drying for another 5 h (20°C, 1 mbar) the ratio of nucleoside/CHBrClF/$CHCl_2F$ was 1:0.30:0.04 by ^{1}H NMR (400.27 MHz, 4Mar2315/20); mp. 69-70°C.

CHBrClF: ^{1}H NMR (400.27 MHz, $CDCl_3$; 4Mar1615/150): δ 7.60 (d, *J* = 52.0 Hz, CHBrClF, 1.00), 7.46 (d, *J* = 52.3 Hz, 0.06).

Crystals (100 mg, dried for 15 min) were heated to 80 °C and kept at that temperature for 5 min in a flask under reduced pressure (0.5 mbar). The formed CHBrClF was collected in a small flask cooled with liquid nitrogen and diluted with dry diethyl ether. The glassy residue of the nucleoside was a mixture of β-anomer/α-anomer 1.00:0.02 (^{1}H NMR, 4Mar2315/10). The ee of CHBrClF was determined using GC (Agilent Technologies 7890 A GC Systems, Lipodex A column - hexakis-(2,3,6-tri-*O*-pentyl)-α-cyclodextrin, 25 m, 26°C, carrier gas: H_2), t_R = 3.18 min (minor enantiomer), t_R = 3.30 min (major enantiomer): 11%.

7.6 [^{16}O,^{17}O,^{18}O]-Phosphoenolpyruvate

(*S*)-(-)-2-Chloro-1-phenylethyl benzoate [(*S*)-6.39] and (*S*)-(-)-2-chloro-1-phenylethyl [carboxy-$^{18}O_2$] benzoate {(*S*)-[$^{18}O_2$]6.39}



(*R*)-**6.37** (*S*)-**6.39**

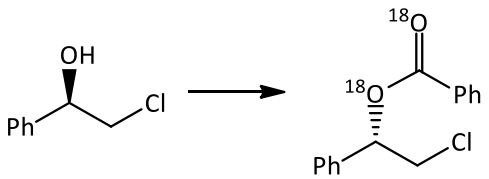
DIAD (0.49 g, 2.4 mmol, 0.47 mL) was added to a mixture of (*R*)-(-)-2-chloro-1-phenylethanol [(*R*)-**6.37**, 0.31 g, 2 mmol, 0.26 mL], benzoic acid (**6.38**, 0.29 g, 2.4 mmol) and PPh_3 (0.63 g, 2.4 mmol) in dry toluene (5 mL) under argon at 0°C.[142] After stirring for 1.5 h at RT, few drops of water were added and the mixture was concentrated under reduced pressure. The crude product was purified by flash chromatography (hexanes: ethyl acetate = 10:1, R_f = 0.60) to yield (*S*)-**6.39** (0.48 g, 92%) as colorless oil, $[\alpha]_D^{20}$ = -38.62 (c = 1.305, acetone).

IR (ATR): ν = 1719, 1452, 1315, 1265, 1176, 1108, 1069, 1026, 999 cm^{-1}.

4mar2613, 190: ^{1}H NMR (400.27 MHz, $CDCl_3$, 7.24): δ = 8.13-8.07 (m, 2H, H_{Ar}), 7.59-7.54 (m, 1H, H_{Ar}), 7.48-7.42 (m, 4H, H_{Ar}), 7.39-7.30 (m, 3H, H_{Ar}), 6.19 (dd, *J* = 7.8, 4.5 Hz, 1H, CHO), 3.89 (AB Sys, J_{AB} = 11.7 Hz, J_{AX} = 7.8 Hz, J_{BX} = 4.5 Hz, 2H, CH_2Cl).

4jul1714, 141: ^{13}C NMR (100.62 MHz, $CDCl_3$, 77.0): δ = 165.4 (C=O), 137.2 ($C_{q,Ar}$), 133.2 (CH_{Ar}), 129.79 (2xCH_{Ar}), 129.75 ($C_{q,Ar}$), 128.8 (CH_{Ar}), 128.7 (2xCH_{Ar}), 128.4 (2xCH_{Ar}), 126.6 (2xCH_{Ar}), 75.6 (CH), 46.7 (CH_2).

Anal. Calcd for $C_{15}H_{13}ClO_2$ (260.72): C, 69.10; H, 5.03; O, 12.27. Found: C, 69.07; H, 4.99; O, 12.32.



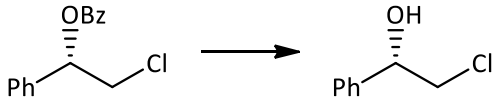
(*R*)-**6.37** (*S*)-[$^{18}O_2$]**6.39**

Similarly, [carboxy-$^{18}O_2$] benzoic acid ([$^{18}O_2$]**6.38**, 1.94 g, 15.39 mmol), prepared from $H_2{}^{18}O$ (98.3% ^{18}O),[55] was used to convert (*R*)-(-)-2-chloro-1-phenylethanol [(*R*)-**6.37**, ee > 97%] to ^{18}O-labeled (*S*)-[$^{18}O_2$]**6.39** (3.32 g, 89%), $[\alpha]_D^{28}$ = -37.34 (c = 1.165, acetone).

IR (ATR): ν = 1693, 1494, 1451, 1315, 1267, 1088, 1067, 1025 cm^{-1}.

All NMR spectra were identical to those of the unlabeled species.

(*S*)-(+)-2-chloro-1-phenylethanol [(*S*)-6.37] and (*S*)-(+)-2-chloro-1-phenyl-[1-$^{18}O_1$]ethanol {(*S*)-[^{18}O]6.37}

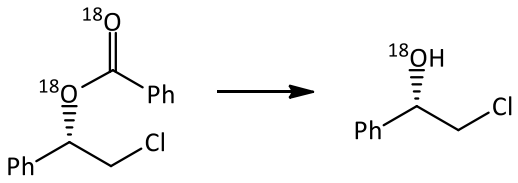


(*S*)-**6.39** (*S*)-**6.37**

DIBAL (5.51 mmol, 5.51 mL, 1.0 M solution in toluene) was added to a solution of benzoate (*S*)-**6.39** (0.44 g, 1.69 mmol) in dry THF (4 mL) under argon at -78°C and the mixture was slowly warmed to RT overnight (16 h) and water (2 mL) and HCl (2 M, 5 mL) were added.[142] The aqueous phase was extracted with CH_2Cl_2 (3x5 mL) and the combined organic phase was washed with water (5 mL) and saturated aqueous solution of $NaHCO_3$ (5 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by flash chromatography (hexanes: ethyl acetate = 5:1, R_f = 0.32) to yield chlorohydrin (*S*)-**6.37** (0.18 g, 68%) as colorless oil, $[\alpha]_D^{20}$ = + 51.41 (c = 1.025, acetone), bought (*R*)-(-)-2-chloro-1-phenylethanol: $[\alpha]_D^{20}$ = - 50.41 (c = 1.095, acetone).

Ee determined by HPLC (Chiralcel OD-H, 5% *i*PrOH in hexanes, 5 mg/mL, 10 µL inj, 1 mL/min) is **at least** 89% (*S* comes first and has a tail that could contain *R*), t_r (*S*) = 9.67, t_r (*R*) = 10. 65.

4apr0913, 250: ^{1}H NMR (400.27 MHz, $CDCl_3$, 7.24): δ = 7.39-7.28 (m, 5H, H_{Ar}), 4.89 (td, *J* = 8.8, 3.3 Hz, 1H, CHO), 3.69 (AB system, J_{AB} = 11.2 Hz, J_{AX} = 8.8 Hz, J_{BX} = 3.3 Hz, 2H, CH_2Cl), 2.61 (d, *J* = 3.3 Hz, 1H, OH).



(*S*)-[$^{18}O_2$]**6.39** (*S*)-[^{18}O]**6.37**

Similarly, labeled (*S*)-[$^{18}O_2$]**6.39** (2.01 g, 7.60 mmol) was converted to ^{18}O-labeled chlorohydrin (*S*)-[^{18}O]**6.37** (1.10 g, 91%), $[\alpha]_D^{20}$ = + 45.93 (c = 1.00, acetone).

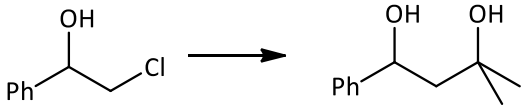
Ee determined by GC (Beta Dex 225 30 m x 0.25 µm, 120°C for 10 min, then ramp +1°C/min to 145°C, He, 1 mL/min, t_r (*R*) = 20.75 min, t_r (*S*) = 21.81 min) >99%.

IR (ATR): ν = 3376, 1494, 1454, 1426, 1248, 1200, 1056, 1007 cm^{-1}.

^{1}H NMR spectrum was identical to that of the unlabeled species.

4apr2613, 320: PM 504: ^{13}C NMR (100.62 MHz, $CDCl_3$, 77.0): δ = 139.9 ($C_{q,Ar}$), 128.7 (2xCH_{Ar}), 128.5 (CH_{Ar}), 126.0 (2xCH_{Ar}), 74.1 (CH, 2.0 Hz to the right from unlabeled), 50.9 (CH_2).

(±)-3-Methyl-1-phenylbutane-1,3-diol [(±)-6.40] and (*R*)-(+)-3-methyl-1-phenyl-1,3-[1-$^{18}O_1$] diol {(*R*)-[^{18}O]6.40}

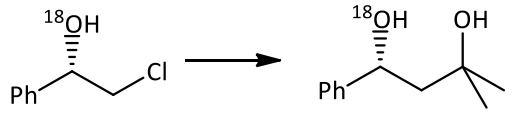


(±)-**6.37** (±)-**6.40**

A mixture of chlorohydrin (±)-**6.37** (0.66 g, 5 mmol) and *n*BuLi (5.5 mmol, 2.2 mL, 2.5 M in hexanes) in dry THF (7 mL) under Ar was stirred for 15 min at -78°C when a dark blue mixture of 4,4'-di-*tert*-butylbiphenyl (DTBB, 3.96 mmol, 15 mmol) and lithium (0.11 g, 15 mmol, new!, granular, 4-10 mesh particle size, high sodium, 99%) in dry THF (17 mL) stirred under argon for 4 h was added over a period of 30 min.[144] The mixture was stirred for 4 h at -78°C and the resulting solution was colorless at first but became dark with the addition of excess lithium reagent. Acetone (0.87 g, 15 mmol, 1.1 mL) was added after stirring at -78°C for 16 h. Water (10 mL) was added after 1 h followed by neutralization with concentrated HCl (pH paper). After the mixture was extracted with CH_2Cl_2 (3x15 mL), the combined organic phases were washed with water (10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by flash chromatography (hexanes: ethyl acetate = 3:1, R_f = 0.18) to yield racemic 1,3-diol (±)-**6.40** (0.51 g, 57%) as colorless crystals; mp 63-64°C (hexanes).

The NMR spectra are identical to those found in the literature.[165]

4apr1913, 210: ^{1}H NMR (400.27 MHz, $CDCl_3$, 7.24): δ = 7.38-7.30 (m, 4H, H_{Ar}), 7.27-7.22 (m, 1H, H_{Ar}), 5.07 (dd, J = 11.0, 2.2 Hz, 1H, CHOH), 3.10 (br. s, 1H, OH), 1.83 (AB Sys, J_{AB} = 14.7 Hz, J_{AX} = 11.0 Hz, J_{BX} = 2.2 Hz, 2H, CH_2), 1.43 (s, 3H, CH_3), 1.27 (s, 3H, CH_3).



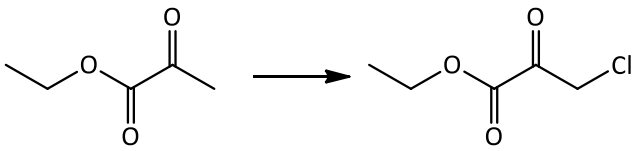
(*S*)-[^{18}O]**6.37** (*R*)-[^{18}O]**6.40**

Similarly, labeled chlorohydrin (*S*)-[^{18}O]**6.37** (0.89 g, 5.62 mmol) was converted to labeled 1,3-diol (*R*)-[^{18}O]**6.40** (0.54 g, 53%) as colorless crystals; mp. 67-68°C (hexanes/CH_2Cl_2); $[\alpha]_D^{28}$ = +54.17, (c = 1.115, acetone); ee by HPLC (Chiralcel OD-H, 7.5% iPrOH in hexanes, 1 mL/min, 10 mg/mL, 10 µL injected) at least 99.2%, t_r (*S*) = 7.83 min, t_r (*R*) = 8.97 min; MS: 98.2% ^{18}O.

IR (ATR): ν = 2806, 2526, 1650, 1579, 1453, 1415, 1321, 1272, 1184, 1113, 928 cm^{-1}.

NMR spectra were identical to those of the unlabeled species.

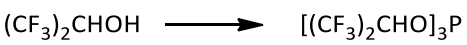
Ethyl 3-chloropyruvate



Sulfuryl chloride (20.92 g, 0.16 mol, 12.54 mL) was added to ethyl pyruvate (15 g, 0.13 mol, 14.28 mL) at 0°C over a period of 30 min and the solution was then stirred at RT for 26 h. The crude product was fractioned using a Vigreux column (20 cm, 114°C/46 mm Hg; lit.: 79°C/9 mm Hg) to yield ethyl 3-chloropyruvate (15.92 g, 82%) as colorless oil.[166]

4dec2012, 261: ^{1}H NMR (400.27 MHz, $CDCl_3$, 7.24): δ = 4.57 (s, 2H, CH_2O), 4.36 (q, *J* = 7.1 Hz, 2H, $\underline{CH_2}CH_3$), 1.37 (t, *J* = 7.1 Hz, 3H, $CH_2\underline{CH_3}$).

Tris-(1,1,1,3,3,3-hexafluoro-2-propyl) phosphite



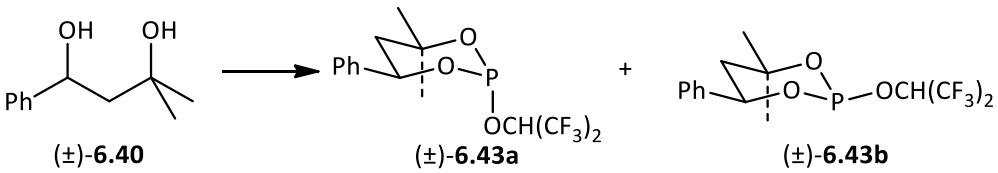
1,1,1,3,3,3-Hexafluoro-2-propanol (26.46 g, 157.5 mmol, 16.59 mL) was slowly added to nBuLi (150 mmol, 60 mL, 2.5 M in hexane) in hexanes (80 mL) under argon at -78°C. The mixture was slowly warmed to RT over 2 h where it was stirred for 1 h. After it was concentrated under reduced pressure and dissolved in dry Et_2O (60 mL), PCl_3 (6.67 g, 48.75 mmol, 4.25 mL) was added under argon at -20°C. The mixture was stirred at RT overnight (16 h), filtered, concentrated under reduced pressure and the crude product was fractionally distilled using a Vigreux column (15 cm,

42-44°C/10 mm Hg; lit.: 60°C/ 25 mm Hg) to yield tris-(1,1,1,3,3,3-hexafluoro-2-propyl) phosphite (19.08 g, 73%) as colorless oil containing a very small amount of bis(hexafluoroisopropyl) phosphite.[146] The compound was stored under Ar in the fridge because it is very easily oxidized to the corresponding phosphate (^{31}P NMR in $CDCl_3$: -2.47) on contact with air.

4mar2113, 250: ^{1}H NMR (400.27 MHz, toluene-d_8, 2.09): δ = 4.24 (dsept, J = 9.6 Hz, 4.8 Hz, 1H, CH).

4mar2113, 251: ^{31}P NMR (162.03 MHz, toluene-d_8): δ = 140.1-139.6 (m).

(±)-2-[(1,1,1,3,3,3-hexafluoropropan-2-yl)oxy]-4,4-dimethyl-6-phenyl-1,3,2-dioxaphosphinanes [(±)-6.43a and (±)-6.43b]; (2*S*,6*R*)-(+)- and (2*R*,6*R*)-(+)-2-[(1,1,1,3,3,3-hexafluoropropan-2-yl)oxy]-4,4-dimethyl-6-phenyl-1,3,2-dioxaphosphinanes [(*R*)-6.43a and (*R*)-6.43b]; (2*S*,6*R*)-(+)- and (2*R*,6*R*)-(+)- 2-[(1,1,1,3,3,3-hexafluoropropan-2-yl)oxy]-4,4-dimethyl-6-phenyl-1,3,2-[1-$^{18}O_1$]dioxaphosphinanes {(*R*)-[^{18}O]6.43a and (*R*)-[^{18}O]6.43b}



(±)-**6.40** (±)-**6.43a** (±)-**6.43b**

A mixture of racemic diol (±)-**6.40** (0.36 g, 2 mmol), tris-(1,1,1,3,3,3-hexafluoro-2-propyl) phosphite (1.12 g, 2.1 mmol, air sensitive!) and Et_3N (1 mmol, 0.14 mL) in CH_2Cl_2 (8 mL) was stirred under argon for 40 min and then concentrated under reduced pressure. The crude product was purified by bulb to bulb distillation (65-100°C/1.4 mbar) to yield cyclic phosphites (±)-**6.43a** and (±)-**6.43b** (0.75 g, 100%) as a mixture of colorless isomers [a (*trans*): b (*cis*) = 1:0.51, that were separated by semipreparative HPLC (Nucleosil 50-5 column, 40 mL/min, 25 mg/mL, 1.8 mL injected, 10% CH_2Cl_2 in hexanes)].

trans-(±)-**6.43a**: t_r = 2.32 min, mp. 37-38°C (hexanes), $OCH(CF_3)_2$ is axial, X-ray structure (Figure 7.1).

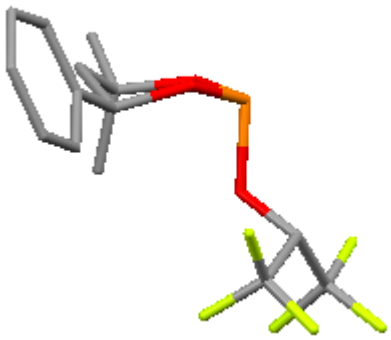


Figure 7.1. X-ray structure of *trans*-(±)-**6.43a**.

IR (ATR): ν = 1375, 1271, 1211, 1191, 1167, 1105, 1020, 1003, 965 cm^{-1}.

4aug0213, 140: ^{1}H NMR (400.27 MHz, $CDCl_3$, 7.24): δ = 7.39-7.28 (m, 5H, H_{Ar}), 5.51 (td, *J* = 12.0, 2.5 Hz, 1H, CHPh), 4.61 (dsept, *J* = 7.9, 5.9 Hz, 1H, OCH), 2.20 (broad dd, *J* = 14.2, 12.0 Hz, 1H, CH_2), 1.87 (ddd, *J* = 14.2, 3.2, 2.1 Hz, 1H, CH_2), 1.64 (s, 3H, CH_3), 1.35 (s, 3H, CH_3).

4aug0213, 142: ^{13}C NMR (100.65 MHz, $CDCl_3$, 77.0): δ = 140.7 (d, *J* = 3.0 Hz, $C_{q,Ar}$), 128.6 (2xCH_{Ar}), 128.2 (CH_{Ar}), 125.7 (2xCH_{Ar}), 122.7 (m, CF_3), 120.0 (m, CF_3), 78.0 (d, *J* = 8.2 Hz, C_q), 70.0 (dsept, *J* = 33.9, 23.2 Hz, OCH), 68.7 (d, *J* = 3.4 Hz, CHPh), 46.4 (d, *J* = 5.2 Hz, CH_2), 32.5 (d, *J* = 4.5 Hz, CH_3), 28.0 (CH_3).

4aug0213, 141: ^{31}P NMR (162.03 MHz, $CDCl_3$): δ = 132.0 (sept, *J* = 7.6 Hz).

Anal. Calcd for $C_{14}H_{15}F_6O_3P$ (376.23): C, 44.69; H, 4.02. Found: C, 44.78; H, 4.22.

cis-(±)-**6.43b**: t_r = 2.77 min, colorless oil.

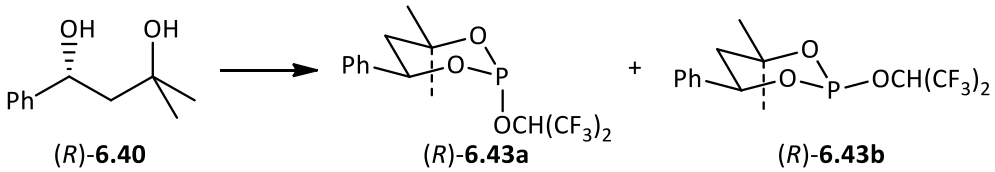
IR (ATR): ν = 2917, 1375, 1290, 1228, 1197, 1107, 1057, 968 cm^{-1}.

4aug0313, 150: ^{1}H NMR (400.27 MHz, $CDCl_3$, 7.24): δ = 7.38-7.26 (m, 5H, H_{Ar}), 5.26 (td, *J* = 12.6, 3.4 Hz, 1H, CHPh), 4.71 (dsept, *J* = 7.5, 5.9 Hz, 1H, OCH), 2.76 (dd, *J* = 14.9, 12.6 Hz, 1H, CH_2), 1.88 (ddd, *J* = 14.9, 3.4, 3.0 Hz, 1H, CH_2), 1.52 (s, 3H, CH_3), 1.40 (s, 3H, CH_3).

4aug0313, 152: ^{13}C NMR (100.65 MHz, $CDCl_3$, 77.0): δ = 141.0 ($C_{q,Ar}$), 128.6 (2xCH_{Ar}), 128.1 (CH_{Ar}), 126.0 (2xCH_{Ar}), 122.7 (m, CF_3), 119.9 (m, CF_3), 77.2 (d, *J* = 6.5 Hz, C_q), 73.9 (d, *J* = 7.4 Hz, CHPh), 70.46 (dsept, *J* = 33.8, 6.4 Hz, OCH), 44.7 (d, *J* = 15.8 Hz, CH_2), 31.3 (CH_3), 28.3 (d, *J* = 1.3 Hz, CH_3).

4aug0313, 151: ^{31}P NMR (162.03 MHz, $CDCl_3$): δ = 132.3 (sept, J = 7.9 Hz).

Anal. Calcd for $C_{14}H_{15}F_6O_3P$ (376.23): C, 44.69; H, 4.02. Found: C, 44.59; H, 4.28.



(*R*)-**6.40** (*R*)-**6.43a** (*R*)-**6.43b**

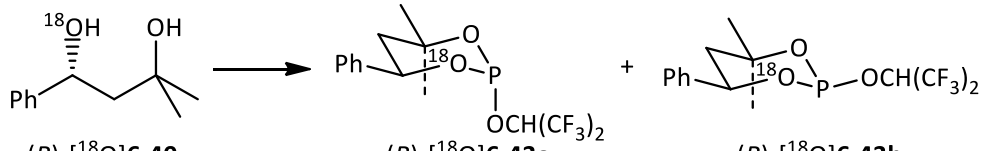
Similarly, (*R*)-**6.40** (1.66 g, 9,22 mmol) was converted to a mixture (2.40 g, 69%) of crystalline cyclic phosphites [(*R*)-**6.43a**: (*R*)-**6.43b** = 1:0.33, that were separated by semipreparative HPLC (achiral, 40 mL/min, 30 mg/mL, 1.8 mL injected, 10% CH_2Cl_2 in hexanes].

(*R*)-**6.43a**: t_r = 2.32 min, crystallized from hexanes, melts at room temperature, $[\alpha]_D^{28}$ = +22.67, (c = 1.005, acetone), $OCH(CF_3)_2$ is axial.

All spectra are identical to those of the racemic species (±)-**6.43a** (spectra: 4oct2413, 400, 401, 402).

(*R*)-**6.43b**: t_r = 2.77 min, colorless oil, $[\alpha]_D^{28}$ = +109.18, (c = 1.035, acetone).

All spectra are identical to those of the racemic species (±)-**6.43b** (spectra: oct2814, 20, 21, 26).

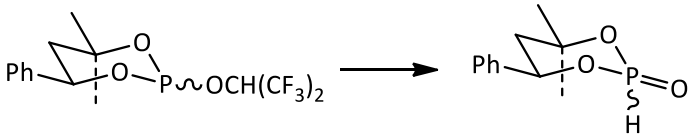


(*R*)-[^{18}O]**6.40** (*R*)-[^{18}O]**6.43a** (*R*)-[^{18}O]**6.43b**

Similarly, ^{18}O-labeled (*R*)-[^{18}O]**6.40** (0.35 g, 1.92 mmol) was converted to a mixture (0.70 g, 96%) of crystalline cyclic phosphites {(*R*)-[^{18}O]**6.43a** (*trans*): (*R*)-[^{18}O]**6.43b** (*cis*) = 1:0.31)} which was used directly.

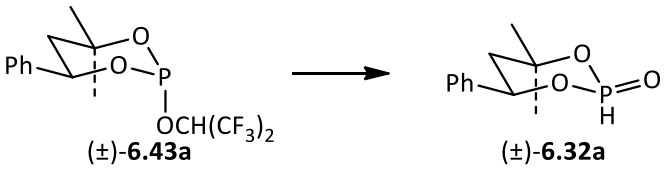
NMR spectra were identical to those of the unlabeled compounds.

(±)-4,4-Dimethyl-6-phenyl-1,3,2-dioxaphosphinane-2-oxides [(±)-6.32a and (±)-6.32b]; (2*S*,6*R*)-(-)- and (2*R*,6*R*)-(-)-4,4-dimethyl-6-phenyl-1,3,2-dioxaphosphinane-2-oxides [(*R*)-6.32a and (*R*)-6.32b]; (2*S*,6*R*)-(-)- and (2*R*,6*R*)-(-)-4,4-dimethyl-6-phenyl-1,3,2-[1-$^{18}O_1$]-dioxaphosphinane-2-[2-^{17}O]oxides {(*R*)-[^{17}O,^{18}O]6.32a and (*R*)-[^{17}O,^{18}O]6.32b}



(±)-**6.43a,b** (±)-**6.32a,b**

A mixture of racemic phosphites (±)-**6.43** (0.75 g, 2 mmol, A:B = 1:0.51), H_2O (7 mmol, 0.13 mL, added through a microinjection) and TMSCl (0.11 g, 1 mmol, added through a microinjection) in dry THF (5 mL) was stirred under argon for 30 min. 1,1,1,3,3,3-Hexamethyldisilazane (0.18 g, 1.1 mmol) was added (under argon!) and the solution was concentrated under reduced pressure. The crude product was dried (45°C/1 mbar) for 5 min and purified by flash chromatography (ethyl acetate, R_f = 0.50) to yield a crystalline mixture (0.31 g, 69%) of cyclic phosphites [(±)-**6.32a** (*trans*): (±)-**6.32b** (*cis*) = 1:0.40].



(±)-**6.43a** (±)-**6.32a**

Similarly, isomer *trans*-(±)-**6.43a** (A, 0.42 g, 1.12 mmol) was converted to phosphite *cis*-(±)-**6.32a** [0.23 g, 91%, contained 5.7% of *trans*-(±)-**6.32b**] as colorless solid which could not be recrystallized.

cis-(±)-**6.32a**:

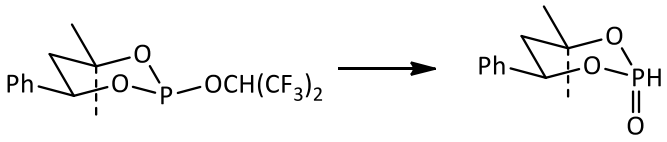
IR (ATR): ν = 1376, 1269, 1210, 1137, 1052, 1023, 971, 946 cm^{-1}.

4aug0213, 160: ^{1}H NMR (400.27 MHz, $CDCl_3$, 7.24): δ = 7.38-7.30 (m, 5H, H_{Ar}), 7.14 (d, J = 682.6 Hz, 1H, PH), 5.47 (td, J = 12.0, 2.6 Hz, 1H, CHPh), 2.29 (dd, J = 14.8, 12.0 Hz, 1H, CH_2), 1.93 (td, J = 14.8, 2.1 Hz, 1H, CH_2), 1.64 (s, 3H, CH_3), 1.49 (d, J = 1.9 Hz , 3H, CH_3).

4aug0213, 162: ^{13}C NMR (100.65 MHz, $CDCl_3$, 77.0): δ = 138.7 (d, J = 8.8 Hz, $C_{q,Ar}$), 128.8 (2xCH_{Ar}), 128.7 (CH_{Ar}), 125.5 (2xCH_{Ar}), 82.9 (d, J = 7.2 Hz, C_q), 76.0 (d, J = 5.1 Hz, CHPh), 45.6 (d, J = 6.7 Hz, CH_2), 31.6 (d, J = 5.4 Hz, CH_3), 26.4 (d, J = 1.4 Hz, CH_3).

4aug0213, 161: ^{31}P NMR (162.03 MHz, $CDCl_3$): δ = -2.7.

Anal. Calcd for $C_{11}H_{15}O_3P$ (226.08): C, 58.41; H, 6.68. Found: C, 58.56; H, 6.59.



(±)-**6.43b** (±)-**6.32b**

Similarly, isomer *cis*-(±)-**6.43b** (0.15 g, 0.39 mmol) was converted to phosphite *trans*-(±)-**6.32b** [0.07 g, 80%, contained 10% of the *cis*-(±)-**6.32a**] as colorless solid which could not be recrystallized.

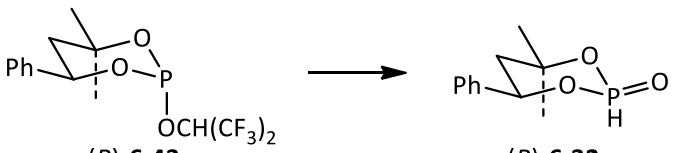
trans-(±)-**6.32b**:

IR (ATR): ν = 2981, 1267, 1140, 1062, 1027, 971, 942 cm^{-1}.

4aug2813, 270: ^{1}H NMR (400.27 MHz, $CDCl_3$, 7.24): δ =7.39-7.27 (m, 5H, H_{Ar}), 7.13 (d, *J* = 717.3 Hz, 1H, PH), 5.66 (td, *J* = 12.0, 2.5 Hz, 1H, CHPh), 2.16 (broad dd, *J* = 14.8, 12.0 Hz, 1H, CH_2), 2.02 (dd, *J* = 14.8, 2.5, 1.1 Hz, 1H, CH_2), 1.69 (s, 3H, CH_3), 1.46 (d, *J* = 1.0 Hz , 3H, CH_3).

4aug2813, 272: ^{13}C NMR (100.65 MHz, $CDCl_3$, 77.0): δ = 138.9 (d, *J* = 7.2 Hz, $C_{q,Ar}$), 128.7 (2xCH_{Ar}), 128.6 (CH_{Ar}), 125.4 (2xCH_{Ar}), 82.0 (d, *J* = 7.3 Hz, C_q), 75.7 (d, *J* = 6.2 Hz, CHPh), 45.1 (d, *J* = 8.0 Hz, CH_2), 31.1 (d, *J* = 6.0 Hz, CH_3), 27.7 (CH_3).

4aug2813, 271: ^{31}P NMR (162.03 MHz, $CDCl_3$): δ = -1.6.

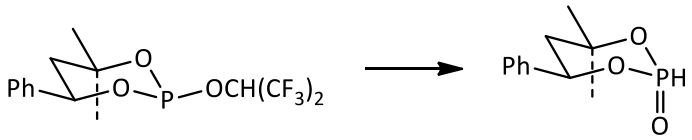


(*R*)-**6.43a** (*R*)-**6.32a**

Similarly, *trans*-(*R*)-**6.43a** (0.48 g, 1.27 mmol) was converted to phosphite *cis*-(*R*)-**6.32a** [0.24 g, 83%, contained 7% of *trans*-(*R*)-**6.32b**] as colorless solid which could not be recrystallized.

cis-(*R*)-**6.32a**, $[\alpha]_D^{28}$ = -25.82, (c = 1.065, acetone):

All spectra are identical to those of (±)-**6.32a** (spectra: nov0513, 10, 11, 16).

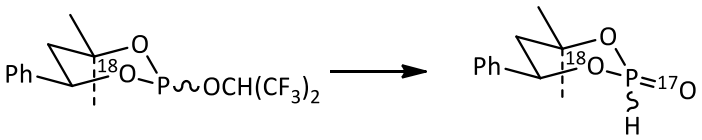


(*R*)-**6.43b** (*R*)-**6.32b**

Similarly, *cis*-(*R*)-**6.43b** (0.18 g, 0.49 mmol) was converted to phosphite *trans*-(*R*)-**6.32b** [0.09 g, 84%, contained 13% of *cis*-(*R*)-**6.32a**] as colorless solid which could not be recrystallized.

trans-(*R*)-**6.32b**, $[\alpha]_D^{28}$ = -7.46, (c = 0.925, acetone):

All spectra are identical to those of (±)-**6.32b** (spectra: oct3013, 20, 21, 26).



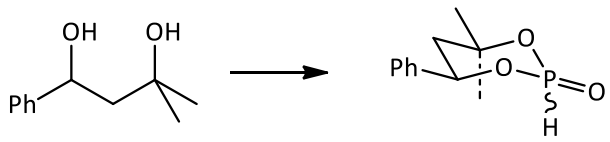
(*R*)-[^{18}O]**6.43a,b** (*R*)-[^{17}O,^{18}O]**6.32a,b**

Similarly, labeled (*R*)-[^{18}O]**6.43** [0.70 g, 1.85 mmol, a (*trans*): b (*cis*) = 1:0.31] and $H_2{}^{17}O$ (70% ^{17}O, 28% ^{16}O and 2% ^{18}O) were converted to a mixture (0.33 g, 77%) of cyclic phosphites (*R*)-[^{17}O,^{18}O]**6.32** [**a** (*cis*): **b** (*trans*) = 1:0.27] as a colorless oil, MS: 98.9% ^{18}O, 65.6% ^{17}O.

NMR spectra were identical to those of the unlabeled species (spectra: 4sept1013, 310, 311, 312).

Synthesis of cyclic phosphites through phosphoramidite

(±)-4,4-Dimethyl-6-phenyl-1,3,2-dioxaphosphinane-2-oxides [(±)-6.32a and (±)-6.32b]; (2*S*,6*R*)-(-)- and (2*R*,6*R*)-(-)-4,4-dimethyl-6-phenyl-1,3,2-[1-$^{18}O_1$]-dioxaphosphinane-2-[2-$^{17}O_1$]oxides {(*R*)-[^{17}O,^{18}O]6.32a and (*R*)-[^{17}O,^{18}O]6.32b}

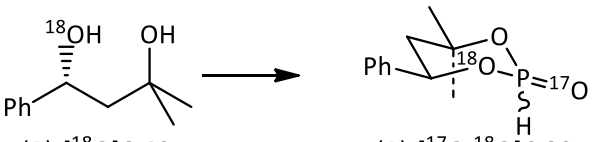


(±)-**6.40** (±)-**6.32a,b**

A mixture of racemic diol (±)-**6.40** (0.90 g, 5 mmol) and tris(dimethylamino)phosphine (1.14 g, 7 mmol, 1.28 mL) in dry ACN (17 mL) was stirred in a microwave oven at 110°C for 1 h. The mixture was concentrated under reduced pressure and the crude dioxaphosphinanes were reacted with H_2O (0.18 g, 10 mmol, 0.18 mL) and TMSCl (0.76 g, 7 mmol, 0.89 mL) in dry THF (15 mL) under Ar for 10 min at 50°C. After hexamethyldisilazane (0.89 g, 5.5 mmol, 1.16 mL) was added, the mixture

was concentrated in vacuo and the crude product was purified by flash chromatography (ethyl acetate, R_f = 0.69) to yield the isomers [0.99 g, 89%, (±)-**6.32a** (*cis*): (±)-**6.32b** (*trans*) =0.68:1, could be separated with CH_2Cl_2: acetone = 20:1 if desired] as oil.

NMR spectra were identical to those of the dioxaphosphinanes prepared from (±)-**6.43** (spectra: 4aug0614, 232, 233).

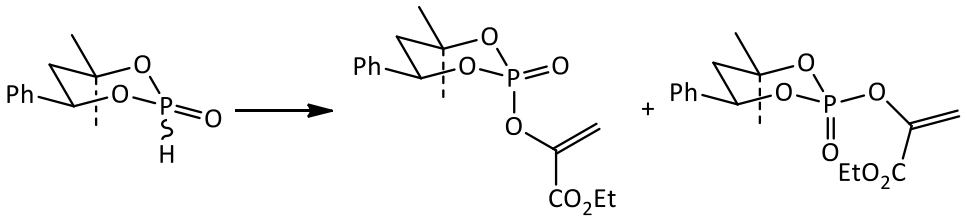


(*R*)-[^{18}O]**6.40** (*R*)-[^{17}O,^{18}O]**6.32**

Similarly, ^{18}O-labeled (*R*)-[^{18}O]**6.40** (0.91 g, 5 mmol) with $H_2{}^{17}O$ (70% ^{17}O, 28% ^{16}O and 2% ^{18}O) was converted to a mixture (0.73 g, 64%) of cyclic phosphites (*R*)-[^{17}O,^{18}O]**6.32** [**a** (*cis*): **b** (*trans*) = 0.75:1] as oil, MS: 98.6% ^{18}O, 64.3% ^{17}O.

The NMR spectra were identical to those of the unlabeled species (spectra: 4aug0814, 270, 271).

(±)-Ethyl 2-[(4,4-dimethyl-2-oxido-6-phenyl-1,3,2-dioxaphosphinan-2-yl)oxy]acrylate [(±)-6.35a and (±)-6.35b]; ethyl 2-{(2*R*,6*R*)-((4,4-dimethyl-2-oxido-6-phenyl-1,3,2-dioxaphosphinan-2-yl)oxy}acrylate and ethyl 2-{(2*S*,6*R*)-((4,4-dimethyl-2-oxido-6-phenyl-1,3,2-dioxaphosphinan-2-yl)oxy}acrylate [(*R*)-6.35a and (*R*)-6.35b]; ethyl 2-{(2*R*,6*R*)-((4,4-dimethyl-2-[2-^{17}O]oxido-6-phenyl-1,3,2-[1-$^{18}O_1$]dioxaphosphinan-2-yl)oxy}acrylate and ethyl 2-{(2*S*,6*R*)-((4,4-dimethyl-2-[2-^{17}O]oxido-6-phenyl-1,3,2-[1-$^{18}O_1$]dioxaphosphinan-2-yl)oxy}acrylate {(*R*)-[^{17}O,^{18}O]6.35a and (*R*)-[^{17}O,^{18}O]6.35b}



(±)-**6.32a,b** (±)-**6.35a** (±)-**6.35b**

A mixture of *N,N*-diethyl-1,1,1-trimethylsilylamine (4.34 g, 29.89 mmol) and a mixture of cyclic phosphites (±)-**6.32a,b** [0.97 g, 4.27 mmol, a (*cis*): b (*trans*) = 1:1.37] in dry toluene (15 mL) was stirred under argon for 40 h at 50°C. The mixture was concentrated under reduced pressure and the crude silylated product was dried at RT (0.2 mbar/1.5 h). The residue was dissolved in dry toluene (15 mL) under argon and ethyl 3-chloropyruvate (0.77 g, 5.12 mmol) was added. After

stirring for 1.5 h under argon at RT, the reaction mixture was concentrated under reduced pressure. The residue, a mixture of diastereomeric enol phosphates, was separated by flash chromatography (hexanes:ethyl acetate = 2:1, A: R_f = 0.33, B: R_f = 0.18) to yield enolphosphate *trans*-(±)-**6.35a** (X-ray structrure, Figure 7.2, 0.38 g, 26%), mp. 78-79°C (hexanes) and enolphosphate *cis*-(±)-**6.35b** (0.61 g, 42%) as colorless needles, mp. 76-77 °C (hexanes/CH_2Cl_2).

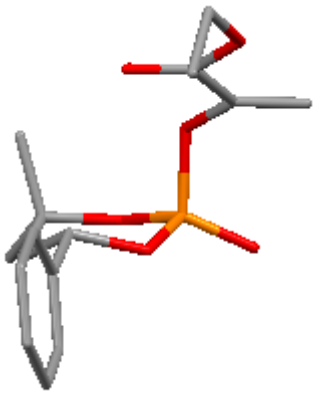


Figure 7.2. X-ray structure of *trans*-(±)-**6.35a**.

trans-(±)-**6.35a**:

IR (ATR): v = 2984, 1720, 1627, 1376, 1292, 1178, 1158, 1141, 1030, 991, 967 cm^{-1}.

Feb 0413, 11: ^{1}H NMR (400.13 MHz, $CDCl_3$, 7.24): δ = 7.38-7.29 (m, 5H, H_{Ar}), 5.93 (t, *J* = 2.4 Hz, 1H, CH_2=C), 5.83 (t, *J* = 2.4 Hz, 1H, CH_2=C), 5.77 (td, *J* = 12.0, 1.5 Hz, 1H, CHPh), 4.29-4.17 (m, 2H, CH_2CH_3), 2.21 (dd, *J* = 14.7, 12.0 Hz, 1H, CH_2), 1.93 (ddd, *J* = 14.7, 2.5, 1.7 Hz, 1H, CH_2), 1.74 (s, 3H, CH_3), 1.50 (d, *J* = 2.8 Hz, 3H, CH_3), 1.28 (t, *J* = 7.1 Hz , 3H, CH_2CH_3).

Feb 0413, 10: ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 161.9 (d, *J* = 8.3 Hz, C=O), 143.2 (d, *J* = 7.5 Hz, C_q), 138.8 (d, *J* = 10.4 Hz, C_q), 128.69 (2xCH_{Ar}), 128.66 (CH_{Ar}), 125.6 (2xCH_{Ar}), 111.0 (d, *J* = 3.9 Hz, CH_2=C), 84.9 (d, *J* = 8.2 Hz, $C_q(CH_3)_2$), 77.7 (d, *J* = 5.7 Hz, CHPh), 61.9 (CH_2CH_3), 45.4 (d, *J* = 4.9 Hz, CH_2), 31.5 (d, *J* = 9.7 Hz, CH_3), 25.5 (CH_3), 14.1 (CH_2CH_3).

Feb 0413, 15: ^{31}P NMR (161.97 MHz, $CDCl_3$): δ = -12.8.

Anal. calcd. for $C_{16}H_{21}O_6P$: C 56.47%, H 6.22%, O 28.21%; found: C 56.45%, H 6.02%, O 28.31%.

cis-(±)-**6.35b**:

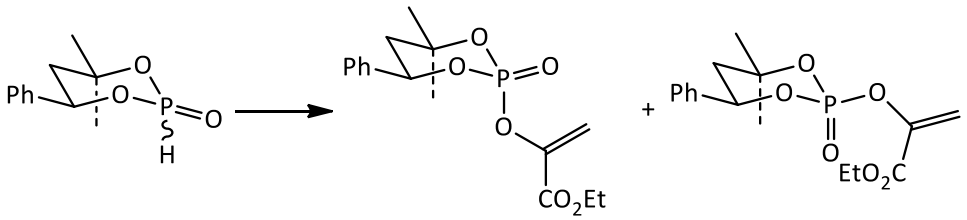
IR (ATR): ν = 2983, 1725, 1647, 1454, 1374, 1309, 1294, 1213, 1156, 1179, 1141, 1044, 1003 986, 967 cm^{-1}.

Mar1913, 51: ^{1}H NMR (400.13 MHz, $CDCl_3$, 7.24): δ = 7.33-7.30 (m, 5H, H_{Ar}), 5.96 (t, *J* = 2.4 Hz, 1H, CH_2=C), 5.75 (t, *J* = 2.4 Hz, 1H, CH_2=C), 5.63 (ddd, *J* = 12.4, 4.6, 2.6 Hz, 1H, CHPh), 4.30-4.20 (m, 2H, CH_2CH_3), 2.64 (dd, *J* = 15.1, 12.4 Hz, 1H, CH_2), 1.98 (td, *J* = 15.1, 2.6 Hz, 1H, CH_2), 1.66 (s, 3H, CH_3), 1.52 (d, *J* = 1.1 Hz, 3H, CH_3), 1.28 (t, *J* = 7.1 Hz , 3H, CH_2CH_3).

Mar1913, 50: ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 161.8 (d, *J* = 8.2 Hz, C=O), 143.6 (d, *J* = 7.6 Hz, C_q), 138.8 (d, *J* = 6.2 Hz, C_q), 128.72 (CH_{Ar}), 128.71 (2xCH_{Ar}), 125.8 (2xCH_{Ar}), 110.2 (d, *J* = 4.2 Hz, CH_2=C), 83.9 (d, *J* = 7.1 Hz, $C_q(CH_3)_2$), 78.8 (d, *J* = 6.1 Hz, CHPh), 61.8 (CH_2CH_3), 43.4 (d, *J* = 9.7 Hz, CH_2), 30.2 (d, *J* = 3.7 Hz, CH_3), 27.5 (d, *J* = 3.9 Hz, CH_3), 14.1 (CH_2CH_3).

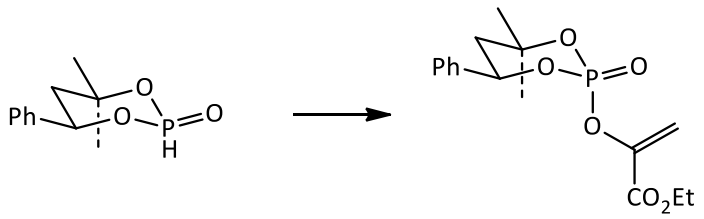
Mar1913, 56: ^{31}P NMR (162.03 MHz, $CDCl_3$): δ = -12.2.

Anal. calcd. for $C_{16}H_{21}O_6P$: C 56.47%, H 6.22%, O 28.21%; found: C 56.54%, H 5.84%, O 28.32%.



(*R*)-**6.32a,b** (*R*)-**6.35a** (*R*)-**6.35a**

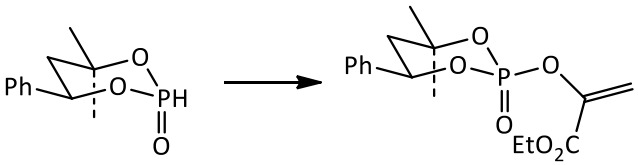
Similarly, a mixture of cyclic phosphites (*R*)-**6.32a,b** (0.16 g, 0.73 mmol) was converted to a mixture [0.12 g, 52%, ratio before chromatography: a (*trans*): b (*cis*) = 1.66:1] of protected phosphoenolpyruvates (*R*)-**6.35a**: (*R*)-**6.35b** = 1:1. (*R*)-**6.35a** (*trans*) was recrystallized from hexanes/CH_2Cl_2 to yield colorless needles, mp. 98.5-99.5°C, $[\alpha]_D^{20}$ = -24.25, (c = 1.13, acetone). The (*R*)-**6.35b** (*cis*) was recrystallized from hexanes/CH_2Cl_2 to yield colorless flakes, mp. 100-101°C, $[\alpha]_D^{20}$ = -17.08, (c = 0.89, acetone).



(±)-**6.32a** (±)-**6.35a**

Similarly, *cis*-(±)-**6.32a** (0.28 g, 1.23 mmol) was converted to enolphosphate *trans*-(±)-**6.35a** (0.24 g, 56%, contained no *cis*-(±)-**6.35b**) as colorless solid which was not recrystallized.

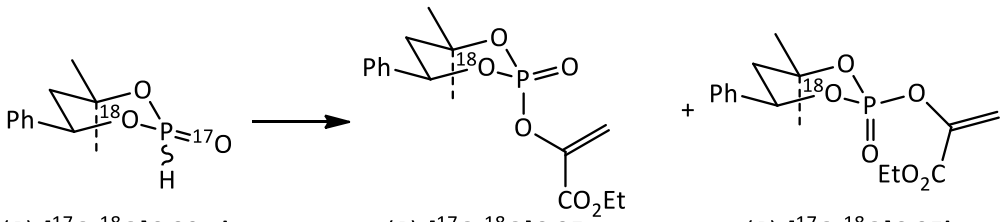
NMR spectra were identical to those of the racemic species (spectra: 4aug0514, 320, 321).



(±)-**6.32b** (±)-**6.35b**

Conditions had to be altered in order to discourage partial inversion of configuration at phosphorus (~7% when prepared according to previous procedure). A solution of homogeneous *trans*-(±)-**6.32b** (0.12 g, 0.55 mmol) in dimethyltrimethylsilylamine (3 mL) was stirred under argon at 50°C for 1 h. The mixture was concentrated under reduced pressure and the crude silylated product was dried at RT (0.2 mbar/1.5 h). The residue was dissolved in dry toluene (3 mL) under argon and ethyl 3-chloropyruvate (0.10 g, 0.66 mmol) was added. After stirring for 1.5 h under argon at RT, the reaction mixture was concentrated under reduced pressure. The crude product (contained 1-2% *trans*-(±)-**6.35a**) was purified by flash chromatography (hexanes: ethyl acetate = 2:1, R_f = 0.18) to yield homogeneous *cis*-(±)-**6.35b** (0.13 g, 67%) as colorless solid.

NMR spectra were identical to those of the racemic species (spectra: 4feb1015 170, 280).

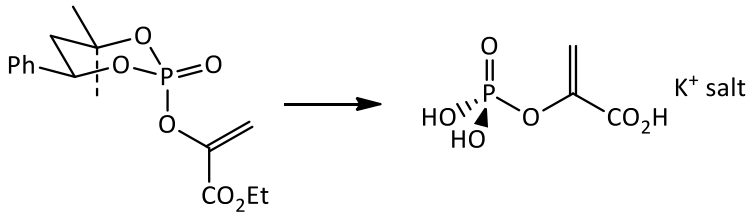


(*R*)-[^{17}O,^{18}O]**6.32a,b** (*R*)-[^{17}O,^{18}O]**6.35a** (*R*)-[^{17}O,^{18}O]**6.35b**

Similarly, a mixture of labeled phosphites (*R*)-[^{17}O,^{18}O]**6.32a,b** (0.71 g, 3.08 mmol, a:b = 0.75:1) was converted to a mixture [0.94 g, 90%, ratio before chromatography: a (*trans*): b (*cis*) = 0.87:1] of labeled protected phosphoenolpyruvates (*R*)-[^{17}O,^{18}O]**6.35** a:b = 1:1.75. (*R*)-[^{17}O,^{18}O]**6.35a** (*trans*) was recrystallized the same way as the unlabeled species from hexanes to yield colorless needles, mp. 93-94°C, $[\alpha]_D^{28}$ = -22.58, (c = 1.085, acetone), MS: >99% ^{18}O, 63.4% ^{17}O. (*R*)-[^{17}O,^{18}O]**6.35b** (*cis*) was not recrystallized, MS: 98.7% ^{18}O, 64.5% ^{17}O.

NMR spectra were identical to those of the unlabeled species (spectra: (±)-**6.35a** – 4sep1213, 160, 161, 162; (±)-**6.35b** – 4sep1313, 20, 21).

Phosphoenol pyruvate (PEP, 6.23); {(R_P)- and (S_P)-[$^{16}O_1$,^{17}O,$^{18}O_1$]phosphoenolpyruvate {(R_P)-[^{16}O,^{17}O,^{18}O]6.23 and (S_P)-[^{16}O,^{17}O,^{18}O]6.23}

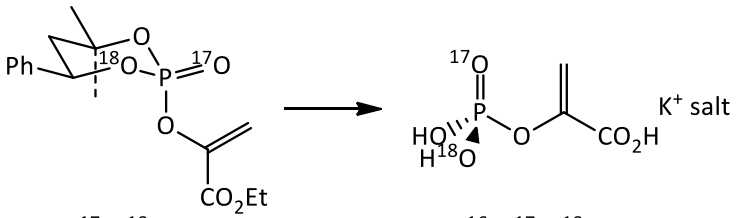


(*R*)-**6.35a** **6.23**

Protected enolphosphate trans-(*R*)-**6.35a** (0.16 g, 0.48 mmol), TMSBr (2.4 mmol, 0.32 mL) and allyl TMS (0.96 mmol, 0.15 mL) in dry dichloroethane (2 mL) was stirred under argon for 1.5 h when it was concentrated under reduced pressure (0.5 mbar). After the addition of aqueous KOH (9.6 mL, 0.2 M) the solution was immediately extracted with CH_2Cl_2 and the aqueous phase stood for 21 h until the deprotection of the ester (^{31}P NMR check) was finished. The mixture was then brought to pH = 7.4 with dry CO_2 and KOH (0.5M) and lyophilized to yield the phosphoenol pyruvate **6.23** (0.23 mmol, 48%, the amount determined by comparison with internal standard – racemic 2-amino-1-hydroxyethylphosphonic acid) as potassium salt.

4jun0313, 50: ^{1}H NMR (400.13 MHz, D_2O, 4.80): δ = 5.40 (br. s, 1H, CH_2=C), 5.23 (br. s, 1H, CH_2=C).

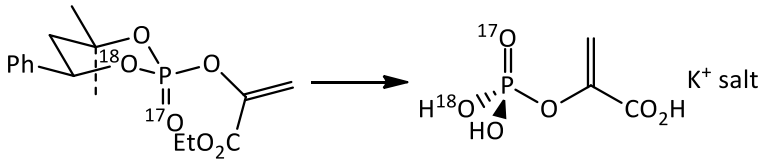
4jun0313, 51: ^{31}P NMR (162.03 MHz, $CDCl_3$): δ = -0.6.



(*R*)-[^{17}O,^{18}O]**6.35a** (R_P)-[^{16}O,^{17}O,^{18}O]**6.23**

Similarly, labeled protected phosphoenolpyruvate (*R*)-[^{17}O,^{18}O]**6.35a** (*trans*, 0.34 g, 1.00 mmol) was converted to labeled phosphate [(R_P)-^{16}O,^{17}O,^{18}O]**6.23** (0.51 mmol, 51%, the amount determined by comparison with internal standard – racemic 2-amino-1-hydroxyethylphosphonic acid) as a potassium salt.

NMR spectra were identical to those of the unlabeled species.

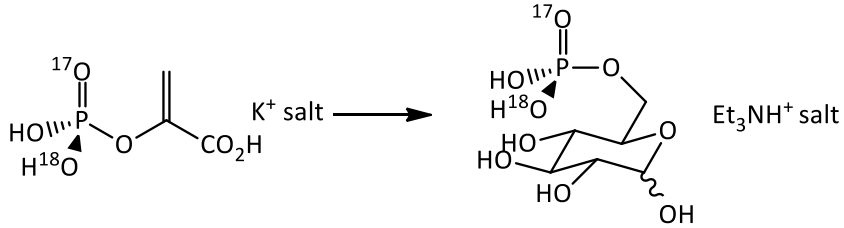


(*R*)-[^{17}O,^{18}O]**6.35b** (*S*$_P$)-[^{16}O,^{17}O,^{18}O]**6.23**

Similarly, labeled protected phosphoenolpyruvate (*R*)-[^{17}O,^{18}O]**6.35b** (*cis*, 0.28 g, 0.82 mmol) was converted to labeled phosphate [(*S*$_P$)-^{16}O,^{17}O,^{18}O]**6.23** (0.20 mmol, 24%, the amount determined by comparison with internal standard – racemic 2-amino-1-hydroxyethylphosphonic acid) as a potassium salt.

NMR spectra were identical to those of the unlabeled species.

(*R*$_p$)-[^{16}O,^{17}O,^{18}O]Glucose-6-phosphate salt {(*R*$_p$)-[^{16}O,^{17}O,^{18}O]6.29}

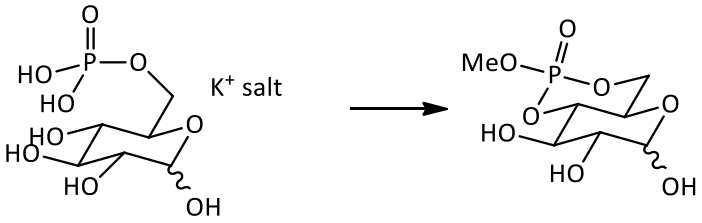


(*R*$_P$)-[^{16}O,^{17}O,^{18}O]**6.23** (*R*$_P$)-[^{16}O,^{17}O,^{18}O]**6.29**

A mixture of labeled (*R*$_P$)-[^{16}O,^{17}O,^{18}O]**6.23** (0.19 mmol), aq. triethanolamine hydrochloride (2.46 mL, 0.5 M, pH = 7.6), aq. KCl (0.03 mL, 3.7 M), aq. $MgSO_4$ (0.20 mL, 0.5 M), ADP (0.02 g, 0.04 mmol, K^+ salt), glucose monohydrate (0.11 g, 0.56 mmol), pyruvate kinase (49.6 units) and hexokinase (69.6 units) in water (10 mL) was stirred for 21 h. Crude product was purified by ion exchange chromatography (AG1-X8, HCO^{3-} form, 20 mL, 10 mM → 120 mM gradient of aq. triethylammonium bicarbonate, detected with a malachite green reagent[149] (50 mL fractions, product in 6-10) to yield labeled (*R*$_P$)-[^{16}O,^{17}O,^{18}O]**6.29** (0.13 mmol, 70%, the amount determined by comparison with internal standard – racemic 2-amino-1-hydroxyethylphosphonic acid) as a mixture of anomers (1:1.2) as colorless solid.

^{31}P NMR (162.03 MHz, D_2O Lock): δ = 4.2 (s), 4.1 (s).

Cyclic glucose-4,6-phosphate methyl ester 6.31



6.29 **6.31**

Glucose-6-phosphate dipotassium salt hydrate (**6.29**, 0.17 g, 0.5 mmol) was passed through Dowex 50Wx8, H^+ (5 mL, water) until the eluate was neutral in order to get the free acid.[140] The eluate was concentrated in vacuo and coevaporated with toluene (2x10 mL) in vacuo. *n*-Octylamine (0.07 g, 0.5 mmol, 83 µL), dry 1,4-dioxane (10 mL) and MeOH (20 mL, until the solution was homogeneous) were added and the mixture was again concentrated in vacuo and coevaporated with dry dioxane (2x10 mL) to yield crude amine salt (0.217 g, 70%, the amount determined by comparison with internal standard – racemic 2-amino-1-hydroxyethylphosphonic acid) as colorless foam.

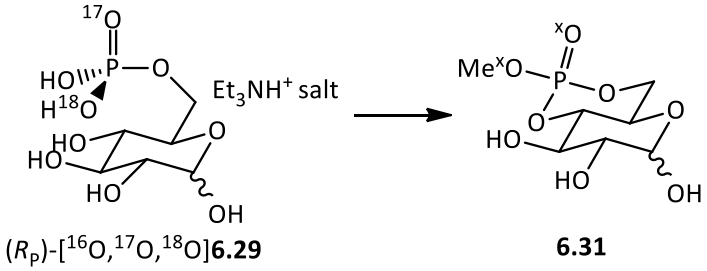
^{31}P NMR (162.03 MHz, D_2O Lock): δ = 0.7.

Crude ammonium salt (0.15 mmol) and activated MS 4Å (60 pieces) were stirred in dry dioxane (8 mL) for 18 h. Solutions of diphenyl phosphorochloridate (0.13 mmol, 27 µL) in dry dioxane (1.5 mL) and tributylamine (0.21 mmol, 51 µL) in dry dioxane (1.5 mL) were added and the mixture was stirred for 20 min until the reaction was complete (checked with ^{31}P NMR):

4jul1013, 60: ^{31}P NMR (162.03 MHz, D_2O Lock), significant signals: δ = -9.5 (d, J = 17.7 Hz, CH_2OP), -9.62 (d, J = 17.7 Hz, CH_2OP), -22.7 (d, J = 17.7 Hz).

The reaction mixture was filtered through cotton and washed with dry dioxane (2 mL). Dry DMF (8 mL) and potassium *tert*-butoxide (0.75 mmol, 0.75 mL, 1M in *t*BuOH) were added and the solution became cloudy right away. After stirring for 45 min, the reaction mixture was centrifuged, washed with DMF (3x10 mL) and the precipitate was dissolved in water and the pH was set to 7.5 (diluted HCl). 18-Crown-6 ether (0.12 g, 0.45 mmol) was added and the solution was concentrated in vacuo, coevaporated with dry dioxane (3x10 mL) and the crude product was methylated with MeI (0.24 mL) in dry DMSO (1.6 mL) for 19 h. Crude cyclic phosphate methyl ester **6.31** was purified with flash chromatography (CH_2Cl_2: MeOH = 4:1, R_f = 0.42) to yield traces of the desired product **6.31** in co-eluting DMSO (0. 33 g)

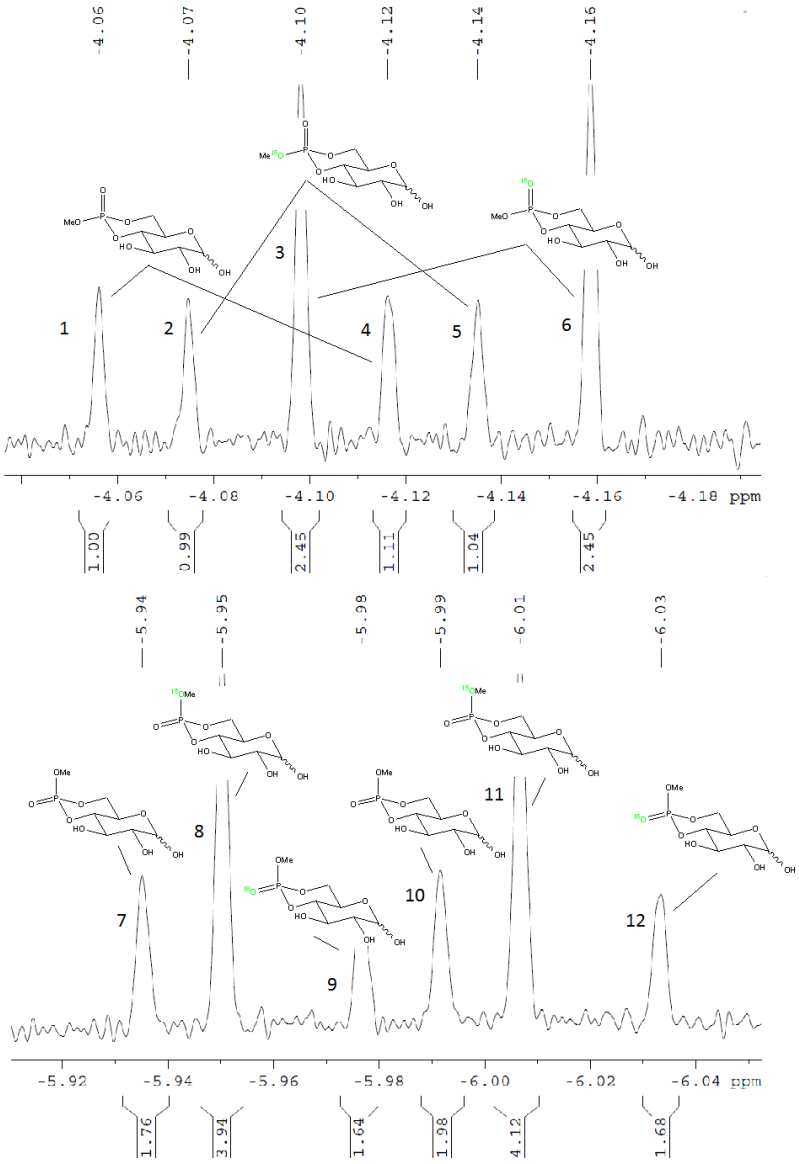
4jul1813, 330: ^{31}P NMR (162.03 MHz, DMSO-d_6:MeOH-d_4 = 1:1): -3.1 (d, J = 4.0 Hz, MeO equatorial), -4.8 (dd, J = 22.1, 5.0 Hz, MeO axial).



(R_P)-[^{16}O,^{17}O,^{18}O]**6.29** **6.31**

Similarly, labeled G-6-P (R_P)-[^{16}O,^{17}O,^{18}O]**6.29** (*cis*, 0.28 g, 0.82 mmol) was converted to traces od the labeled methyl ester **6.31**. The ee of (R_P)-[^{16}O,^{17}O,^{18}O]**6.23** was determined to be 84 ± 15%.

^{31}P NMR (242.94 MHz, DMSO-d_6:MeOH-d_4 = 1:1):



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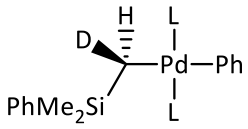
9 Abstract

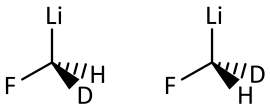
The microscopic configurational stability of palladium complex (*R*)-[D_1]**2.19** prepared from the corresponding dimethyl(phenyl)silyl-[D_1]methylboronate of 99% ee at the silicon bearing carbon atom during the Suzuki-Miyaura coupling was successfully investigated and the intermediate complex was found to be microscopically configurationally stable (Figure 9.1).



(*R*)-[D_1]**2.19**

Figure 9.1. Silyl-[D_1]methylpalladium complex **2.19** studied.

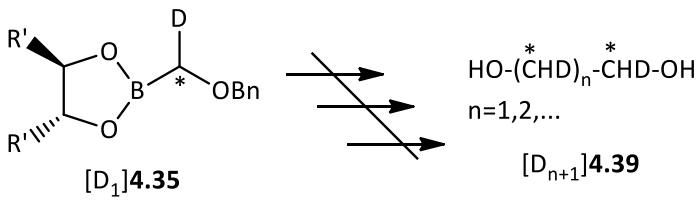
Fluoro-[D_1]methyllithium ([D_1]**3.33**) prepared by tin-lithium exchange from tributyl(fluoro-[D_1]methyl)tin of 99% ee was found to be microscopically configurationally stable relative to its addition to acetophenone up to 0°C. Unfortunately its chemical instability prevented further investigations at higher temperatures or at the macroscopic timescale (Figure 9.2).



(*R*)-**3.33** (*S*)-**3.33**

Figure 9.2. (*R*)- and (*S*)-[D_1]**3.33**.

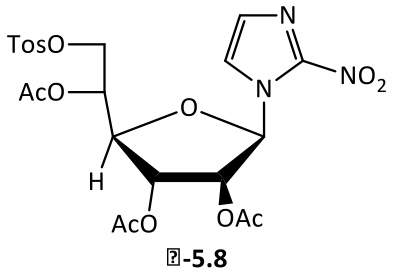
The synthesis of 1,ω–diols [D_{n+1}]**4.39** with various chain lengths and stereospecifically deuterated at each carbon atom was unsuccessful because it was not possible to access boronates [D_1]**4.35**. A variety of possible precursors could neither be obtained in homogeneous form nor be reduced with $LiAlD_4$ or $LiBET_3D$ (Figure 9.3). Additionally, the homologation methodology developed by Matteson et al. yielded unsatisfactory results so the work on this project was discontinued.



[D_1]**4.35** [D_{n+1}]**4.39**

Scheme 9.1. Attempted synthesis of 1,ω–diols [D_{n+1}]**4.39** from benzyloxy-[D_1]methylboronate [D_1]**4.35**.

The yield of the precursor β-**5.8** for a new PET tracer was increased from 37% to 49% (Figure 9.3). It was found that it cocrystallised with dichloromethane and chloroform.



β-**5.8**

Figure 9.3. Precursor β-**5.8** for a PET tracer.

The selective isolation of one enantiomer of bromochlorofluoromethane (**5.2**) from the racemate was not successful as the ee of the cocrystallized **5.2** with the higher retention time was only 11% (Figure 9.4).

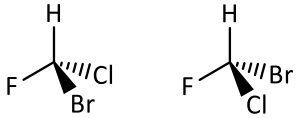
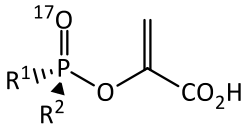


Figure 9.4. (*R*)- and (*S*)-bromochlorofluoromethane [(*R*)- and (*S*)-**5.2**]**.**

The first purely chemical synthesis of (R_P)- and (S_P)-[$^{16}O_1$,^{17}O,$^{18}O_1$]phosphoenolpyruvate **6.23** was achieved in 12.6% yield over 6 steps starting from (*R*)-2-chloro-1-phenylethanol of 97% ee and [$^{18}O_2$]benzoic acid (Figure 9.5).

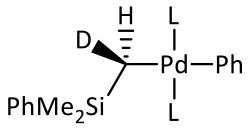


(R_P)-[^{16}O,^{17}O,^{18}O]**6.23**: R^1=OH, R^2=^{18}OH
(S_P)-[^{16}O,^{17}O,^{18}O]**6.23**: R^1=^{18}OH, R^2=OH

Figure 9.5. (R_P)- and (S_P)-[$^{16}O_1$,^{17}O,$^{18}O_1$]phosphoenolpyruvate **6.23**.

10 Zusammenfassung

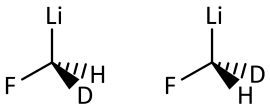
Der Palladiumkomplex (*R*)-[D_1]**2.19** wurde ausgehend vom entsprechenden enantiomerenreinen Dimethyl(phenyl)silyl-[D_1]methylboronat hergestellt. Die mikroskopische konfigurative Stabilität des Komplexes während einer Suzuki-Miyaura Kupplung wurde erfolgreich untersucht und es zeigte sich, dass er mikroskopisch konfigurativ stabil ist (Abbildung 10.1).



(*R*)-[D_1]**2.19**

Abbildung 10.1. Silyl-[D_1]methylpalladiumkomplex **2.19**.

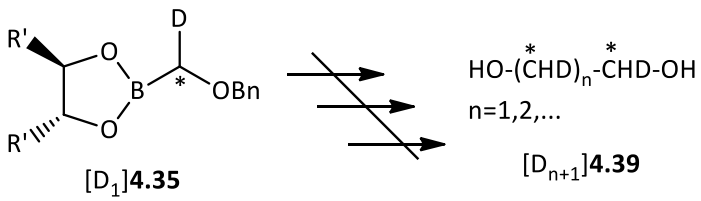
Fluoro-[D_1]methyllithium ([D_1]**3.33**), welches durch Zinn-Lithium Austausch zugänglich war, erwies sich bezüglich der Addition an Acetophenon bis zu einer Temperatur von 0°C als mikroskopisch konfigurativ stabil. Leider verhinderte die chemische Instabilität Untersuchungen bei höheren Temperaturen oder auf der makroskopischen Zeitskala (Abbildung 10.2).



(*R*)-**3.33** (*S*)-**3.33**

Abbildung 10.2. (*R*)- und (*S*)-[D_1]**3.33**.

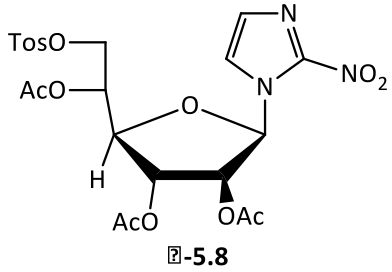
Die Synthese von 1,ω–Diolen [D_{n+1}]**4.39** verschiedener Kettenlänge mit stereospezifischer Deuterierung an jedem Kohlestoffatom war nicht erfolgreich, da die Boronate [D_1]**4.35** nicht zugänglich waren (Schema 10.1). Keine der angestrebten Vorstufen konnte in reiner Form hergestellt werden. Auch die Reduktion mit $LiAlD_4$ oder $LiBET_3D$ scheiterte. Des Weiteren waren die erhaltenen Ausbeuten der Homologierungsmethode nach Matteson et al. nicht zufriedenstellend. Daher wurde die Arbeit an diesem Projekt eingestellt.



[D_1]**4.35** [D_{n+1}]**4.39**

Schema 10.1. Versuchte Synthese von 1,ω–Diole [D_{n+1}]**4.39** aus dem Boronat [D_1]**4.35**.

Die Ausbeute des Precursors β-**5.8** für einen PET-Tracer konnte von 37% auf 49% gesteigert werden (Abbildung 10.3). Es wurde festgestellt, dass die Substanz mit Dichlormethan und Chloroform co-kristallisiert.



-5.8

Abbildung 10.3. Precursor β-**5.8** für einen PET-Tracer.

Die selektive Abtrennung eines Enantiomers von Bromchlorfluoromethan **5.2** aus einer racemischen Mischung war nicht erfolgreich. Der Enantiomerenüberschuss des cokristallisierten Enantiomers mit höherer Retentionszeit betrug nur 11% (Abbildung 10.4).

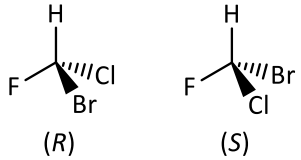
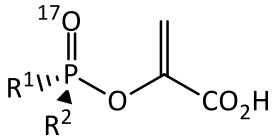


Abbildung 10.4. (*R*)- und (*S*)-Bromchlorfluoromethan [(*R*)- und (*S*)-**5.2**]**.**

Des Weiteren gelang die erste rein chemische Synthese von (R_P)- und (S_P)-[$^{16}O_1$,^{17}O,$^{18}O_1$]Phosphoenolpyruvat **6.23**, mit einer Gesamtausbeute von 12.6% über 6 Stufen, ausgehend von (*R*)-2-Chlor-1-phenylethanol (ee 97%) und [$^{18}O_2$]Benzoesäure. Das Produkt hatte einen ee von 84% (Abbildung 10.5).



(R_P)-[^{16}O,^{17}O,^{18}O]**6.23**: R^1=OH, R^2=^{18}OH
(S_P)-[^{16}O,^{17}O,^{18}O]**6.23**: R^1=^{18}OH, R^2=OH

Abbildung 10.5. (R_P)- und (S_P)-[$^{16}O_1$,^{17}O,$^{18}O_1$]Phosphoenolpyruvat **6.23**.

10 Curriculum Vitae

Petra Križková

Education	
	*October 2010 – Spring 2015* University of Vienna, Vienna, Austria ▪ Doctoral study, planned title: Dr. Rer. Nat. ▪ Field: Organic chemistry ▪ Doctoral thesis: Supervisor - Ao. Univ.-Prof. Dr. Friedrich Hammerschmidt – Synthesis and reactions of chiral, nonracemic compounds with general formula XCHDY and [^{16}O,^{17}O,^{18}O]phosphoenolpyruvate. *October 2008 – Summer 2010* University of Vienna, Vienna, Austria ▪ Master study, title: Master of Science ▪ Fields: organic chemistry, analytical chemistry, biological chemistry ▪ Master thesis: Supervisor - Ao. Univ.-Prof. Dr. Friedrich Hammerschmidt – Chiral Methylmetals – Configurational Stability and Applications *August 2005 – May 2008* Valparaiso University, Valparaiso, Indiana, USA ▪ Title: Bachelor of Science, Field: Chemistry ▪ GPA: 3.93 (Scale: 4.00 best, 1.00 worst) *September 2004 – May 2005* Faculty of Natural Sciences, Comenius University, Bratislava, Slowakei ▪ Field: Biology *1996 – 2004* Gymnázium sv. Uršule, Bratislava, Slovakia *2002 – 2003* Bear Creek High School, Stockton, California, USA

Work experience	
	*Since October 2010* University of Vienna, Vienna, Austria ▪ University assistant (prae doc) ▪ University lecturer: Biologisch-chemisches Praktikum, Teil B (2011-2012), Organisch-chemisches Praktikum - und Proseminar (2012-2015), Chemisches Grundpraktikum II B (2014-2015) *July 2009* University of Vienna, Vienna, Austria ▪ Research assistant in the group of Ao. Univ.-Prof. Dr. Friedrich Hammerschmidt ▪ Synthesis of potential cancer markers *2006 - 2008* Valparaiso University, Valparaiso, Indiana, USA ▪ Lab assistant for biochemistry and analytical and organic chemistry ▪ TA for organic chemistry, physics and math
Awards	
	2006 Undergraduate Award for Achievement in Organic Chemistry (Valparaiso University) *2007* Undergraduate Award in Analytical Chemistry (Valparaiso University) *2008* Valparaiso University Outstanding Senior Chemistry Award (Valparaiso University) Member of Phi Lambda Upsilon (The National Honorary Chemical Society, USA) and The Phi Beta Kappa Society (Academic Honor Society, USA) Graduation with Summa cum Laude (Valparaiso University)

Conferences	
	2011 Vienna International Symposium in Organic Chemistry (VISOC) ▪ Lecture - Chiral Methylmetals – Configurational Stability and Application German – Austrian – French – Hungarian - Italian Conference in Organic and Biomolecular Chemistry 2011 (GAFHI 2011) ▪ Poster - Configurational Stability of Chiral Methylpalladium Complexes as Intermediates of Coupling Reactions 14. Österreichische Chemietage ▪ Lecture - Configurational Stability of Chiral Methylpalladium Complexes as Intermediates of Coupling Reactions *2013* 14th Tetrahedron Symposium ▪ Poster - Configurational Stability of Chiral Methylpalladium Complexes as Intermediates of Coupling Reactions
Publications	
	''On the Stereochemistry of 2-Hydroxyethylphosphonate Dioxygenase'' Whitteck, J. T.; Malova, P.; Peck, S. C.; Cicchillo, R. M.; Hammerschmidt, F. and van der Donk, W. A. *JACS* **2011**, *133*, 4236-4239. ''*Mechanism and Substrate Recognition of 2-Hydroxyethylphosphonate Dioxygenase*'' Peck, S. C.; Cooke, H. A.; Cicchillo, R. M.; Malova, P.; Hammerschmidt, F.; Nair, S. K. and van der Donk, W. A. *Biochemistry* **2011**, *50*, 6598-6605. ''*On the Configurational Stability of Chiral Heteroatom-Substituted [D_1]Methylpalladium Complexes as Intermediates of Stille and Suzuki–Miyaura Cross-Coupling Reactions''* Malova Krizkova, P.; Hammerschmidt, F. *Eur. J. Org. Chem.* **2013**, *2013*, 5143–5148. ''*On the Configurational Stability of Chiral, Nonracemic Fluoro- and Iodo-[D_1]Methyllithiums''* Kail, D. C.; Malova Krizkova, P.; Wieczorek, A.; Hammerschmidt, F. *Chem. - A Eur. J.* **2014**, *20*, 4086–4091.

Courses	
	2011 In die universitäre Lehre starten – Basisqualifzierung für EinsteigerInnen *2012* NMR Sommerschule
Membership	
	GÖCH *Phi Lambda Upsilon* (The National Honorary Chemical Society, USA) *Phi Beta Kappa Society* (Academic Honor Society, USA)