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DISSERTATION

Titel der Dissertation

„Preparation and Determination of Configurational Stability of Chiral Bromo- and Thio-[D_1]Methyllithiums“

Verfasserin

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My best thanks to …

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"Everything should be made as simple as possible, but not simpler."

Albert Einstein

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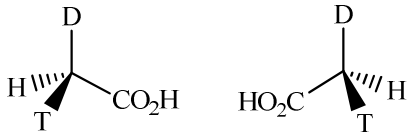
Abbreviations

(+)-DIP-chloride	(+)-B-ChloroDiIsoPinocampheylborane
(v.) br.	(Very) Broad
Ac	Acetyl
Ar	any Aromatic substituent
ATR	Attenuated Total Reflectance
Boc	*t*-ButOxyCarbonyl
BOM	BenzylOxyMethyl
DEAD	DiEthyl AzoDicarboxylate
DIAD	DiIsopropyl AzoDicarboxylate
DIBAH	DiIsoButylAluminum Hydride
DMSO	DiMethyl SulfOxide
DTBAD	Di-Tert-Butyl AzoDicarboxylate
E	any Electrophile
EDG	Electron Donating Group
ESI	ElectroSpray Ionization
EWG	Electron Withdrawing Group
HMPA	*N*,*N*,*N'*,*N'*,*N''*,*N''*-HexaMethylPhosphorAmide
HRMS	High Resolution Mass Spectroscopy
IR	Infrared Spectroscopy
MOM	MethOxyMethyl
Ms	MeSylate (Methanesulfonyl)
MS	Mass Spectroscopy
NBS	*N*-BromoSuccinimide
NMR	Nuclear Magnetic Resonance

PMB	*Para*-MethoxyBenzyl
R	any organic substituent
RT	Room Temperature
SSIP	Solvent Separated Ion Pair
THF	TetraHydroFuran
THP	TetraHydroPyran
TLC	Thin Layer Chromatography
TMEDA	*N*,*N*,*N'*,*N'*-TetraMethylEthyleneDiAmine
TMP	2,2,6,6-TetraMethylPiperidine
TMS	TriMethylSilyl
X	any heteroatom

1. Introduction

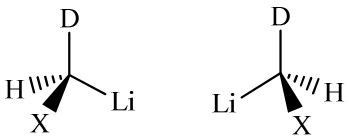
Ever since it was recognized that chiral reagents, including enzymes, can differentiate between enantiomers, the synthesis of chiral molecules was of great interest. In late 1960's, Arigoni and Lüthy prepared both enantiomers of chiral acetic acid (**1.1**) which had a methyl group chiral by virtue of all three isotopes of hydrogen; protium, deuterium and tritium (Figure 1.1).[1]



(*R*)-[D_1,T]**1.1** (*S*)-[D_1,T]**1.1**

Figure 1.1. Chiral acetic acid

They were also the first ones who used the term 'chiral methyl group'. In my thesis I have concentrated on the investigation of the configurational stability of chiral bromo- and thio-[D_1]methyllithiums (**1.2**, X = Br, S, Figure 1.2), as well as the optimization of their preparation.



(*R*)-[D_1]**1.2** (*S*)-[D_1]**1.2**

X = heteroatom (X = O, N, halogen, S)

Figure 1.2. Chiral methyllithiums

1.1. Organolithiums

Organolithiums are compounds containing a carbon atom directly linked to a lithium atom - the smallest metal atom with the atomic number 3. The carbon-lithium bond is highly polarized due to the electropositive lithium, which increases the negative charge on the carbon

atom. A nucleophilic species called carbanion is formed. This term was first used in 1933 by Wallis and Adams to distinguish it from the already known species containing a positively charged carbon atom called 'carbonium' ion.[2] Owing to the polar character of the carbon-lithium bond and the proneness of organolithiums to form a variety of aggregates, their structural chemistry and reactivity are extremely complex.[3]

1.1.1. Classes of organolithiums

Two main classes can be distinguished between organolithiums; *unfunctionalized* and *α-heteroatom-substituted* ones. The latter group can be divided into two subgroups, the *non-dipole* and *dipole-stabilized* organolithiums.

Unfunctionalized organolithiums

They do not play a crucial role in organic synthesis and are mentioned only for the sake of their historical significance. 2-Lithiooctane was the first chiral, nonracemic organolithium prepared and reacted with carbon dioxide to yield an optically active acid of low ee.[4]

α-Heteroatom-substituted organolithiums

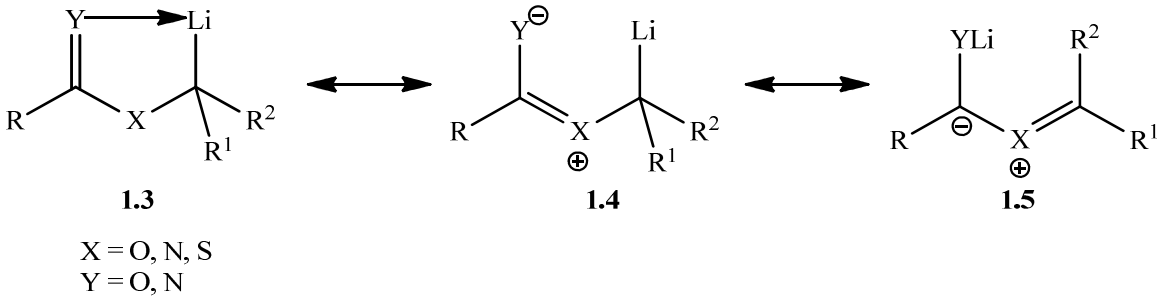
They are substituted with a heteroatom such as oxygen, nitrogen, a halogen or sulfur. We distinguish *non-dipole* and *dipole-stabilized* organolithiums depending on the way they are stabilized.[5]

a) *Non-dipole stabilized organolithiums*

The lithium-bearing carbon atom has a tetrahedral structure. Their configurational stability is increased with substituents, especially oxygen and nitrogen. Additionally, these organolithiums can be stabilized by chelation. Normally they react with electrophiles with retention of configuration.

b) *Dipole-stabilized organolithiums*

If a heteroatom X forms a positively charged end of the dipole, the local inductive effect will stabilize the carbanionic center. Interaction of the negatively charged heteroatom Y with the lithium cation gives an additional stabilizing effect by forming a five membered chelate ring (Scheme 1.1.)[6,7]

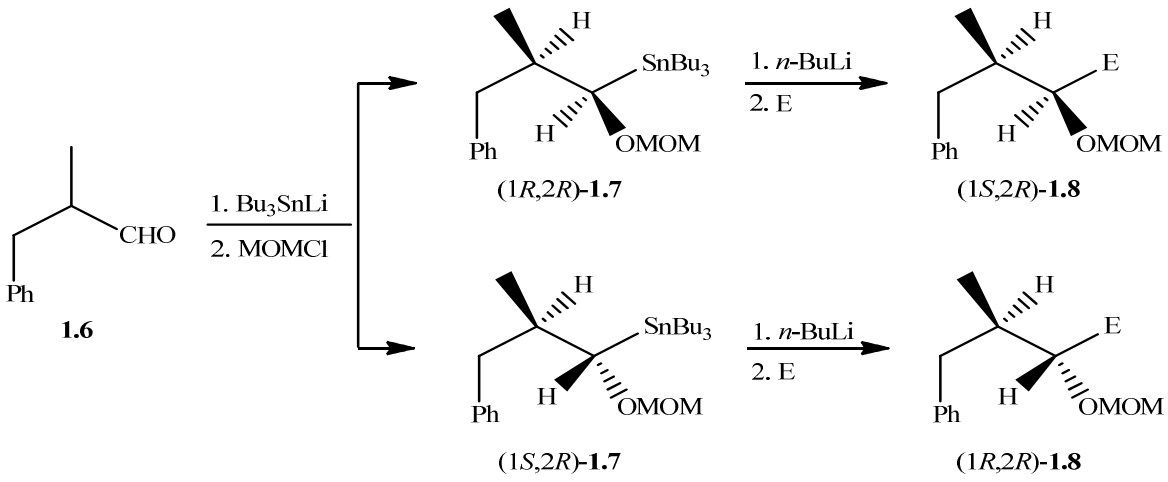


Scheme 1.1. Dipole stabilization of organolithiums

1) *α*-Oxyalkyllithiums

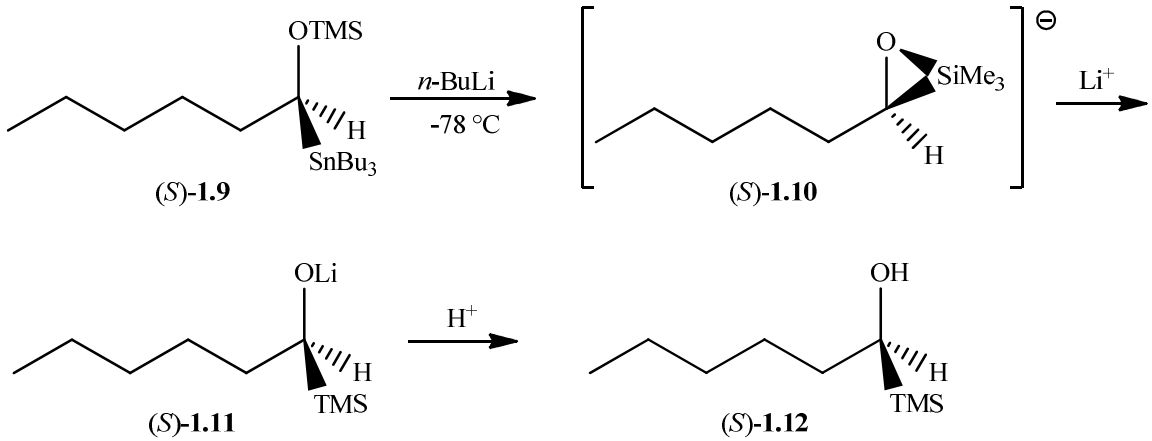
Generating configurationally stable *α*-alkoxy-substituted organolithiums by direct metalation is a difficult process. Electron pair repulsion between the lone pairs of oxygen and the C-Li bond overcomes the favorable electron-withdrawing effect of the oxygen atom itself, prohibiting deprotonation. However, direct metalation can give stable, synthetically desired synthons, if the *α*-alkoxyalkyllithium is stabilized by an adjacent double bond. The stabilization is obtained by delocalization of the negative charge.[6]

α-Alkoxyorganolithiums captured the imagination of chemists in 1980, when Still and Sreekumar reported their first preparation in a chiral, nonracemic form.[8] They found that these *α*-oxyorganolithiums with MOM- or BOM-protecting group were configurationally stable up to −30 °C (Scheme 1.2).



Scheme 1.2. MOM-protected *α*-oxyorganolithiums

Non-dipole-stabilized organolithiums are represented also by *α*-silyloxyorganolithiums. They undergo *retro*-Brook rearrangements with retention of configuration yielding enantiopure *α*-hydroxysilanes.[9,10] All of them are broadly applied in organic synthesis (Scheme 1.3).



Scheme 1.3. Non-dipole stabilized *α*-silyloxyorganolithiums

The dipole-stabilized organolithiums are the most stable and most important ones. Hoppe et al. converted primary alcohols to carbamates with a Cb, Cby or Cbx protecting group at the oxygen atom (Figure 1.3).

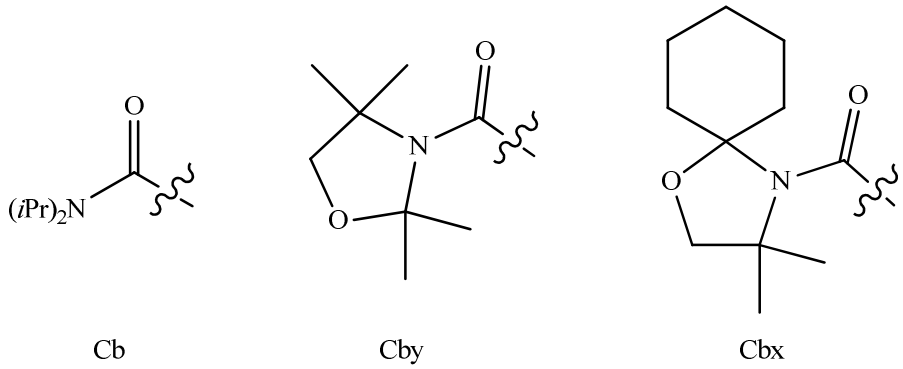
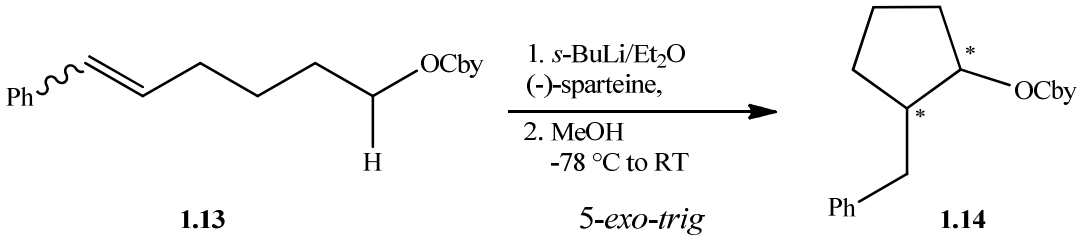


Figure 1.3. Alcohol protecting groups

The shielded carbonyl groups direct metalation with *s*-BuLi at −78 °C to the *α*-position of oxygen. Alkyl-, heteroalkyl, allyl- or benzyl-substituted organolithiums were found to be configurationally stable (for a long time) in Et_2O at −78 °C.[11]

Moreover (−)-sparteine/*s*-BuLi mediated lithiation/substitution sequences allowed the production of highly enantioenriched compounds starting from achiral precursors (Scheme 1.4).[12]

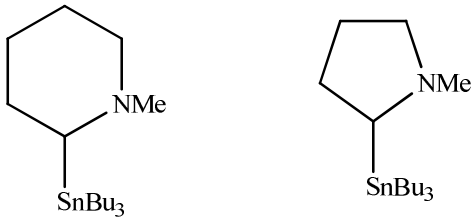


1.13 5-*exo-trig* **1.14**

Scheme 1.4. Synthesis of enantioenriched **1.14** from an achiral precursor

2) α-Aminoalkyllithiums

α-Aminoalkyllithiums are presumed to be less configurationally stable than the α-oxy ones. The proximal C-Li bond is destabilized by a considerably stronger antibonding interaction than that of oxygen, due to the ability of the nitrogen lone pair to coordinate to the lithium. To enable direct deprotonation at the α-position in certain cases, a superbase reagent has to be used. If nitrogen's lone pair is conjugated with a carbonyl group or delocalized into an aromatic ring, then deprotonation is also facilitated. The electron-rich oxygen atom of a carbonyl group additionally stabilizes an organolithium by formation of a five-membered chelate ring.[13] Therefore α-aminoalkyllithiums demand lower temperatures and absence of chelating agents to obtain the same results as with α-alkoxyorganolithiums.[14] Preparation of enantiopure non-dipole stabilized and acyclic species in good yields is virtually impossible. Therefore, they are synthetically unimportant. Until now, the only exceptions are the stable α-aminoorganolithiums prepared by Beak et al.[15-17] They managed to generate lithiated *N*-methyl pyrrolidine and piperidine configurationally stable up to −40 °C (Figure 1.4). These compounds retained or inverted their configuration at the stereogenic center during the reaction with an electrophile, depending on its nature.

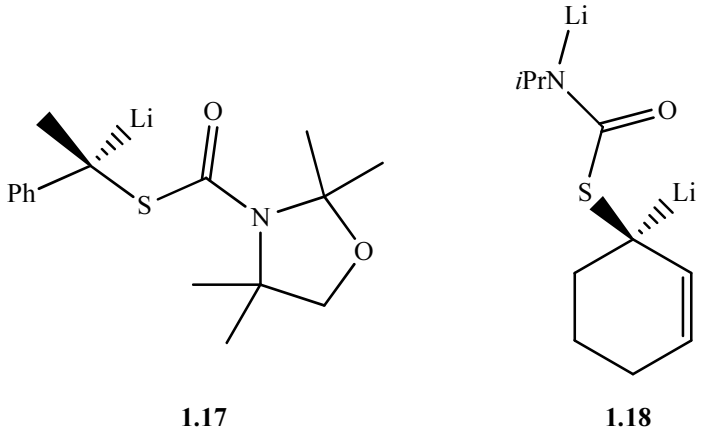


1.15 **1.16**

Figure 1.4. Precursors for lithiated *N*-methyl piperidine and pyrrolidine

3) α-Thioalkyllithiums

Generally, only microscopic configurational stability was observed for α-lithiated sulfides derived from primary substituents. Only tertiary thioalkyllithiums such as the dipole-stabilized ones **1.17** and **1.18** displayed macroscopic configurational stability at −78 °C (Figure 1.5).[5] This group of alkyllithiums will be discussed in detail in chapter 2.2.

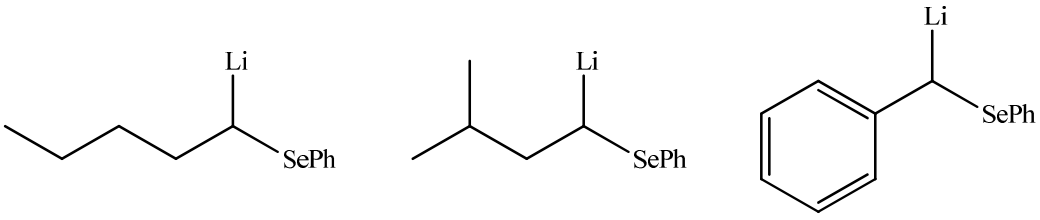


1.17 **1.18**

Figure 1.5. Dipole-stabilized α-thioalkyllithiums

4) α-Selenoalkyllithiums

A variety of findings were acquired during the investigation of the configurational stability of α-lithioselenides.[18,19] It was found that α-(phenylselenyl)alkyllithium **1.19** is configurationally stable at –105 °C in a mixture of THF and Et_2O, **1.20** is labile at –65 °C in Et_2O and **1.21** is unstable at –78 °C in THF (Figure 1.6). The reactivity of organolithiums can be modulated by using ligands.

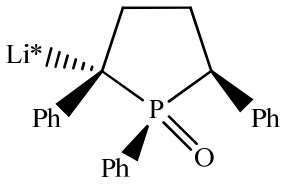


1.19 **1.20** **1.21**

Figure 1.6. Several α-(phenylselenyl)alkyllithiums

5) Alkyllithiums with phosphorus at the α-carbon atom

Mechanistic studies demonstrated that because of the lithium-oxygen affinity, most of the α-lithiophosphonates and α-lithiophosphonamidates do not contain lithium ion in contact with carbon atom.[20] There are only a few examples of phosphorus stabilized organolithiums, where a direct bond between carbon and lithium is observed.[21] In that case carbanions have an almost planar structure and sp^2 hybridization is assumed for the carbon atom.[20,22] Enantioenriched lithiated phosphane oxides were found to be configurationally labile, however, lithiated triphenylphospholane (**1.22**) was found to be configurationally stable in the presence of (−)-sparteine (Figure 1.7).[23]



1.22

Li* = Li•(-)-sparteine

Figure 1.7. (−)-Sparteine stabilized lithiated triphenylphospholane

6) α-Haloalkyllithiums

α-Haloorganolithiums are useful reagents for organic synthesis even though they were found to be extremely chemically unstable.[24] Köbrich was one of the first who studied many haloorganolithiums. He investigated the chemical stability and reactivity of chloro-substituted methyllithiums and found that chloromethyllithium is less stable than dichloromethyllithium, which is at the same time more stable than trichloromethyllithium.[25,26] A detailed discussion of α-bromoorganolithiums will follow in chapter 2.1.

1.1.2. Preparation of alkyllithiums

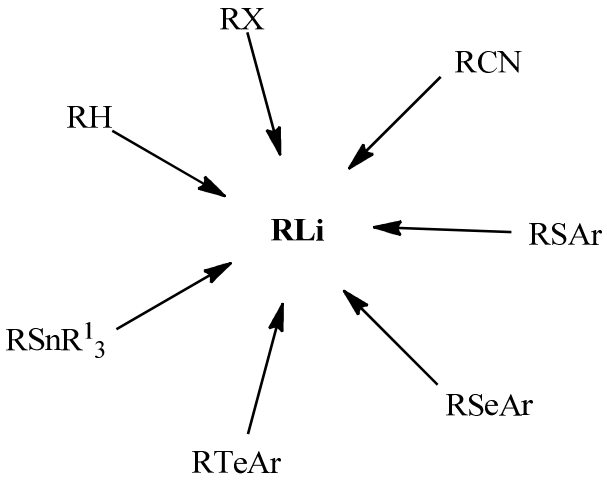
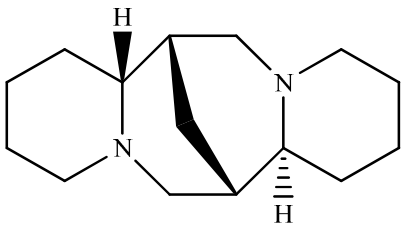


Figure 1.8. Preparation of organolithium compounds[27]

Organolithiums are used in all research laboratories either as bases or as nucleophiles. They can be prepared by several synthetic methods such as deprotonation, halogen-lithium exchange, transmetalation and reductive lithiation.

Deprotonation is the method of choice for compounds activated by an electron-withdrawing substituent (C=O, CN, SO_2R…). Homochiral lithium amides proved to be very useful for that purpose. The enantioselective metalation of carbamates and *N*-Boc-protected benzylamines was achieved by using *s*-BuLi or *n*-BuLi in combination with (−)-sparteine (**1.23**, Figure 1.9). These complexes were able to distinguish enantiotopic protons resulting in highly enantioenriched heteroatom-substituted alkyllithiums.[11]



1.23

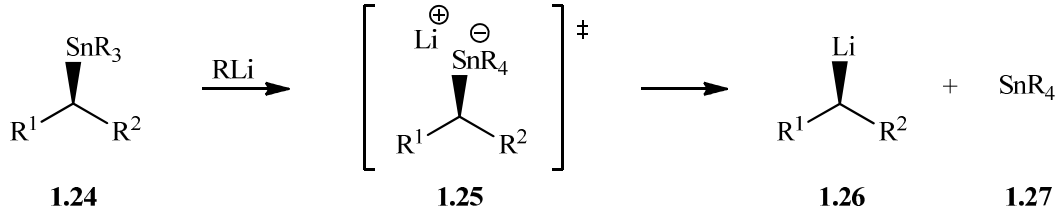
Figure 1.9. (−)-Sparteine

Reductive lithiation is a reaction of lithium metal with organic halides, sulfides, selenides or tellurides. Reductive decyanation can be used for the preparation of tertiary *α*-aminoorganolithiums.[28]

Transmetalation is a reaction in which substituents are exchanged between two metal centers. Tin-lithium exchange is the most important transmetalation reaction, which allows preparation of organolithiums from organostannanes with *n*-BuLi. It was also a method of choice in my work, hence it will be described more in detail.

Tin-lithium exchange

Tin-lithium exchange is very useful as it allows the generation of salt free alkyllithiums.[29] It was described for the first time by Seyferth and Weiner in the late 1950's as a novel synthesis of allyll- and methallyllithiums.[30-32] This transmetalation is thermodynamically controlled and proceeds rapidly and stereospecifically with retention of configuration at the tin-bearing carbon atom (Scheme 1.5).[8,33]



1.24 **1.25** **1.26** **1.27**

Scheme 1.5. Mechanism of tin-lithium exchange

Usually, Bu_3SnR is reacted with *n*-BuLi at low temperature to yield Bu_4Sn and RLi (**1.26**). The equilibrium is shifted to the right, when R^- is (much) less basic than Bu^-. Additionally, it is a smooth process without the formation of side products except inert Bu_4Sn.[8,33] Halogen-lithium exchange gives salt containing alkyllithium in admixture possibly with Wurtz coupling products. The reactivities of salt free and salt containing organolithiums differ considerably. The only challenge with tin-lithium exchange is the preparation of the respective enantiopure organostannanes. A wide spectrum of solvents can be used, but the most popular is THF at low temperatures. The mechanism of tin-lithium exchange can be explained by formation of pentacoordinated ate-complex **1.25**. Still proposed that the ate-complex is more stable than alkyllithium and tetraalkyltin themselves, what is the driving force for the reaction.[34] The generated RLi is hardly isolated, but quenched with an electrophile.

1.1.3. Configurational stability

The methyl carbanion is isoelectronic to ammonia, which inverts its configuration with high frequency. The phrase ‘configurational stability’ used in combination with a carbanion refers to the stability of steric arrangement of its substituents. It is used to describe wheather a generated organolithium retains its configuration during the reaction. It has a meaning only when related to a timescale and temperature. The configurational stability of alkyllithiums depends on temperature, solvent and the reaction itself.

1.1.3.1. Mechanism of inversion of configuration (enantiomerization)

The barrier to enantiomerisation can be determined by line shape analysis of appropriate NMR signals.[5] Different mechansims were proposed for this process:

1. Dissociative mechanism

At first the lithium ion is separated from the tetrahedral alkyllithium.[35] A solvent separated ion pair (SSIP) is formed and the carbanion enantiomerizes via a planar carbanion with a sp^2-hybridized carbon atom. Rotation of the carbanion and recombination of the ions give the alkyllithium with inverted configuration.

2. Conducted tour mechanism

This alternative mechanism was proposed by Cram and Gosser.[36] They proposed that the lithium ion dissociates from the carbanionic center thanks to coordination with a Lewis base in the same molecule and is then delivered to the opposite side of the carbanion. This theory is supported by the crystal structure analysis of α-lithio-*N*,*N*-dimethylbenzylamine, in which a C-Li-N bridge is observed.

3. Bond rotation

The last mechanism proposed by Gais et al. for α-thioorganolithiums was also found to apply to compounds containing selenium as an α-substituent.[37] The rotational barrier for the C-S or C-Se bond is increased by bulky substituents (steric hindrance).

1.1.3.2. Types of configurational stability

Macroscopic configurational stability

If an organolithium retains its configuration between generation and reaction with an electrophile added after some time (aging), it is considered to be macroscopically configurationally stable.[13,38] This term concerns a timescale of minutes or more.

Microscopic configurational stability

If an alkyllithium retains its configuration on time-scale of an intramolecular reaction or the addition to an electrophile already present in solution when it is generated, it is said to be microscopically configurationally stable.[13,38] This term relates to a timescale of seconds or less.

1.1.3.3. Investigation of configurational stability

Hoffman et al. developed an elegant method to investigate the configurational stability of an organolithium based on kinetic resolution during its addition to an electrophile.[5,13,38] Two experiments have to be performed. The first one is the control reaction of a racemic organolithium with a racemic electrophile. If the diastereomeric ratio of the products lies between 1.5 and 3.0, then the electrophile is suitable for the Hoffmann test. The second experiment is the reaction of a racemic organolithium with an enantiopure electrophile. If the diastereomeric ratio is the same in both experiments, the organolithium is configurationally labile. However, if the diastereomeric ratios differ, the organolithium is at least partially configurationally stable.

There are four different energy diagrams possible for the Hoffman test. In Figure 1.10. diagrams for a configurationally labile organolithium are presented.

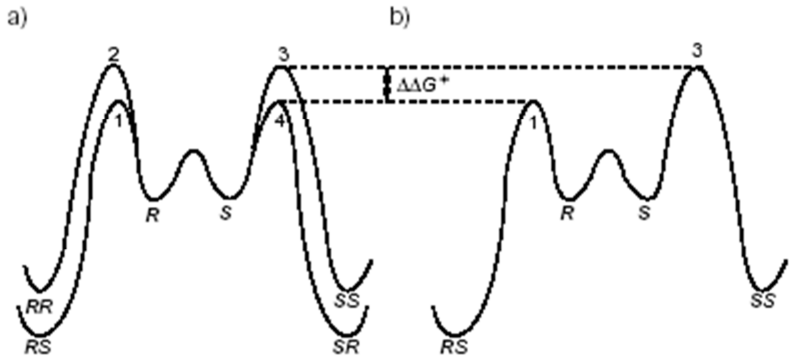


Figure 1.10. Energy diagram for configurationally labile organolithiums

Diagram a) displays the reaction of a configurationally labile organolithium with a racemic electrophile. Four different pathways are possible for the equilibrating enantiomeric organolithiums. 1 and 2 are in enantiomeric relation to 3 and 4. The decisive factor for which route the reaction will proceed is the transition state energy difference $\Delta\Delta G^{\ddagger}$, since the transition state energies for the formation of both diastereomers are much bigger than the barrier to enantiomerisation of the organolithium.

Diagram b) shows the reaction of a configurationally labile organolithium with an enantiopure (*S*)-electrophile. Only two pathways (1 and 3), diastereomeric to each other, are available for the equilibrating intermediate. The difference in the transition state energy $\Delta\Delta G^{\ddagger}$ is still the decisive factor.

In Figure 1.11. diagrams for a configurationally stable organolithium are presented.

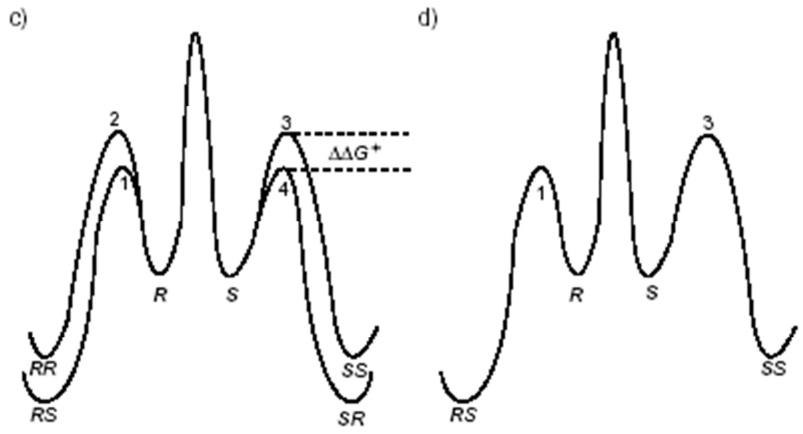


Figure 1.11. Energy diagram for configurationally stable organolithiums

Diagram c) represents the reaction of a configurationally stable organolithium with a racemic electrophile. Again four different pathways are possible for the racemic organolithium, whereas 1 and 2 are available only for the (*R*)-enantiomer and 3 and 4 for the (*S*)-enantiomer of the organolithium. As before, 1 and 2 are in enantiomeric relation to 3 and 4 and the overall diastereoselectivity depends on the transition state energy difference $\Delta\Delta G^{\ddagger}$.

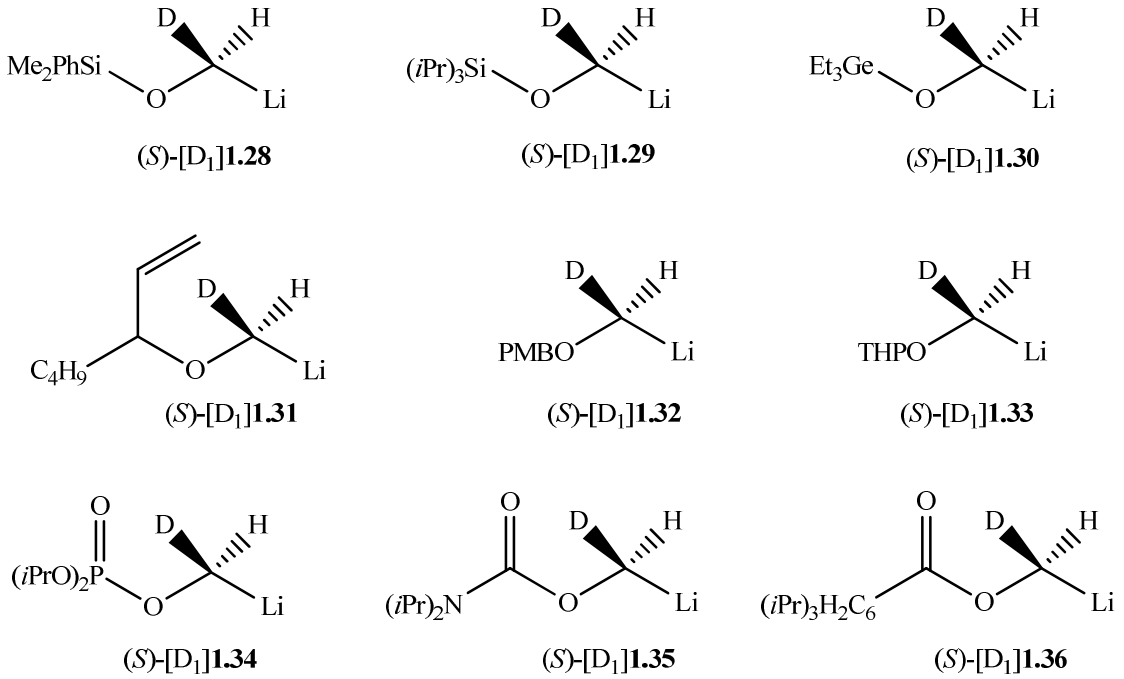
Diagram d) shows the reaction of a configurationally stable organolithium with an enantiopure (*S*)-electrophile. The only possible pathway for the (*R*)-enantiomer of the organolithium compound is 1 and for the (*S*)-enantiomer 3. If the reaction goes to completion, then the diastereomeric ratio of the final products depends only on the enantiomeric ratio of the organolithiums in the ground state. Consequently, the diastereoselectivity ratio will be 1, since the enantiomers of the racemic organolithium are configurationally stable.

1.2. Methyllithiums

1.2.1. Known chiral [D_1]methyllithiums and their configurational stability

1.2.1.1. Chiral oxy-[D_1]methyllithiums

Chiral oxy-[D_1]methyllithiums have been extensively investigated in our group by Kapeller since 2004 (Figure 1.12).[39,40]



(*S*)-[D$_1$]**1.28** (*S*)-[D$_1$]**1.29** (*S*)-[D$_1$]**1.30**

(*S*)-[D$_1$]**1.31** (*S*)-[D$_1$]**1.32** (*S*)-[D$_1$]**1.33**

(*S*)-[D$_1$]**1.34** (*S*)-[D$_1$]**1.35** (*S*)-[D$_1$]**1.36**

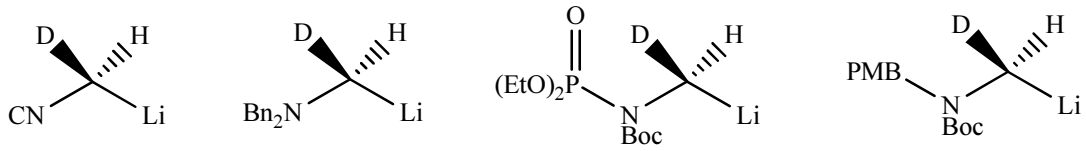
Figure 1.12. Known chiral oxy-[D$_1$]methyllithiums

All of them were found to be microscopically configurationally stable and most of them even macroscopically. Those with an *N*,*N*-diisopropylcarbamoyl protecting group ([D$_1$]**1.35**) are macroscopically configurationally stable at −78 °C for at least 10 minutes in Et$_2$O/TMEDA and for about 3 hours in THF. However, their chemical stability decreases with increasing the reaction temperature. They decompose rapidly at −50 °C.[41] The aroyloxy-substituted analogues, the (2,4,6-triisopropylbenzoyl)oxymethyllithiums ([D$_1$]**1.36**), are somewhat less macroscopically configurationally stable, as they are stable only for several minutes at −78 °C (ee of 98%).[42] (Diisopropoxyphosphinyl)oxy-substituted methyllithiums ([D$_1$]**1.34)** were found to be microscopically configurationally stable up to 0 °C relative to the phosphate-phosphonate rearrangement.[40,41] The configurational stability of chiral methyllithiums undergoing intramolecular rearrangements was also studied. Oxymethyllithiums generated as intermediates of intramolecular isomerizations such as [2,3]-Wittig and *retro*-Brook rearrangements were tested for their configurational stability. Silyloxymethyllithiums [D$_1$]**1.28** and [D$_1$]**1.29** undergo *retro*-Brook rearrangements with retention of configuration and exhibit complete microscopic configurational stability (ee 95-97%) at temperatures from −78 °C up to 0 °C. In the case of germyloxymethyllithiums [D$_1$]**1.30** a small amount of enantiomerization interfered evidently (ee 90-92%). The [2,3]-Wittig rearrangement of microscopically configurationally stable chiral allyloxymethyllithiums [D$_1$]**1.31** proceeded with inversion of configuration at −78 °C (ee 94%).[43] Another group of chiral

oxymethyllithiums were those with a PMB- or THP-protecting group ([D_1]**1.32** and [D_1]**1.33**). They displayed macroscopic configurational stability up to −35 °C, the temperature of chemical decomposition. However, these oxymethyllithiums were found to be microscopically configurationally stable up to 0 °C. They are valuable synthons for the synthesis of D-glucose stereospecifically deuterated at C-6, which can be applied for the elucidation of biosynthetic reaction mechanisms.[44]

1.2.1.2. Chiral amino-[D_1]methyllithiums

Kapeller studied a variety of chiral aminomethyllithiums with regard to their configurational stability (Figure 1.13).[39]



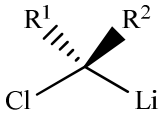
(*S*)-[D_1]**1.37** (*S*)-[D_1]**1.38** (*S*)-[D_1]**1.39** (*S*)-[D_1]**1.40**

Figure 1.13. Known chiral amino-[D_1]methyllithiums

The phosphoramidate-aminophosphonate rearrangement (intramolecular isomerization, a [1,2]-Wittig rearrangement) was chosen to test the microscopic configurational stability of the aminomethyllithiums. *N*-Boc-protected (diethoxyphosphinyl)aminomethyllithiums ([D_1]**1.39**) rearranged with retention of configuration and were microscopically configurationally stable from −78 °C up to 0 °C. *N*-Boc and *N*-PMB-protected aminomethyllithiums ([D_1]**1.39** and [D_1]**1.40**) were found to be macroscopically configurationally labile even at −95 °C (65% ee, racemic at −78 °C). The best results concerning the configurational stability of chiral aminomethyllithiums were obtained with *N*,*N*-dibenzylaminomethyllithiums ([D_1]**1.38**). They were found to be virtually macroscopically configurationally stable for 15 minutes at −95 °C. The stability was strongly influenced by the temperature and complete racemization was already observed at −45 °C.[45] Finally, chiral isocyanomethyllithium ([D_1]**1.37**) was prepared, which completely enantiomerized, even when generated at −95 °C in the presence of benzaldehyde as electrophile.

1.2.1.3. Chiral chloro-[D$_1$]methyllithiums

In the late 1960's Körbich and Fischer reported that chloromethyllithium (**1.41**) was chemically unstable (Figure 1.14).[46]



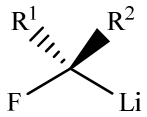
1.41: $R^1 = R^2 = H$
(*R*)-[D_1]**1.41**: $R^1 = D$, $R^2 = H$
(*S*)-[D_1]**1.41**: $R^1 = H$, $R^2 = D$

Figure 1.14. Chiral chloro-[D_1]methyllithiums

Despite that, Kapeller succeeded to prove their microscopic and macroscopic configurational stability (for [D_1]**1.41**), which means that they retain their configuration from generation to decomposition. Chloro-substituted methyllithiums were tested for their microscopic configurational stability at −78 °C, but for their macroscopic configurational stability at −95 °C. Decomposition was rapid at −78 °C, as indicated by the very low yield of the isolated chlorohydrine on the reaction with benzaldehyde.[47]

1.2.1.4. Chiral fluoro-[D$_1$]methyllithiums

It was stated in a review, that fluoromethyllithium (**1.42**) was extremely unstable and that it could not be detected by NMR spectroscopy at −120 °C (only ethene was detected) (Figure 1.15).[48]



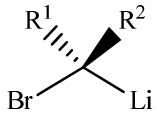
1.42: $R^1 = R^2 = H$
(*R*)-[D_1]**1.42**: $R^1 = D$, $R^2 = H$
(*S*)-[D_1]**1.42**: $R^1 = H$, $R^2 = D$

Figure 1.15. Chiral fluoro-[D_1]methyllithiums

Although many theoretical calculations at various levels have been performed for fluoromethyllithium, it has not been prepared until recently. Kapeller and Hammerschmidt found, that chiral fluoromethyllithiums generated by tin-lithium exchange are microscopically configurationally stable, but extremely labile.[39] Malova repeated the experiments with the unlabeled fluoromethyllithium. She performed the transmetalations in the presence of acetophenone instead of benzaldehyde as electrophile.[49] Under these conditions the yield of formed fluoromethyllithium was higher, because the side reaction, the addition of RLi to acetophenone was reduced and transmetalation increased at the same time. These results were quite surprising, as only a small portion of the fluoromethyllithium decomposed and the major one was added to acetophenone.

1.2.1.5. Chiral bromo-[D_1]methyllithiums

Tarhouni et al managed to generate unlabeled bromomethyllithium (**1.43**) which was stabilized by the presence of LiBr (Figure 1.16).

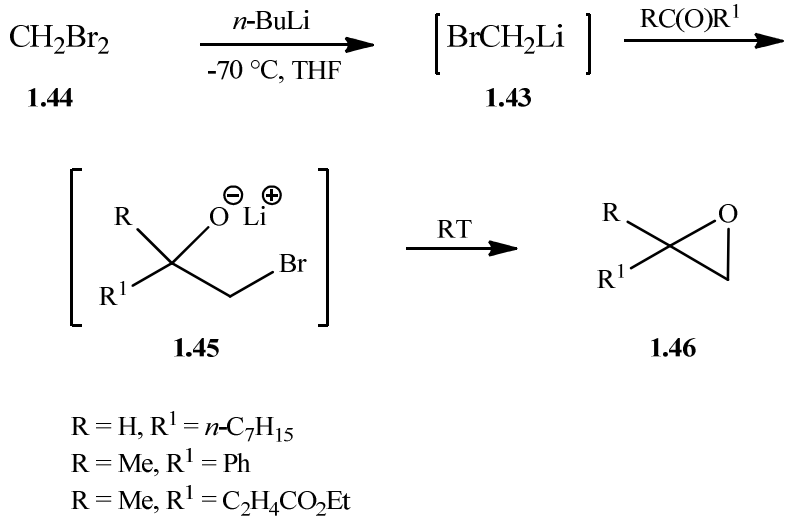


1.43: $R^1 = R^2 = H$
(*R*)-[D_1]**1.43**: $R^1 = D, R^2 = H$
(*S*)-[D_1]**1.43**: $R^1 = H, R^2 = D$

Figure 1.16. Chiral bromo-[D_1]methyllithiums

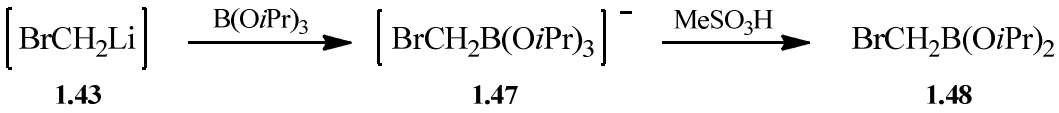
The best results were obtained while adding *s*-BuLi in pentane to a solution of Br_2CH_2, THF, Et_2O, pentane and LiBr at −110 °C. After addition of benzaldehyde, an oxirane was formed.

In 1991 Michnick reported successful synthesis of bromomethyllithium (**1.43**) in situ.[50] It was prepared by bromo-lithium exchange of dibromomethane with *n*-BuLi and intercepted by a carbonyl compound. The yields of the oxiranes were equal or better to those obtained with chloromethyllithium (Scheme 1.6).



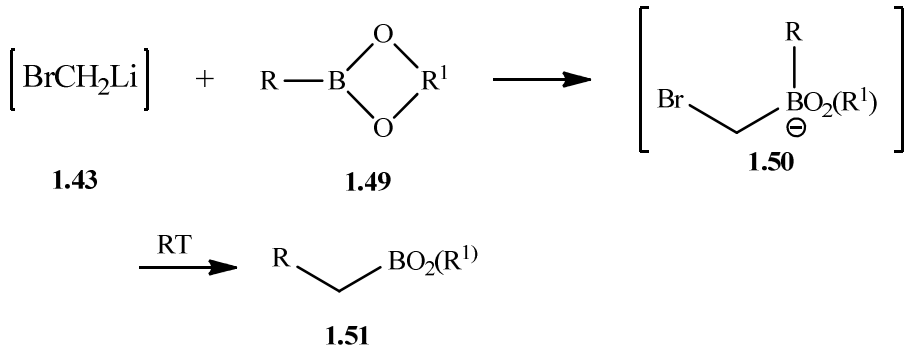
Scheme 1.6. Synthesis of oxiranes *via* bromomethyllithium formation

Diisopropyl bromomethylboronate was synthesized in very good yields (86-89%) from equimolar amounts of dibromomethane, triisopropyl borate and *n*-BuLi added dropwise to the reaction mixture (Scheme 1.7).



Scheme 1.7. Preparation of boronates from dibromomethane

Boronic esters were transformed into their homologues. Very good yields were obtained only for unfunctionalized substrates (Scheme 1.8).



Scheme 1.8. Homologation of boronic esters

As far as I know the chiral bromomethyllithium ([D_1]**1.43**) has not been prepared until now.

1.2.2. Carbenoids

A ‘carbenoid’ is defined as a chemical species bearing a halogen and a metal atom at the same carbon atom. The stability of carbenoids depends distinctively on the metal; sodium and potassium carbenoids are very unstable, whereas lithium carbenoids require very low temperature to be prepared. However, much more stable species, like tin carbenoids, can be generated. Lithium carbenoids were first mentioned by Closs and Moss in 1964 in a paper on arylcyclopropanes prepared from olefins.[51] However carbenoid formation, as a plausible intermediate in the reaction of alkyllithiums with polyhalogen compounds and olefins to produce cyclopropanes, was already reported in 1959 by Miller and Kim.[52]

Carbenoids containing a halogen are much more reactive for cyclopropanation than those with an alkoxy group. Experimental data proved that $LiCH_2X$ (where X = halogen) can cyclopropanate olefins efficiently even at −78 °C. Boche et al. calculated the influence of the leaving group X (X = F, Cl, Br, I and OH) on the carbenoid character of the $LiCH_2X$.[53] The outcome was that activation energies for carbenoids with various halogens were almost equal, whereas the activation energy for carbenoids with an OH group was about 2.5 times higher. It can be explained by the fact that the C-X bond is weakened by the C-Li bond in the carbenoid and complexes. The C-I bond was found to be less affected than C-F bond. Formation of the Li-X bond compensates for the cleavage of the C-X bond, because of the strong decomplexation of the LiX transition state. Whereas high C-OH bond energy is responsible for the higher transition state energy in $LiCH_2OH$.[53]

The most intriguing property of carbenoids is their ambiphilic character, what means that they can react either as a nucleophile or an electrophile depending on the temperature.[54,55] This property can be explained by the simultaneous presence of an electron withdrawing and an electron donating substituent. At low temperatures (about −110 °C) the bond between carbon and metal has a covalent character and the carbenoid behaves as a nucleophile.[56] It reacts with a variety of electrophiles undergoing reactions like acylation, alkylation etc. When the temperature rises (about −80 °C), carbenoids act as electrophiles by metal assisted ionization (MAI). At higher temperatures α-elimination takes place and the carbenoids are converted to carbenes.

It is quite tough to distinguish between carbenoids and carbenes. Stereochemistry may be helpful, owing to the fact that carbene intermediates are achiral, whereas carbenoids can be

chiral, only if they are stable. A chiral carbenoid undergoing a nucleophilic substitution gives a chiral product, while α-addition of a nucleophile to a carbene results in a racemic product.[56]

Köbrich et al. examined the role of solvent in the stabilization of α-halocarbanions. They suggested THF to be the most appropriate to stabilize carbenoids. α-Elimination is slowed down due to the activity of lithium cations as Lewis acid and the reduced electrophilicity caused by the solvation of the lithium cation by polar THF.[57]

A thorough knowledge of carbenoid character allows their application as enentioenriched α-halocarbanions in the stereocontrolled synthesis.[58]

1.2.1. Configurational stability of Carbenoids

Because of their applicability in the synthesis, numerous experiments were performed to synthesize α-haloalkyllithiums.[24] The syntheses of trihalo- and dihaloalkyllithiums as well as α-functionalized α-haloalkyllithiums were successfully completed several times. The synthesis of non-functionalized monoalkyllithiums caused some troubles. Bromo- and chlorocarbenoids decomposed immediately after generation what implies high chemical instability, which is attributed to the easy elimination of LiX. Increasing of the chemical shift with the rise of the polarization of the halogen (I > Br > Cl) for the functional carbon in the NMR spectrum implies that the carbon atom is electron deficient.[59] This is corroborated by the studies of Castro and Villieras who explained the electrophilic behavior and decomposition of carbenoids by intramolecular coordination between halogen and metal.[60,61]

Therefore to increase the stability of a carbenoid, the coordination between the metal ion and the halogen has to be minimized. It explains why the trihalo- and dihalocarbenoids are quite stable in the presence of basic solvents like THF or HMPA, since their nucleophilicity is enhanced. In the case of α-monohaloalkyllithium in the presence of HMPA, α-elimination is favored and the stabilization can be increased by addition for example of a lithium salt which acts as an electron acceptor.[24]

Boche et al. performed ab initio theoretical studies and calculated the energy difference between the planar and the more stable tetrahedral configurations, reflecting the barrier to enantiomeriztion.[62] The outcome of these calculations is presented in Table 1.

X	ΔE kJ/mol
H	12.6
SiH_3	3.4
SH	12.7
OH	46.1
NH_2	46.1
F	56.9

Table 1. Relative energy barriers to inversion of configuration of heteroatom-substituted methyllithiums

The calculations are qualitatively in agreement with the experimental findings. Alkoxy-, amino- and fluoro-substituted organolithiums have high barriers to inversion of configuration. On the other hand, sulfur- and silicon-substituted organolithiums have low energy barriers to inversion of configuration, what explains their poor configurational stability. The much higher configurational stability of amino-, alkoxy- and fluoro-substituted organolithiums is a consequence of stabilization of the tetrahedral configuration by the more electronegative substituents. Moreover the planar configuration is destabilized owing to the repulsive interaction of the lone pairs at O, N and F and the electron pair at the carbanionic carbon atom in that configuration.[62]

Hoffman was the first one who investigated the configurational stability of *α*-bromoalkyllithium compounds.[63-66] Lithium carbenoids were prepared starting from stannanes (ee ≥ 97%) and then quenched with a carbonyl compound as an electrophile. The intermediate lithium salt of halohydrine was transformed into an epoxide (ee 99%) on warming up. An experiment in which acetone was added 10 minutes after the addition of the RLi at −110 °C revealed, that the *α*-bromoalkyllithium was macroscopically configurationally stable.[65] Moreover it was shown that in the presence of the dibromo compound as carbenoid precursor, their equilibration occurred within 20-30 minutes at −110 °C. Otherwise *α*-bromoalkyllithiums are configurationally stable.[65] Hoffmann demonstrated that the diastereoselectivity depended on the sequence in which the reactants were combined even more than on the temperature.[63] Four methods can be applied.

- In situ method; carbenoids are generated in the presence of an electrophile
- Reverse in situ method; mixture of substrate and electrophile is added to the *n*-BuLi.

- Successive method; electrophile is added 10 minutes after generation of carbenoid.
- Reverse successive method; substrate is added to the *n*-BuLi followed by an electrophile after 10 minutes.[63,65]

1.2.3. Chiral thio-[D_1]methyllithiums

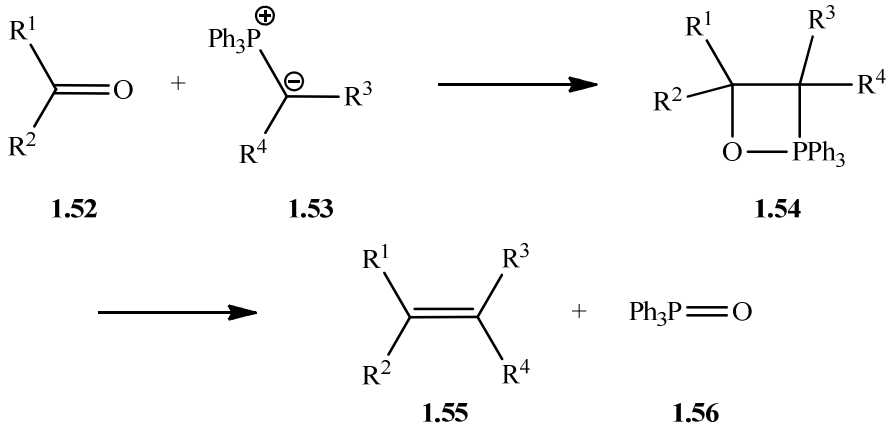
1.2.3.1. Sigmatropic rearrangements

A sigmatropic rearrangement involves the shift of a σ-bond across a conjugated π-system. It is characterized as [n,m] shift, where n is the number of atoms in one system and m the number of atoms in the second across which the σ-bond migrates. Sigmatropic rearrangement can proceed suprafacially or antarafacially. In the case of a suprafacial migration, the group migrates across the same face, whereas in the antarafacial migration the group moves from one face of the conjugated system to the other.

Wittig rearrangements

These rearrangements are dealt with extensively here, because part of my PhD thesis focuses on the [2,3]-thia-Wittig rearrangement of chiral allylthio- and arylmethylthio-[D_1]methyllithiums.

Georg Wittig is primarily famous for the discovery of alkene synthesis from an aldehyde or a ketone and a phosphonium ylide in 1954, known as the Wittig reaction (Scheme 1.9).[67]

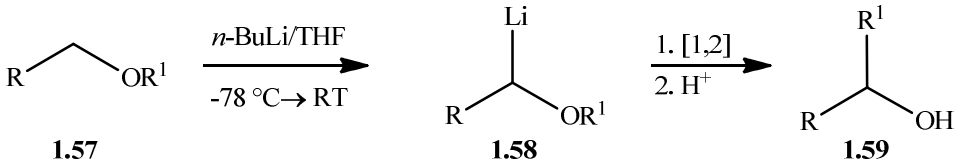


Scheme 1.9. Wittig reaction

He was awarded the Nobel Prize in Chemistry in 1979 and till now chemists in research institutions and industry benefit from his discovery. Wittig is also well known for the [1,2]- and [2,3]-Wittig rearrangements.

[1,2]-Wittig rearrangement

Wittig explored the [1,2]-rearrangement of certain ethers to isomeric alcohols induced by alkyllithiums even before the discovery of the Wittig reaction (Scheme 1.10).[68]



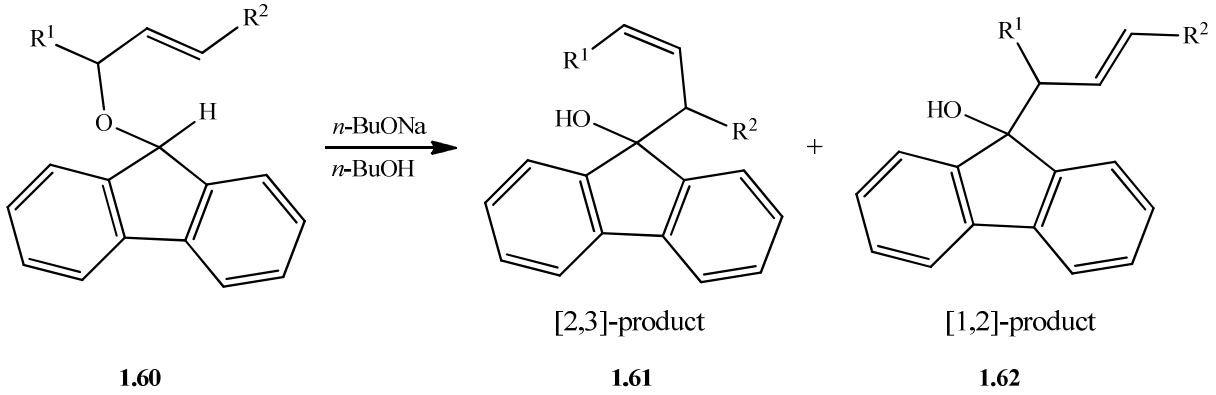
1.57 **1.58** **1.59**

Scheme 1.10. [1,2]-Wittig rearrangement

The mechanism of this reaction has been studied thoroughly. It was found to follow a radical dissociation-recombination mechanism.[69] The migrating carbon atom retains its configuration, whereas inversion of configuration is observed for the lithium-bearing terminus.[70] The [1,2]-Wittig rearrangement is less interesting for researchers than the [2,3] one, because of the limited substrate choice and restrained yields. Appropriate substrates for [1,2]-rearrangements contain substituents which stabilize either an anion or a radical. The migratory aptitude of R^1 increases with the stability of the corresponding radical R^1• (*prim* < *sec* < *tert*-alkyl < benzyl).[70] The yields are higher for stabilized carbanions which can be generated by direct deprotonation. In summary, the [1,2]-Wittig rearrangement is nowadays viewed as a special class of intramolecular radical processes.

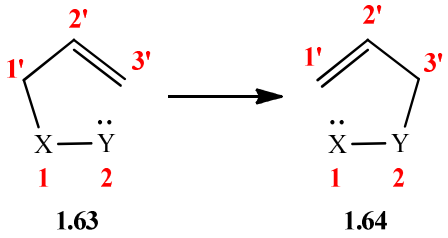
[2,3]-Wittig rearrangement

The first time the [2,3]-Wittig rearrangement was observed was quite accidental. It happened during the investigation of the mechanism of the [1,2]-rearrangement in 1960. When allyl fluorenyl ethers **1.60** were treated with *n*-BuONa, two different products were obtained, indicating a [1,2]- and a [2,3]-rearrangement (Scheme 1.11).[71]



Scheme 1.11. Rearrangements of allyl fluorenyl ethers

The [2,3]-Wittig rearrangement is presented in Scheme 1.12.



Scheme 1.12. [2,3]-Wittig rearrangement

It can be described as a thermal isomerization that proceeds through a six-electron, five-membered cyclic transition state.[72] As an electron pair is shifted from Y to X, the last atom should be a heteroatom able to accommodate the increasing electron density. Hence it will provide, at least partially, the driving force for the rearrangement.[73] Y is usually a heteroatom with non-bonding electron pairs and X an anion or an ylide.

The rate of rearrangement depends notably on the energy gap between HOMO (carbanion) and LUMO (allyl). The smaller the energy gap, and consequently the less stable the carbanion is, the faster the rearrangement.[72,74] Carbanions may be generated either via direct metalation (deprotonation) or transmetalation (i.e. Sn-Li exchange).[72]

After formation of the carbanion, the rearrangement proceeds fast and selectively at low temperatures. The [1,2]-rearrangement becomes competitive above −60 °C and the reaction may result in a mixture of products.[75] Consequently, the range of suitable substrates for [2,3]-rearrangements is limited only by the possibility of carbanion formation at low temperatures to prevent [1,2]-rearrangement.

Suprafacial migration through a six electron pericyclic, 5-membered envelope transition state is allowed. Several different models (A-C) were proposed for the 'folded envelope' conformation of the transition state (Figure 1.17).[76-78] Finally the 'Rautenstrauch model' (A) was found to be the most compatible with *ab initio* calculations and experimental results as well.[79]

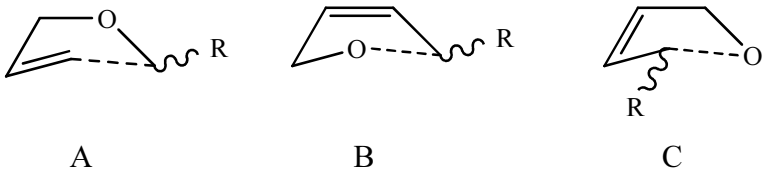
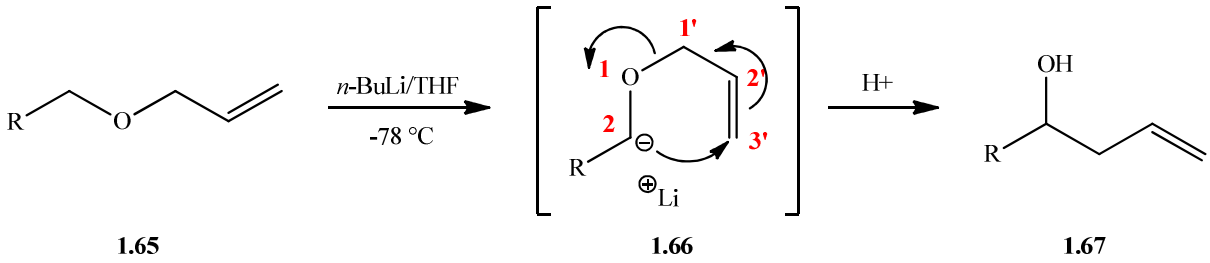


Figure 1.17. Models of transition state for the [2,3]-Wittig rearrangement

A [2,3]-sigmatropic rearrangement proceeds with inversion of configuration at the carbanionic center. It has been assumed that the enantioselectivity is predominantly determined by the lithiation step.[74]

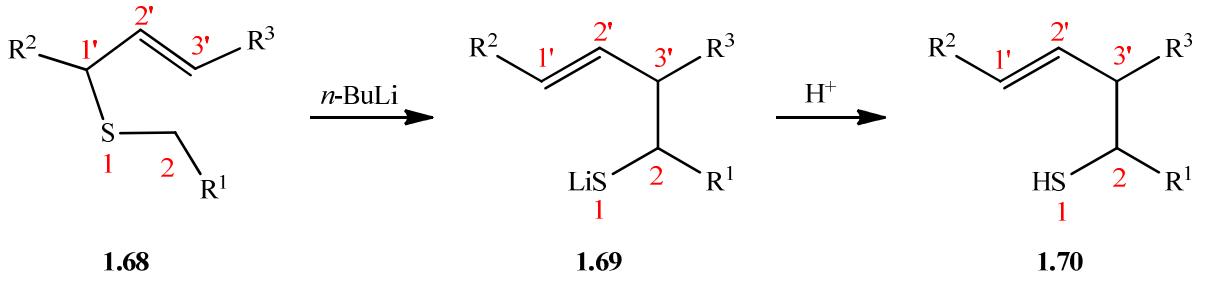
This kind of rearrangement has been widely applied in the synthesis of natural products (Scheme 1.13).[80-83]



Scheme 1.13. Mechanism of the [2,3]-Wittig rearrangement

[2,3]- Thia-Wittig Rearrangement

The sulfur version of the Wittig rearrangement is an isomerization in which an α-metalated sulfide rearranges to give a metal thiolate, usually a lithium thiolate, and a thiol as final product after acidic work-up (Scheme 1.14).



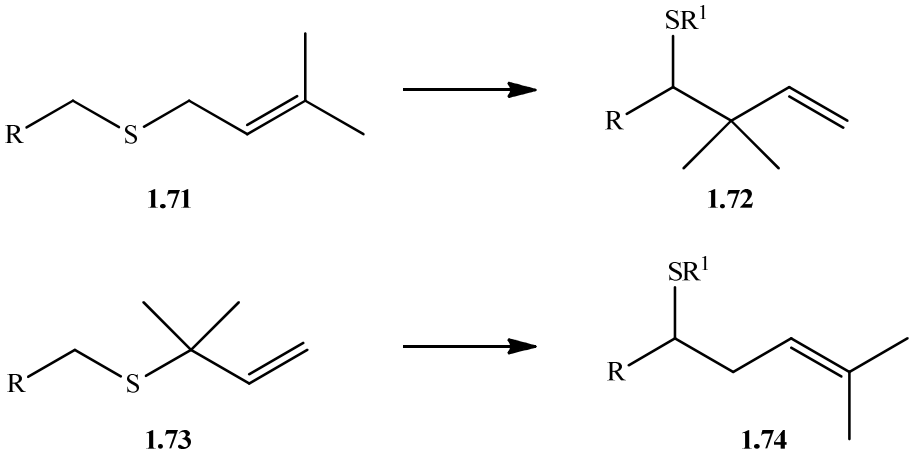
1.68 **1.69** **1.70**

Scheme 1.14. [2,3]-Thia-Wittig rearrangement

The metal thiolate **1.69** may also be quenched with other reagents (i.e. MeI) to give a sulfide. Deprotonation with an alkyllithium or a lithium amide is the most common method to produce an α-thio carbanion.[74] Moreover, tin-lithium exchange is an elegant way to induce a [2,3]-thia-Wittig rearrangement with very good stereoselectivity.[84] The general scheme of this reaction is presented above.

The presence of an electron withdrawing group (EWG = -Ph, -CN or SCH_3,[85] $-CO_2CH_3$[86]) at the R^1 position acidifies the neighboring α-hydrogens and facilitates metalation in preference to the allylic α'-hydrogens. Tin-lithium exchange extends the scope of the [2,3]-thia-Wittig rearrangement to substrates without an activating EWG group.

For the first time the [2,3]-thia-Wittig rearrangement was mentioned in 1971 by Rautenstrauch.[87] He converted a series of allyl alkyl sulfides to thiols and methyl sulfides (Scheme 1.15).



1.71 **1.72**

1.73 **1.74**

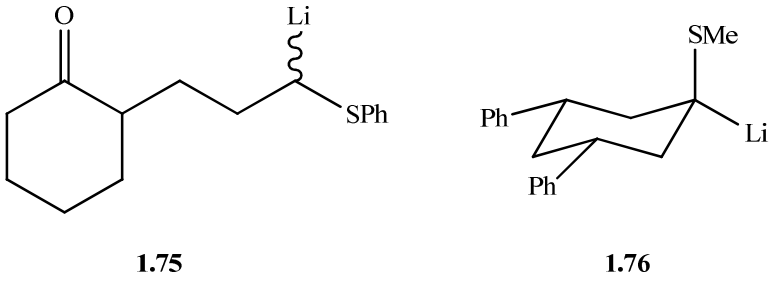
R = Ph, $CHC(CH_3)_2$
R^1 = H, CH_3

Scheme 1.15. First [2,3]-thia-Wittig rearrangements reported by Rautenstrauch

The experiments were performed in THF at temperatures ranging from −30 °C up to +45 °C. The substrates were lithiated with *n*-BuLi for several hours (1-5), followed by hydrolysis or methylation of the lithium thiolates. The carbanions formed by lithiation at the benzyl position rearranged very fast, therefore the rate-determining step was the reaction with *n*-BuLi. Only the products formed by the [2,3]-rearrangement were observed, without any trace of product formed by the competitive [1,2]-rearrangement. Rautenstrauch supposed that it may be the effect of an unstable radical intermediate which would have to be formed before the [1,2]-rearrangement.

1.2.3.2. Configurational stability of intermediate α-thioalkyllithiums

The configurational stability of *α*-thioalkyllithiums on the timescale of a [2,3]-thia-Wittig rearrangement as well as relative to the intermolecular addition of different electrophiles has already been investigated.[88-90] Ritter and Cohen studied the stability of *α*-lithiosulfides (**1.75**, Figure 1.18) on the timescale of the intramolecular addition to the carbonyl group. They found that the loss of stereochemistry at the carbanionic center was slower than ring closure.[89]



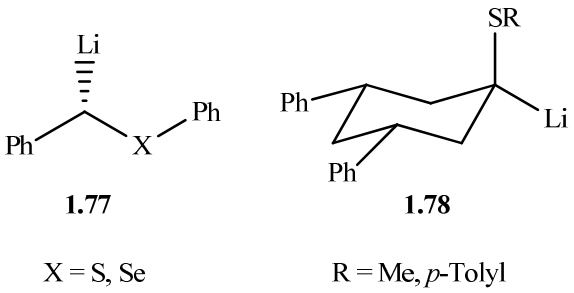
1.75 **1.76**

Figure 1.18. *α*-Thioalkyllithiums undergoing intramolecular reactions

Other examples of carbanions microscopically configurationally stable on the timescale of reaction with an electrophile are equatorially lithiated sulfides prepared by Reich and Bowe **1.76** (Figure 1.18). They found that *α*-thio- and *α*-selenocyclohexyllithiums demonstrate strong stereoelectronic preference for the axially lithiated species. Therefore, the equatorially lithiated species isomerized quickly to the more axially stable form, which was trapped with electrophiles (Me_3SiCl, $EtCO_2H$, Ph_2Se_2, Me_2SO_4).[88]

Hoffmann et al. investigated the configurational stability of sulfur and selenium-substituted benzyllithiums **1.77**. They enantiomerized faster than they added to the electrophile.[90] *α*-

Thiocyclohexyllithiums **1.78** studied by Reich did not demonstrate configurational stability either (Figure 1.19).[88]

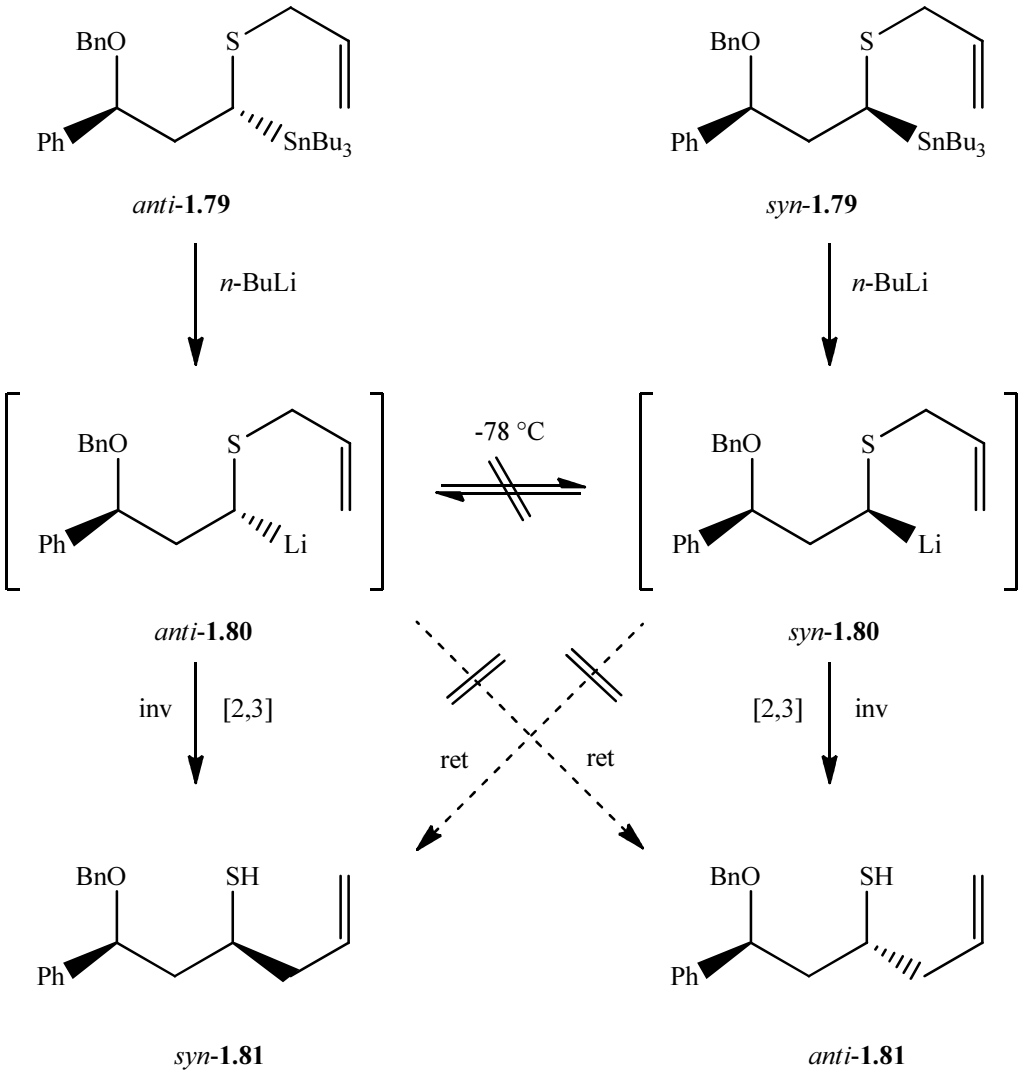


1.77 **1.78**

X = S, Se R = Me, *p*-Tolyl

Figure 1.19. Sulfur and selenium-substituted organolithiums

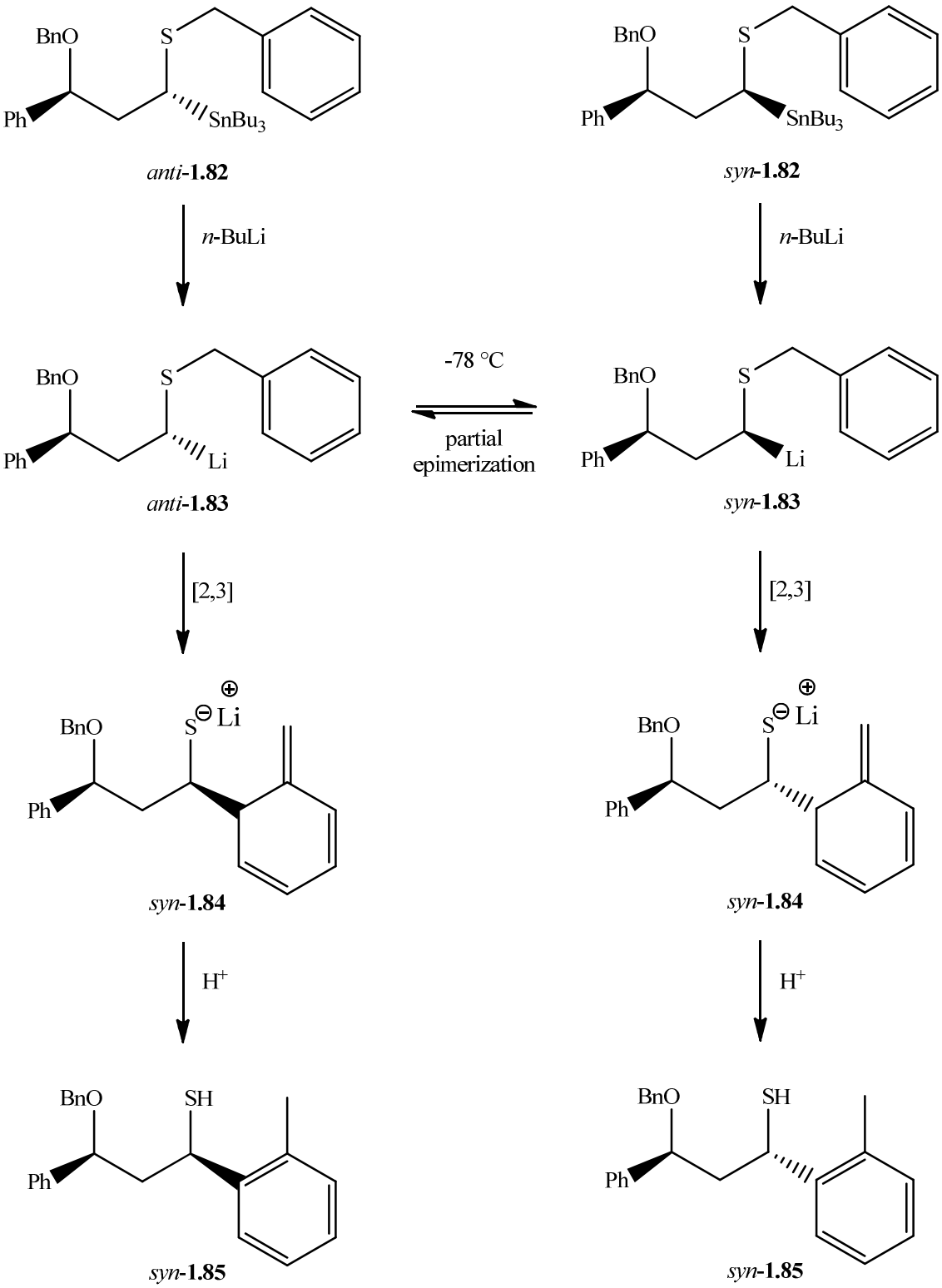
The configurational stability of some lithiated sulfides reported by Reich and Ritter encouraged Brickmann to investigate their stability on the timescale of their rearrangement, not on the timescale of their addition of an electrophile. He proved that the *α*-lithiosulfides **1.80** are configurationally stable for their short life-time until they rearrange. The [2,3]-thia-Wittig rearrangement induced by destannylative lithiation was stereospecific and proceeded with inversion of configuration at the carbanionic center. The [2,3]-thia-rearrangement was found to be identical to the [2,3]-oxa-rearrangement as far as geometry of the carbanion is concerned.[91] The competitive [1,2]-rearrangement did not occur. Brickmanm performed the test with two pairs of isomeric compounds, the diastereomers *anti* and *syn*-**1.79** and *anti* and *syn*-**1.82**. The first ones, *α*-lithiosulfides *anti*- and *syn*-**1.80**, were generated by tin-lithium exchange with retention of configuration. They underwent [2,3]-rearrangements, which were stereospecific and followed an invertive course at the carbanionic center. Therefore, the *α*-allylthioalkyllithiums were microscopically configurationally stable relative to the [2,3]-thia-Wittig rearrangement (Scheme 1.16).



Scheme 1.16. Allyl-substituted α-lithiosulfides investigated by Brückner and Brickmann

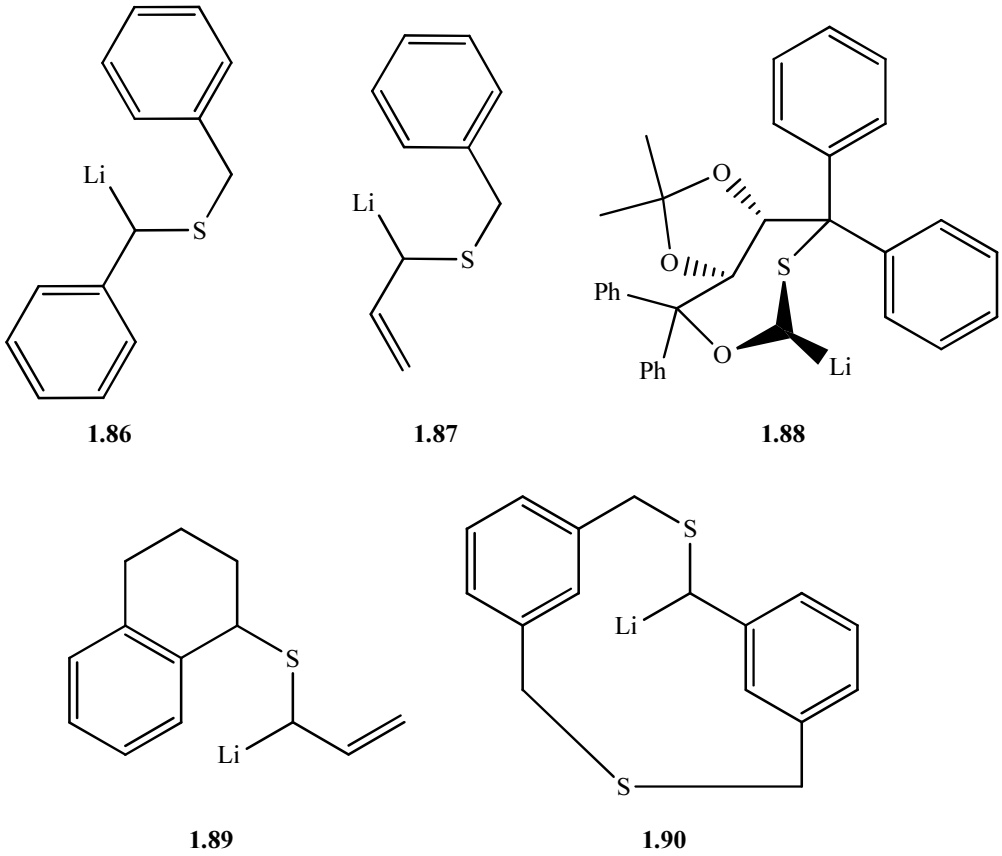
More surprising results were obtained for the α-(benzylthio)alkyllithiums *anti*- and *syn*-**1.83**, which were also generated by tin-lithium exchange and rearranged to thiolates **1.85** (Scheme 1.17). This time the rearrangements were not stereospecific and furnished two mixtures of diastereomers (71:29 for *anti*-**1.85**, 28:71 for *syn*-**1.85**). This result can be explained by the increased activation barrier for dearomatization of the phenyl ring during the [2,3]-thia-Wittig rearrangement. The rate of rearrangement was slower and the lithiosulfides *anti*- and *syn*-**1.83** had enough time to partly epimerize. Without doubts, no product indicative of a [1,2]-rearrangement was found. During the [2,3]-rearrangement of benzyl derivatives, the aromaticity of the ring is lost temporarily. This process is unfavorable from the thermodynamic point of view and therefore could favor the [1,2]-rearrangement. The lack of the [1,2]-shift can be explained by a kinetic barrier. Analogous to the [1,2]-oxa

rearrangement, the rate determining step would be the dissociation of the lithiosulfide to a radicals, what evidently does not occur easily.



Scheme 1.17. Benzyl-substituted α-lithiosulfides investigated by Brückner and Brickmann

There are several studies known concerning the [2,3]-thia-Wittig rearrangement of metalloalkyl benzyl sulfides (Figure 1.20).



1.86 **1.87** **1.88**

1.89 **1.90**

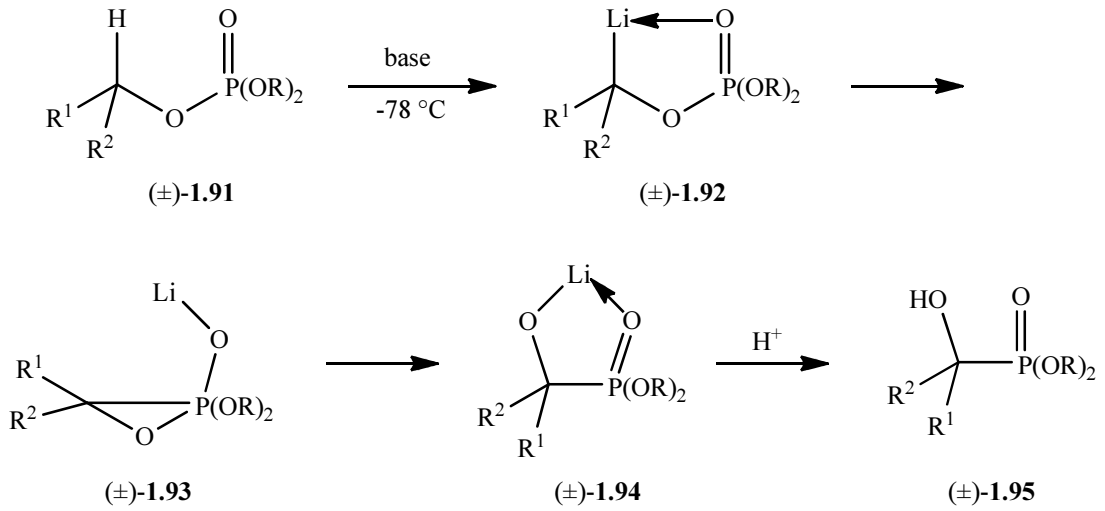
Figure 1.20. Several known metalloalkyl benzyl sulfides

In some cases the rate of the competitive [1,2]-Wittig rearrangement was higher than that of the [2,3]-rearrangement. Hauser et al. reported that lithiated disulfide **1.86** underwent either only a [2,3]-sigmatropic rearrangement or a combination of [2,3]- and [1,2]-rearrangement depending on the reaction conditions.[92,93] Biellmann found that lithiosulfide **1.87**, rearranged mainly in a [2,3] fashion, with no traces of product from the [1,2]-route, however some [4,5]-shift was observed.[94,95] Lithiosulfides **1.88**,[96] **1.89**[97] and **1.90**[95] yielded products exclusively formed by the [2,3]-rearrangement.

1.2.3.3. Phosphate-phosphonate rearrangement

Sturtz coined the term the phosphate-phosphonate rearrangement, which is an isomerization reaction[98,99] - an intramolecular [1,2]-migration of a phosphoryl group. Deprotonation of the phosphate with a strong base (i.e. *n*-BuLi, *s*-BuLi, LDA), generated a short-lived intermediate

– a dipole stabilized carbanion. To facilitate the removal of a proton, at least one substituent (R^1 or R^2) should be an electron withdrawing group such as an aryl[98-100], an alkinyl[101] or a vinyl group.[102] Hammerschmidt proved the microscopic configurational stability of the intermediate phosphinyloxy-substituted benzyllithiums.[103] It was reasoned that the intramolecular phosphorylation takes place via an oxaphosphirane **1.93**, giving a lithiated *α*-hydroxyphosphonate **1.94**. Acidic work-up yielded *α*-hydroxyphosphonate **1.95** (Scheme 1.18).[104]



Scheme 1.18. Phosphate-phosphonate rearrangement

The conversion of *α*-hydroxyphosphonates to phosphates, the phosphonate-phosphate rearrangement, was also studied thoroughly.[105] It proceeds by the reverse mechanism of the phosphate-phosphonate rearrangement. It is assumed that the isomerizations with heteroatoms such as sulfur or NBoc instead of oxygen proceed analogously.

It is well known, that breaking up the oligomers enhances the reactivity of alkyllithiums. The lithium cation coordinates to the oxygen atom of the P=O group, which induces the deaggregation of the alkyllithium base and increases the acidity of the hydrogens *α* to the oxygen atoms of the phosphate.[106] Application of tin-lithium exchange may solve the regioselectivity of deprotonation.[104] It is a smooth reaction which gives the desired product in high yield.

Configurational stability of (dialkoxyphosphinyloxy)alkyllithiums

Hammerschmidt et al. investigated the configurational stability of dipole stabilized carbanions **1.96** – **1.102** (Figure 1.21).[41,100,103,107]

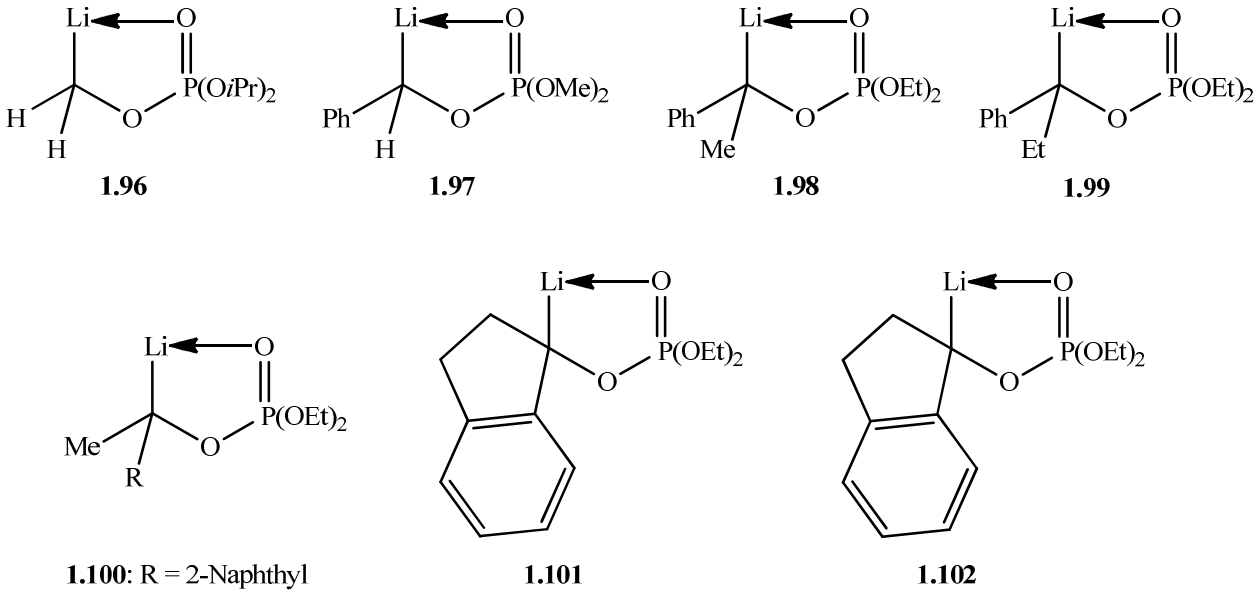


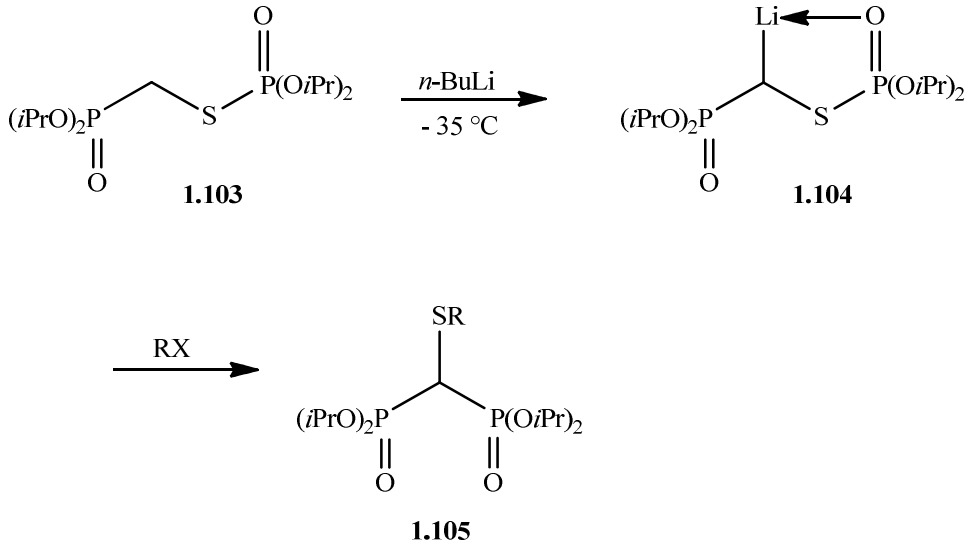
Figure 1.21. Several (dialkoxyphosphinyloxy)alkyllithiums

They found that they are microscopically configurationally stable on the timescale of the phosphate-phosphonate rearrangement, which proceeds with retention of configuration. The absolute configuration of the *α*-hydroxyphosphonate derived from **1.100** was based on a single crystal X-ray structure analysis.[103]

Thiophosphate-mercaptophosphonate rearrangement

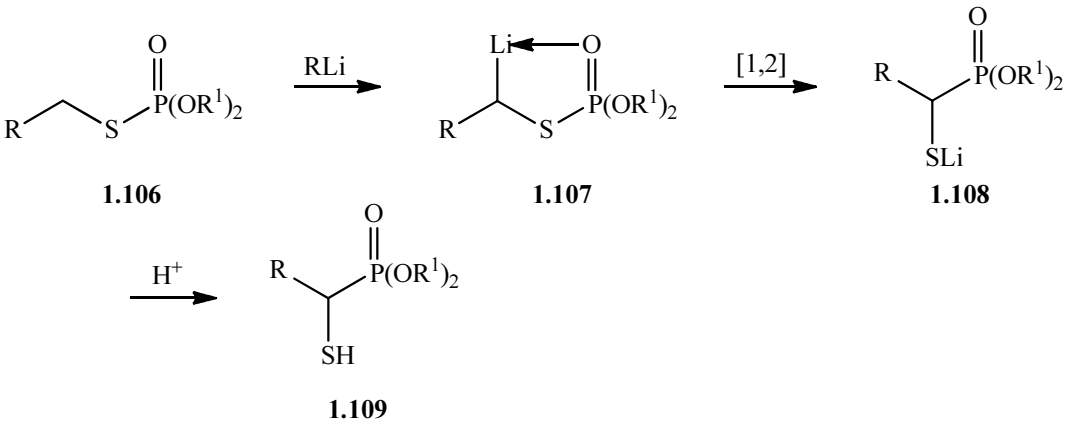
If the phosphate is replaced by an *S*-alkyl thiophosphate, metalation occurs *α* to the sulfur atom analogously to the phosphate. A short-lived (phosphinylthio)alkyllithium is formed, which isomerizes to an *α*-mercaptophosphonate (thiophosphate-mercaptophosphonate rearrangement).

α-Mercaptophosphonates are of great interest in synthetic chemistry.[108] They are potential precursors for biologically active compounds, for example the substituted phosphonates which are glutamine synthetase inhibitors.[109] Several methods for the preparation of mercaptophosphonates were already reported: phosphate-*β*-mercaptophosphonate,[110] [2,3]-sigmatropic rearrangement[111,112] and finally phosphate-*α*-mercaptophosphonate rearrangement (Scheme 1.19).



Scheme 1.19. Preparation of *α*-mercaptophosphonates via phosphate-*α*-mercaptophosphonate rearrangement

Hammerschmidt and Philippitsch studied the scope and stereoschemistry of thiophosphate-mercaptophosphonate rearrangement.[113] Surprisingly, *S*-alkyl *O*,*O*-dialkyl thiophosphates (**1.106**) were metalated by tritylllithium and lithium amides, depending on the substituent R (Scheme 1.20).



Scheme 1.20. Rearrangement of *S*-alkyl thiophosphates

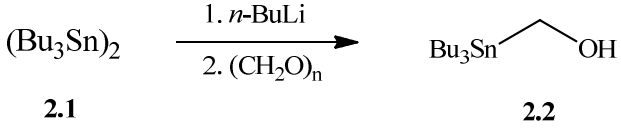
The generated α-(dialkoxyphosphinylthio)alkyllithiums are suspected to be short-lived. It was proven that these thioalkyllithiums are microscopically configurationally stable up to 0 °C.

2. Results and Discussion

2.1. Chiral bromo-[D_1]methyllithium

Hoffmann et al.[65] were the first to investigate the configurational stability of bromoalkyllithiums later followed by Kapeller,[39,47] who studied the micro- and macroscopic configurational stability of chloro- and fluoromethyllithiums. I decided to expand these investigations to bromomethyllithiums, although they were expected to be chemically more labile than the chloro analogues.

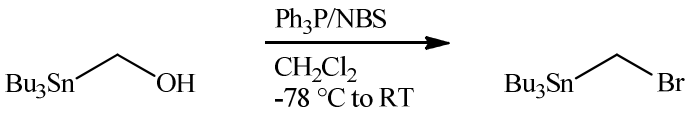
All compounds were first synthesized in the unlabeled form to find the appropriate synthesis and optimize the reaction conditions and yields. Tin-lithium exchange was considered to be the method of choice for the generation of bromomethyllithiums, as it proceeds quantitatively and with retention of configuration. Because of this, the starting materials for all examined methyllithiums were prepared from the unlabeled and labeled tributylstannylmethanols. The procedure for preparation of the unlabeled species described in the literature and already used before in our group was also used by me.[34,39] Hexabutylditin (**2.1**) was reacted with *n*-BuLi and the tributylstannyllithium formed was quenched with paraformaldehyde to give tributylstannylmethanol (**2.2**) in yields up to 70% (Scheme 2.1).



2.1 **2.2**

Scheme 2.1. Preparation of nondeuterated tributylstannylmethanol

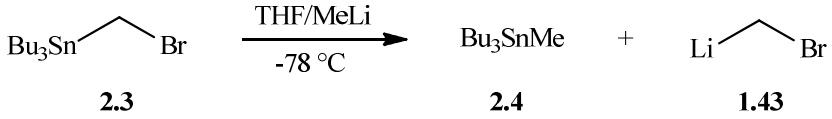
This alcohol was converted to the bromide **2.3** in very good yield (up to 90%), using a known procedure with Ph_3P/NBS[114,115] (Scheme 2.2).



2.2 **2.3**

Scheme 2.2. Synthesis of (bromomethyl)tributylstannane

The ease of transmetalation of (bromomethyl)tributylstannane was experimentally tested (Scheme 2.3).

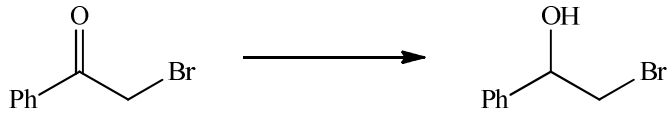


2.3 **2.4** **1.43**

Scheme 2.3. Determination of ease of transmetalation

(Bromomethyl)tributylstannane was transmetalated at –78 °C and the reaction was quenched with trifluoroacetic acid 30 seconds after the addition of the 1 M MeLi. The ^{1}H NMR spectrum of the crude product revealed, that it was virtually homogenous tributylmethylstannane containing no recovered starting material. This experiment demonstrated that the bromomethyltributylstannane can be easily transmetalated quantitatively within 30 seconds or even less.

I planned to intercept the bromomethyllithiums with benzaldehyde. Therefore, I decided to prepare racemic and chiral, nonracemic bromohydrine as reference compounds. The reduction of ω-bromoacetophenone with various reagents gave racemic as well as optically active bromohydrines (Scheme 2.4).

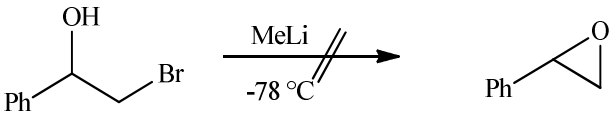


2.5 **2.6**

Scheme 2.4. Preparation of bromohydrine

The racemic product was obtained either using BH_3•THF or DIBAH as a reductant, the latter giving a better yield (59%).[116] To obtain the optically active bromohydrine ω-bromoacetophenone was enantioselectively reduced with (+)-DIP chloride. The yield was low (26%) and the ee as determined by ^{1}H NMR spectroscopy of the corresponding (*R*)-Mosher ester was 94%, whereas ee based on the optical rotation from literature was 92%.[117]

As I wanted to isolate the bromohydrine from the reaction of methyllithium with benzaldehyde, I tested its stability towards formation of oxirane, a well-known reaction (Scheme 2.5).



2.6 **2.7**

Scheme 2.5. Test of stability of lithium alkoxide

The bromohydrine is more polar than the phenyloxirane, which facilitates isolation without losses. Furthermore, the ee of the bromohydrine can be determined easily by simple derivatization with MTPACl/pyridine and recording of an ^{1}H NMR spectrum. Thus, (±)-2-bromo-1-phenylethanol was converted to the lithium alkoxide with 1 M MeLi at –78 °C in dry THF. Trifluoroacetic acid was added after 5 minutes and the reaction mixture was worked up. The crude bromohydrine did not contain phenyloxirane as demonstrated by the ^{1}H NMR spectroscopy after spiking the probe with authentic, commercially available phenyloxirane. Consequently, the lithium 2-bromoalkoxide is chemically stable at –78 °C for at least 5 minutes and does not give phenyloxirane, which could interfere with the yield of the desired bromohydrine. It is known from the literature, that oxirane formation is usually brought about by allowing the reaction mixture to warm up to room temperature.

Before I started the experiments with chiral bromomethyllithiums, I wanted to test their chemical stability with the unlabeled species. The microscopic configurational stability was evaluated when the electrophile was present on addition of the alkyllithium used for the transmetalation. Benzaldehyde was chosen as electrophile, because it reacts smoothly with organolithiums and gives products which can be isolated conveniently. An additional benefit of this choice is the fact that Kapeller also used benzaldehyde in her studies on halomethyllithiums, which allows an easy comparison of the different halomethyllithiums.[39] THF was used as a solvent because it was reported to accelerate transmetalation, particularly at low temperatures.[57] Transmetalation was performed with 1 M MeLi (4 equiv. relative to stannane), which was added dropwise to a solution of bromomethylstannane and benzaldehyde (4 equiv. relative to stannane) in dry THF at –78 °C. The reaction mixture was stirred for 5 minutes and then quenched with trifluoroacetic acid. The experiment was repeated, except that the reaction mixture was stirred for 15 minutes before quenching. The yields (19%) were identical for both experiments. Based on the ^{1}H NMR spectrum of the crude product, 25% of the starting material was transmetalated, of which 80% formed the bromohydrine and the missing 20% of the bromomethyllithium evidently decomposed. 1-Phenylethanol was formed as a side product to tin-lithium exchange in considerable amounts.

This finding proved that the addition of MeLi to benzaldehyde was faster than tin-lithium exchange with the stannane. To change the relative rates, I replaced benzaldehyde by less reactive aldehydes such as 4-methoxy- or 4-methylbenzaldehyde and even a ketone such as acetophenone. Unfortunately none of these electrophiles gave better yields than benzaldehyde (Table 2).

Entry	Electrophile	Yield (%)
1	Benzaldehyde	18
2	4-Methoxybenzaldehyde	0
3	4-Methylbenzaldehyde	0
4	Acetophenone	13

All entries performed in THF at –78 °C

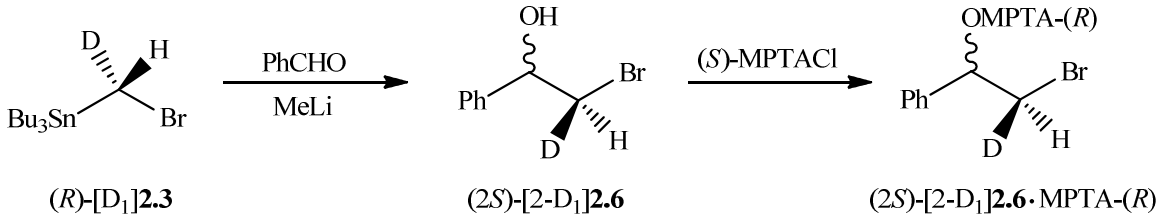
Table 2. Testing the reactivity of electrophiles

Surprisingly, no bromohydrines were isolated in case of the substituted benzaldehydes. Although acetophenone gave a bromohydrine, it is a tertiary alcohol which cannot be easily derivatized with Mosher chloride. The reaction mixture had to be stirred at 50 °C for 12 hours in dioxane compared to secondary alcohols in CH_2Cl_2 at room temperature to enforce esterification. Even then the yield of the ester was low. Consequently, benzaldehyde was the preferred electrophile, although in some cases acetophenone was used as an alternative.

The synthesis of the chirally deuterated stannylmethanols was previously elaborated and described by Kapeller.[39] In short, two diastereomeric boronates were prepared from a stannylmethyl carbamate by borylation and separated by flash column chromatography. The desired alcohols were obtained by reduction with $LiBEt_3D$ and then oxidation of the stannylmethylboronates with hydrogen peroxide in a biphasic system of THF and sodium hydroxide (3.44 M). The configurations of the chirally deuterated tributylstannylmethanols were deduced from the configuration of the corresponding boronates. It was assumed that reductive removal of the carbamoyloxy group proceeded with inversion and the oxidative cleavage of the B-C bond with retention of configuration. Thus (*R*)- and (*S*)-boronate gave (*R*)- and (*S*)-tributylstannyl-[D_1]methanol, respectively. I optimized the reaction conditions for the oxidation step by reducing the amount of solvent from 15 ml to 5 ml for 1 mmol of substrate. Additionally the flash column chromatography of the crude alcohols was performed with cold (3 °C) eluent, which increased the yield.

With good yields in hand for the conversion of the unlabeled stannylmethanol to the corresponding bromide, I repeated the experiment with deuterated stannylmethanol. Although the yield was very good, the ee of the (bromomethyl)tributylstannane was unfortunately unknown.

This deuterated (*R*)-bromomethylstannane was transmetalated in THF with MeLi (1 M in cumene/THF) in the presence of benzaldehyde at –78 °C (Scheme 2.6).



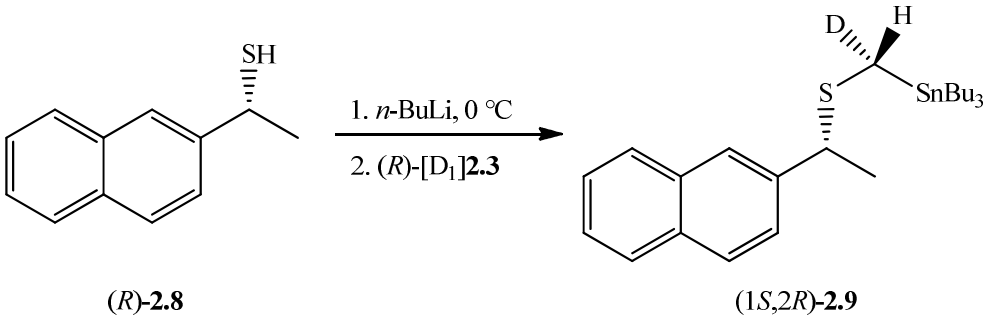
(*R*)-[D$_1$]**2.3** (2*S*)-[2-D$_1$]**2.6** (2*S*)-[2-D$_1$]**2.6**·MPTA-(*R*)

Scheme 2.6. Microscopic configurational stability test of bromo-[D$_1$]methyllithium

The bromohydrine (2*S*)-[2-D$_1$]**2.3** was obtained in poor yield (11%) with an ee of 57% at C-2, determined by ^{1}H NMR spectroscopy of the corresponding (*R*)-Mosher ester. **For convenience, only the ee for the deuterium-bearing carbon atom is given here and throughout the PhD thesis, although the deuterated bromohydrine has two stereogenic centers.** That at C-1 is racemic, as the addition of chiral bromomethyllithium is not diastereoselective. Evidently, the intermediate chiral bromomethyllithium was not microscopically configurationally stable, but enantiomerized partly. The low yield was attributed to the chemical lability of bromomethyllithium and incomplete transmetalation. Bromomethylstannane could be detected in the crude product, indicating that the addition of MeLi to benzaldehyde was faster than transmetalation. The identical enantiomeric excess (57 and 56%) of the both diastereomeric Mosher esters made me very suspicious. Alternatively, it was possible that the starting deuterated bromomethylstannane was not enantiomerically pure as initially assumed. It could easily have had an ee of about 60%, which would result in the same ee at C-2 of the bromohydrine if the chiral bromomethyllithium is microscopically configurationally stable.

Before conducting further experiments addressing the configurational stability of chiral bromomethyllithium, the enantiopurity of chiral (bromomethyl)tributylstannane was examined by the method used for the chloromethylstannane.[39] When the chiral chloro analogue was prepared, its ee was determined independently by derivatization with a homochiral thiol and investigating the formed sulfide by ^{1}H NMR spectroscopy. The lithium

salt of homochiral thiol (*R*)-**2.8** was reacted with the bromo-[D_1]methylstannane to very likely diastereomeric sulfides (Scheme 2.7).

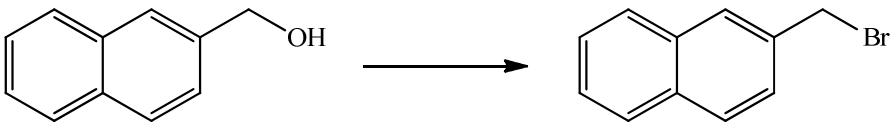


(*R*)-**2.8** (1*S*,2*R*)-**2.9**

Scheme 2.7. Investigation of the enantiopurity of (*R*)-[D_1]**2.3**

As their ratio was found to be 80:20 (by ^{1}H NMR spectroscopy), the ee of the underlying bromo-[D_1]methylstannane was 60%, assuming no deterioration of ee during the S_N2-reaction with the thiol. But bromide ions liberated by substitution are unlikely to be good competing nucleophiles compared to thiolate, which would give partial racemization of the starting bromide. Therefore, the low ee of chiral bromomethylstannane in the experiment with NBS/Ph_3P can be explained by the fact that bromide ions present in the reaction mixture may react with the already generated bromomethylstannane. This unfavorable reaction proceeds by an S_N2 mechanism, causing inversion of configuration. Unsatisfied with this result, I had to look for a better method of replacing the hydroxyl group of deuterated stannylmethanol stereospecifically.

Several methods and various reaction conditions were studied to find the best way to obtain enantiomerically pure bromo-[D_1]methylstannane. For convenience, the procedure was optimized with 2-naphthylmethanol instead of tributylstannylmethanol (Scheme 2.8).



2.10 **2.11**

Scheme 2.8. Optimization of bromide synthesis from primary alcohol

Apart from the entry with NBS, the approaches were based on modified Mitsunobu reactions (Table 3). The reaction with NBS was performed to have a reference reaction and to obtain a reference sample of bromide **2.11**.

Entry	Reagent	Solvent	Temp. (°C)	RBr/ROH[a]	Yield (%)
1	NBS/Ph_3P	CH_2Cl_2	-78	-	99
2	C_2H_5Br/Ph_3P/DIAD	Toluene	-20 → 0	1.68	63
3	C_2H_5Br/Ph_3P/DIAD	CH_2Cl_2	-50 → RT	0.31	24
4	C_2H_5Br/Ph_3P/DIAD	Toluene/CH_2Cl_2 = 2:1	-20 → RT	-	0
5	C_2H_5Br/Ph_3P/DIAD	THF	-20	0.15	13
6	C_2H_5Br/Ph_3P/DTBAD	Toluene	0 → RT	1.86	65
7	Ph_3PHBr/Ph_3P/DIAD	Toluene[b]	0	1.79	53
8	Ph_3PHBr/Ph_3P/DIAD	Toluene[c]	0 → RT	4.73	83

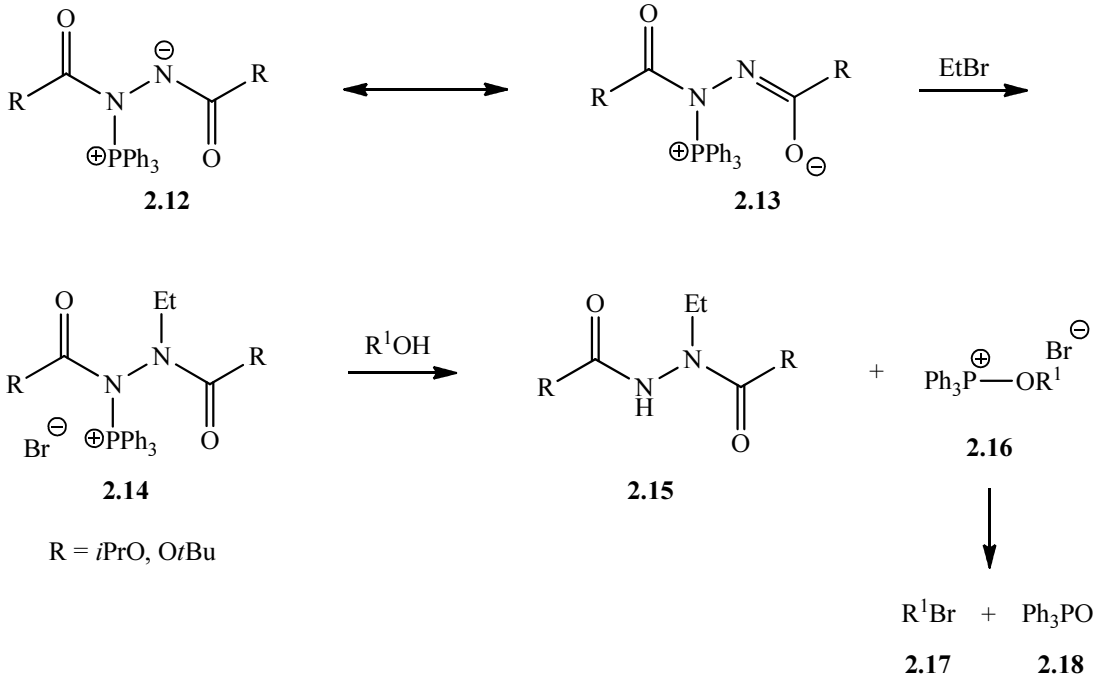
[a] molecular ratio based on ^1H NMR

[b] 5 ml of solvent for 1 mmol of substrate

[c] 4 ml of solvent for 1 mmol of substrate

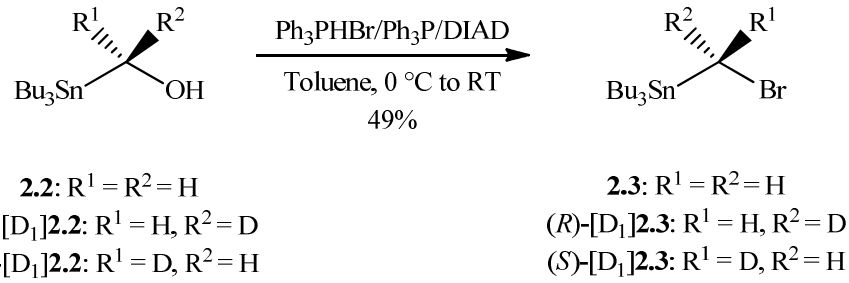
Table 3. Preparation of bromomethylnapthaline: conditions and results

When C_2H_5Br was used as bromide source, it was assumed that the enolate ion **2.13** would be alkylated at nitrogen with release of bromide ions and give **2.14**. This could react with the alcohol in the known way to give alkyl bromide and *N*-ethyl hydrazo ester (Scheme 2.9).



Scheme 2.9. Mechanism of the Mitsunobu reaction with C_2H_5Br (entries 2-6, Table 3)

Unexpectedly, the yield was good only in toluene, but could not be improved. Finally, solid and commercially available Ph_3P•HBr was selected as bromide ion source for the Mitsunobu reaction in combination with toluene as solvent (entries 7 and 8). The best yield for 2-naphthylmethanol was 83%. With tributylstannylmethanol as a substrate, the best obtained yield was only 49% (Scheme 2.10).



2.2: $R^1 = R^2 = H$
(*S*)-[D_1]**2.2**: $R^1 = H$, $R^2 = D$
(*R*)-[D_1]**2.2**: $R^1 = D$, $R^2 = H$

2.3: $R^1 = R^2 = H$
(*R*)-[D_1]**2.3**: $R^1 = H$, $R^2 = D$
(*S*)-[D_1]**2.3**: $R^1 = D$, $R^2 = H$

Scheme 2.10. Preparation of chiral (bromomethyl)tributylstannane

Again the experiment with the unlabeled tributylstannylmethanol did not cause any problems, but the ee of deuterated product was still too low (62%). The first experiment was performed at 0 °C with the reaction time of 90 minutes, analogously to the one with the unlabeled compound (entry 1). Lowering the temperature for the reaction itself, applying the reaction mixture to silica gel column without prior work-up and also lowering the temperature of the eluent to 3 °C increased the ee of the bromomethylstannane. Therefore, the final experiments (entries 3-5, Table 4) were carried out in the cold room (3 °C) using a precooled eluent (3 °C). When the reaction was performed at –25 °C and the flash column chromatography in the cold room, the ee of the bromide reached a value of ≥99% (entry 5, Table 4). Unfortunately, the yield was only 35% but tolerated, as the high ee mattered more.

Entry	Substrate/ Product[a]	Temp. (°C)	Yield (%)	ee (%)
1	(*S*)-**2.2**/(*R*)-**2.3**	0	77	62
2	(*S*)-**2.2**/(*R*)-**2.3**	0	62	77
3[b]	(*R*)-**2.2**/(*S*)-**2.3**	0	48	74
4[b]	(*R*)-**2.2**/(*S*)-**2.3**	−10	45	94
5[b]	(*R*)-**2.2**/(*S*)-**2.3**	−25	35	≥99

[a] Substrate and product are labeled

[b] Experiments performed in cold room (3 °C)

Table 4. Optimization of chiral (bromo-[D_1]methyl)tributylstannane synthesis: conditions and results

In the first experiment to test the microscopic configurational stability of chiral bromo-[D_1]methyllithium, MeLi was added to the stirred solution of benzaldehyde and bromomethylstannane at –78 °C at once and no bromohydrine was formed. I suppose that addition of 1 ml of warm (RT) MeLi increased the temperature of the small reaction volume and induced complete decomposition of the generated bromomethyllithium. Therefore, in the following approaches MeLi was added drop by drop every 5 seconds. Moreover, because the 1 M solution of MeLi in cumene/THF used for the first two experiments was not commercially available any more, the 3 M solution in dimethoxymethane was bought and diluted with THF to obtain a 1 M solution. Experiments, in which the 3 M solution of MeLi was used for tin-lithium exchange yielded no or only traces of product.

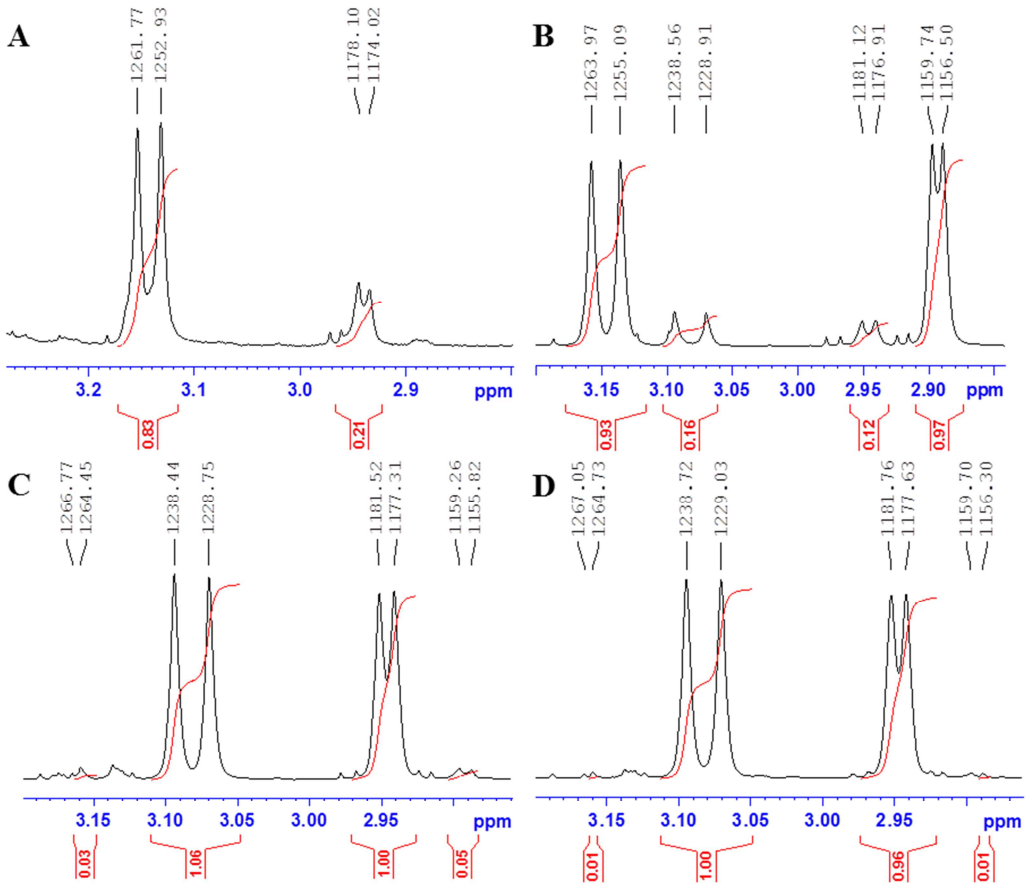
After having optimized all procedures, I could start to test the microscopic configurational stability of chiral bromo-[D_1]methyllithium. Several experiments were conducted at –78 and –95 °C, with benzaldehyde and acetophenone as electrophiles and bromo-[D_1]methylstannanes prepared using different procedures (Table 5).

Entry	Electrophile	Temp. (°C)	Yield (%)	Configuration/ee of [D_1]2.3 (%)	ee of [2-D_1]2.6 (%)
1	Benzaldehyde	-78	11	(*R*)/60	57
2	Benzaldehyde	-78	18	(*R*)/77	76
3	Acetophenone	-78	12	(*R*)/77	75
4[a]	Benzaldehyde	-95	0	(*S*)/74	-
5	Benzaldehyde	-78	9	(*S*)/94	93
6	Acetophenone	-95	31	(*S*)/94	93
7	Benzaldehyde	-78	14	(*S*)/≥99	≥99

[a] Transmetalation performed with undiluted 3 M MeLi in dimethoxymethane

Table 5. Transmetalation/trapping experiments with [D_1]**2.3**

The segments of ^{1}H NMR spectra of [2-D_1]**2.6**-(*R*)-MTPA for entries 1, 2, 5 and 7 are presented below. Spectrum A was recorded for the more polar diastereomeric Mosher ester obtained by preparative TLC, spectra B-D of the mixtures of the diastereomeric esters. The configurations were assigned on the basis of the (*R*)-Mosher ester of (*S*)-2-bromo-1-phenylethanol (ee 94%) prepared by enantioselective reduction with (+)-DIP-chloride. It was assumed that the addition of bromo-[D_1]methyllithium to benzaldehyde follows a retentive course in analogy to chloromethyllithium.[47]



A ee 57%, (1*S*, 2*S*)-[1-D_1]**2.6**-(*R*)-MTPA

B ee 76%, (1*S*, 2*S*)-[2-D_1]- and (1*R*, 2*S*)-[2-D_1] **2.6**-(*R*)-MTPA

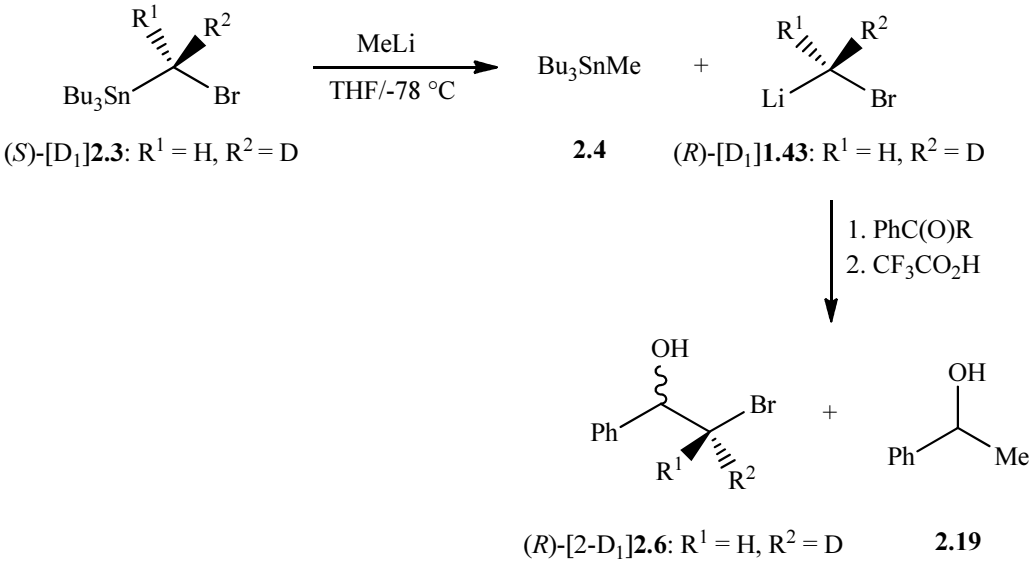
C ee 93%, (1*S*, 2*R*)-[2-D_1]- and (1*R*, 2*R*)-[2-D_1] **2.6**-(*R*)-MTPA

D ee 99%, (1*S*, 2*R*)-[2-D_1]- and (1*R*, 2*R*)-[2-D_1] **2.6**-(*R*)-MTPA

Figure 2.1. Relevant parts of ^{1}H NMR spectra (400 MHz) of [2-D_1]**2.6**-(*R*)-MTPA

The results in the Table 5 show that the ee of bromomethyllithium is always somewhat lower than that of the starting bromide irrespective of the electrophile used. However, the ee as determined by ^{1}H NMR spectroscopy could be a little too high, because the relevant signals were in a region where overlapping signals of impurities could have interfered. Surprisingly, the yield was highest for acetophenone. The first 4 experiments confirmed my assumption that the ee of the deuterated bromohydrine at C-2 depended solely on the ee of the bromo-[D_1]methylstannane. Therefore, a lot of attention was devoted to the investigation of a suitable method for the conversion of the stannyl-[D_1]methanol of 99% ee to bromo-[D_1]methylstannane of the same ee. Eventually I managed to prepare enantiopure bromide,

which was converted to labeled bromohydrine of the same ee. Therefore, chiral bromomethyllithium is microscopically configurationally stable at –78 °C on the timescale of the addition to benzaldehyde or acetophenone. Unfortunately it is chemically too labile to address its macroscopic configurational stability. The low yield for this reaction can be explained by careful inspection of the ^{1}H NMR spectrum of the crude product. For entry 7 with a yield of only 14%, I found the following ratio of products: starting material : PhCHO : bromohydrine ([D_1]**2.6)** : Bu_3SnCH_3 (**2.4**) : $PhCH(OH)CH_3$ (**2.19**) = 2.0 : 1.62 : 0.10 : 0.35 : 4.18 (Scheme 2.11).



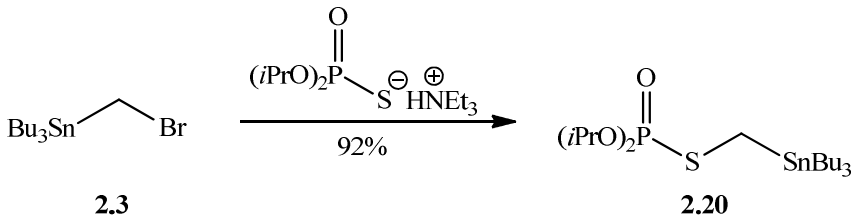
Scheme 2.11. Transmetalation/trapping experiment with (*S*)-[D_1]**2.3**

The ratio of Bu_3SnCH_3 to bromohydrine of 0.35 : 0.10 indicates that only one third of the bromomethyllithium formed by transmetalation adds to benzaldehyde and evidently two thirds decompose (possibly to LiBr and carbene). As the addition of methyllithium to benzaldehyde was faster than transmetalation, only a small amount of the (bromomethyl)tributylstannanes was consumed by tin-lithium exchange, what explains the low yields. The major portion of the starting material was recovered.

2.2. Chiral thio-[D_1]methyllithiums

2.2.1. Chiral (diisopropoxyphosphinylthio)-[D_1]methyllithium - thiophosphate-mercaptophosphonate rearrangement

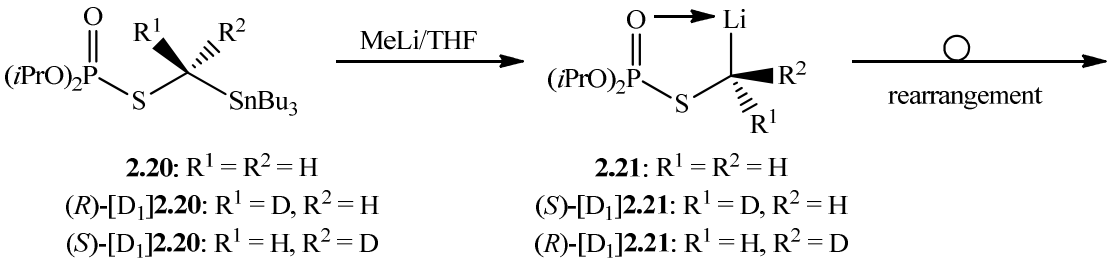
The studies on the configurational stability of thiomethyllithiums started with the synthesis of adequate stannanes as in the case of the bromomethyllithiums. The starting material for the preparation of unlabeled stannane was the already known and easily available bromomethylstannane **2.3**. It reacted smoothly with the triethylammonium salt of *O*,*O*-diisopropyl thiophosphoric acid to form the *S*-tributylstannylmethyl thiophosphate **2.20** in 92% yield (Scheme 2.12).



2.3 **2.20**

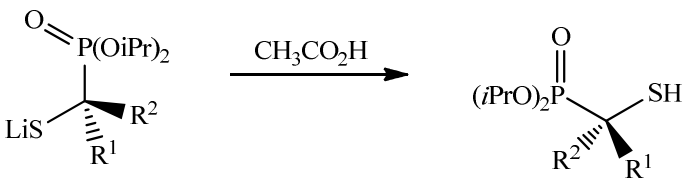
Scheme 2.12. Preparation of nondeuterated stannane precursor

The stananne was transmetalated with MeLi, generating (phosphinylthio)methyllithium **2.21**, which underwent a thiophosphate-mercaptophosphonate rearrangement characterized by the migration of the phosphinyl group from the sulfur to the carbon atom (Scheme 2.13).



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

2.21: $R^1 = R^2 = H$
(*S*)-[D_1]**2.21**: $R^1 = D$, $R^2 = H$
(*R*)-[D_1]**2.21**: $R^1 = H$, $R^2 = D$



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

2.23: $R^1 = R^2 = H$
(*S*)-[D_1]**2.23**: $R^1 = D$, $R^2 = H$
(*R*)-[D_1]**2.23**: $R^1 = H$, $R^2 = D$

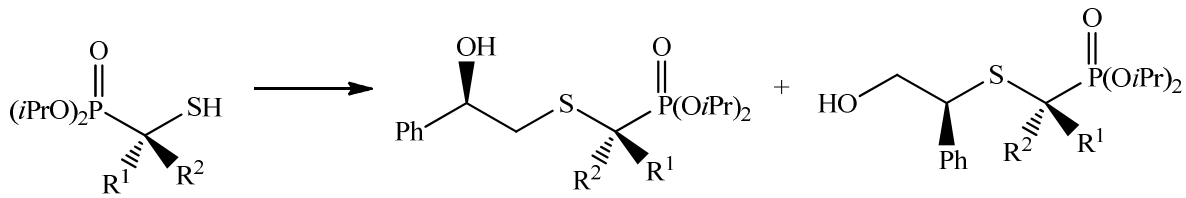
Scheme 2.13. Thiophosphate-mercaptophosphonate rearrangement of **2.20**

Two minutes after the addition of MeLi, acetic acid was added. Extractive work-up and flash column chromatography gave mercaptomethylphosphonate **2.23** in 60% yield. Two experiments were performed; one at –78 °C adding the MeLi at a rate of one drop every 3 seconds and the second one at 0 °C adding MeLi drop by drop every second. Even though the yield at 0 °C was only half of that at –78 °C, it was sufficient for the evaluation of the configurational stability of the intermediate thiomethyllithium (Table 6).

Entry	Temp. (°C)	Time (min)	Yield (%)
1	–78	2	60
2	0	1	33

Table 6. Transmetalation/trapping with nondeuterated series

Finally, an appropriate homochiral derivatizing agent for mercaptomethylphosphonate, which would give an AB system in the ^{1}H NMR spectrum for the SCH_2P group and which would thus allow ee determination in the labeled series had to be found. The thiol was reacted with (*R*)-phenyloxirane and gave two diastereomers, which could be easily separated by flash column chromatography (Scheme 2.14). Luckily, the ^{1}H NMR spectra of both derivatives displayed nice ABX systems (X = P) for the SCH_2P group.



2.23: $R^1 = R^2 = H$
(*R*)-[D_1]**2.23**: $R^1 = D$, $R^2 = H$
(*S*)-[D_1]**2.23**: $R^1 = H$, $R^2 = D$

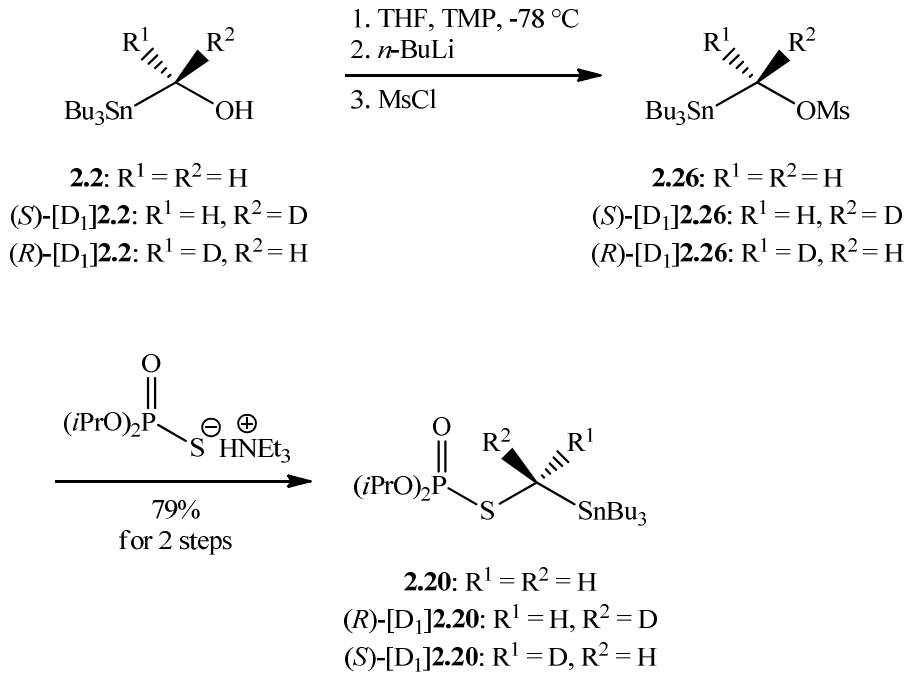
2.24: $R^1 = R^2 = H$
(*R*)-[D_1]**2.24**: $R^1 = D$, $R^2 = H$
(*S*)-[D_1]**2.24**: $R^1 = H$, $R^2 = D$

2.25: $R^1 = R^2 = H$
(*R*)-[D_1]**2.25**: $R^1 = D$, $R^2 = H$
(*S*)-[D_1]**2.25**: $R^1 = H$, $R^2 = D$

Scheme 2.14. Derivatization of **2.23** with (*R*)-phenyloxirane

Since the studies on the thiomethyllithiums were conducted in parallel to the bromomethyllithiums and at that time I still did not have developed the appropriate method for the synthesis of enantiopure bromomethylstannane, another route to thiophosphate [D_1]**2.20** had to be elaborated. Tributylstannylmethyl mesylate (**2.26**) previously prepared and used in our group seemed to be the best precursor for a variety of substituted thiomethylstannanes. The alcohol can be easily mesylated with very good yield, allowing the

synthesis of nondeuterated and deuterated tributylstannylmethyl thiophosphates (Scheme 2.15).



2.2: $R^1 = R^2 = H$
(*S*)-[D_1]**2.2**: $R^1 = H$, $R^2 = D$
(*R*)-[D_1]**2.2**: $R^1 = D$, $R^2 = H$

2.26: $R^1 = R^2 = H$
(*S*)-[D_1]**2.26**: $R^1 = H$, $R^2 = D$
(*R*)-[D_1]**2.26**: $R^1 = D$, $R^2 = H$

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

Scheme 2.15. Preparation of thiophosphates **2.20**

Now, the microscopic configurational stability of short-lived thiomethyllithiums [D_1]**2.21** could be addressed under various reaction conditions (Table 7).

Entry	Substrate/ Product[a]	Temp. (°C)	Time (min)	RLi	Solvent	Yield (%)	ee (%)
1	(*S*)-**2.20**/(*R*)-**2.23**	0	0.25	MeLi	THF	41	23
2	(*S*)-**2.20**/(*R*)-**2.23**	–78	1	MeLi	THF	60	62
3	(*R*)-**2.20**/(*S*)-**2.23**	–95	3	MeLi	THF	25	61
4	(*R*)-**2.20**/(*S*)-**2.23**	–95	20	MeLi[b]	THF	36	52
5	(*R*)-**2.20**/(*S*)-**2.23**	–95	3	*n*-BuLi	THF	68	52
6	(*R*)-**2.20**/(*S*)-**2.23**	–110	15	MeLi[c]	Trapp[d]	0	-
7	(*S*)-**2.20**/(*R*)-**2.23**	–95	1	MeLi[e]	Et_2O	22	77
8	(*S*)-**2.20**/(*R*)-**2.23**	0	1	MeLi	Et_2O	56	0

[a] Substrate and product are labeled.

Retention of configuration for the rearrangement is assumed

[b] 3 M MeLi in dimethoxymethane

[c] 1.6 M MeLi in Et_2O

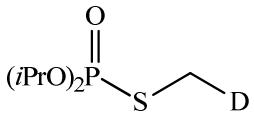
[d] THF: Et_2O:pentane = 4:1:1

[e] 1.05 Equiv. MeLi

Table 7. Transmetalation and rearrangement of [D_1]**2.20**: conditions and results

Unfortunately, no conditions could be found under which phosphinylthiomethyllithiums were configurationally stable. One can see that similar enantiomeric excesses were obtained independent of reaction time and the alkyllithium used for transmetalation at temperatures below –78 °C. The experiment performed in Et_2O gave the highest ee, but in low yield (22%, entry 7). The (phosphinylthio)methyllithium racemized completely at 0 °C in Et_2O, while it showed some modest ee in THF. In the hope to increase the ee the temperature was lowered to –110 °C, but then no product was detected. Although the Trapp mixture was used as solvent, the reaction mixture solidified hindering the stirring and stopping of the reaction.[118] This experiment was repeated several times, but only once traces of product were obtained. Because of the small amount of product, derivatization was not possible and the ee could not be determined. On the other hand *S*-deuteromethyl thiophosphate **2.27** was isolated as a side product, proving that transmetalation had occurred, but not the rearrangement (

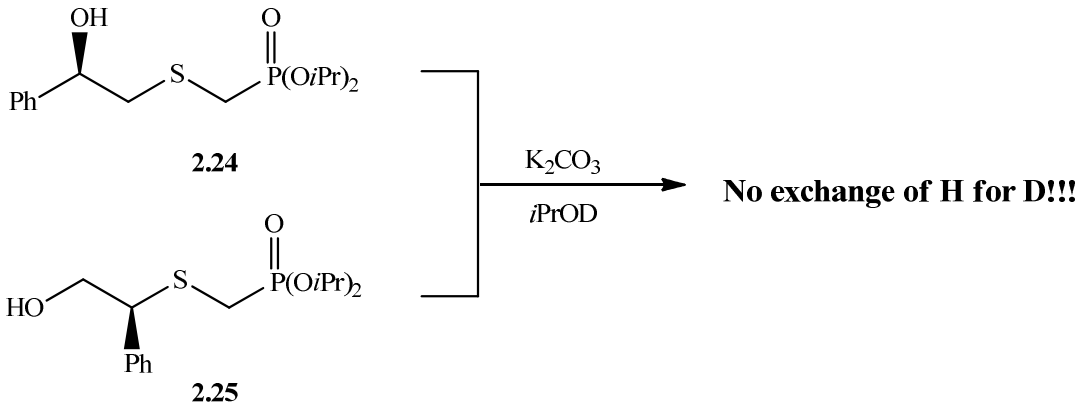
Figure **2.2**).



2.27

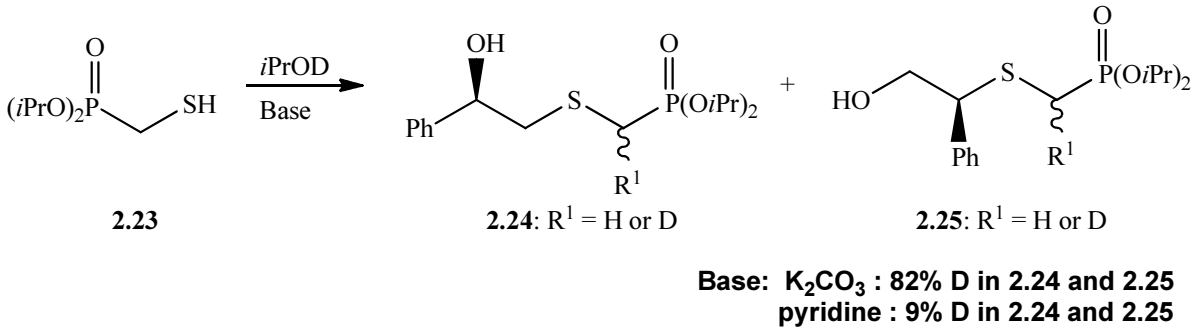
Figure 2.2. *S*-Deuteromethyl thiophosphate

To determine the ee, the method already tested in the unlabeled series with phenyloxirane, was tried. To my surprise, no deuterium was found in the products! To find out at which stage the deuterium exchange took place, some additional experiments were performed. To exclude exchange in the derivatives, their unlabeled forms were stirred with base in deuterated isopropanol for several hours. Deuterium was not incorporated into the two derivatives (Scheme 2.16).



Scheme 2.16. Investigation of the deuterium exchange in products **2.24** and **2.25**

Thus the deuterium exchange had to occur before, not after derivatization. Therefore, unlabeled **2.23** was derivatized in [D_1]isopropanol with K_2CO_3 and pyridine as bases (Scheme 2.17).



Scheme 2.17. Investigation of deuterium exchange during derivatization of mercaptomethylphosphonate **2.23**

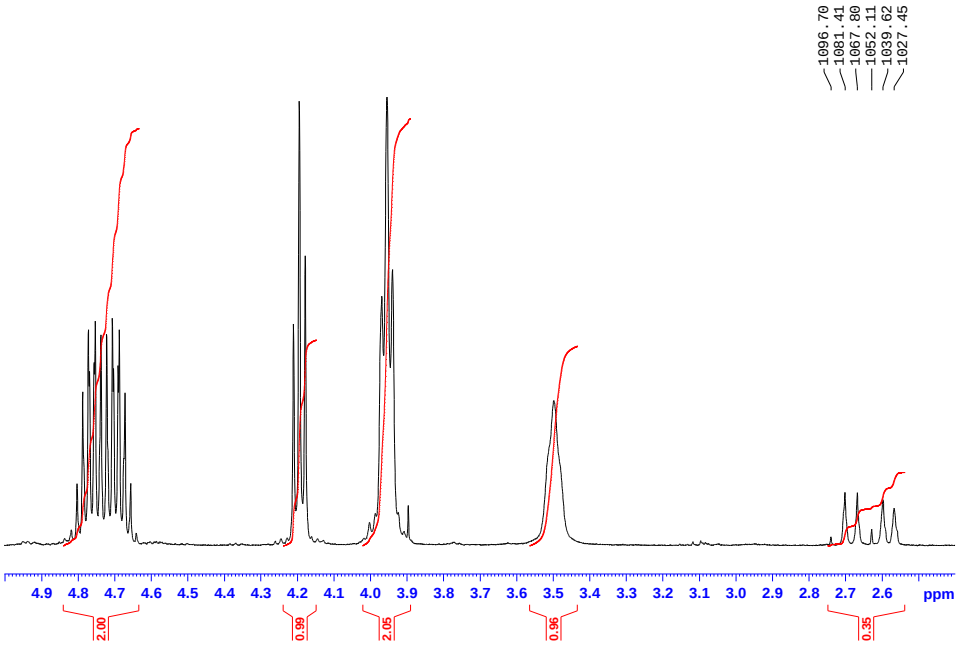


Figure 2.3. Segment of ^{1}H NMR spectrum (400 MHz) of the product **2.25** obtained in the experiment with K_2CO_3

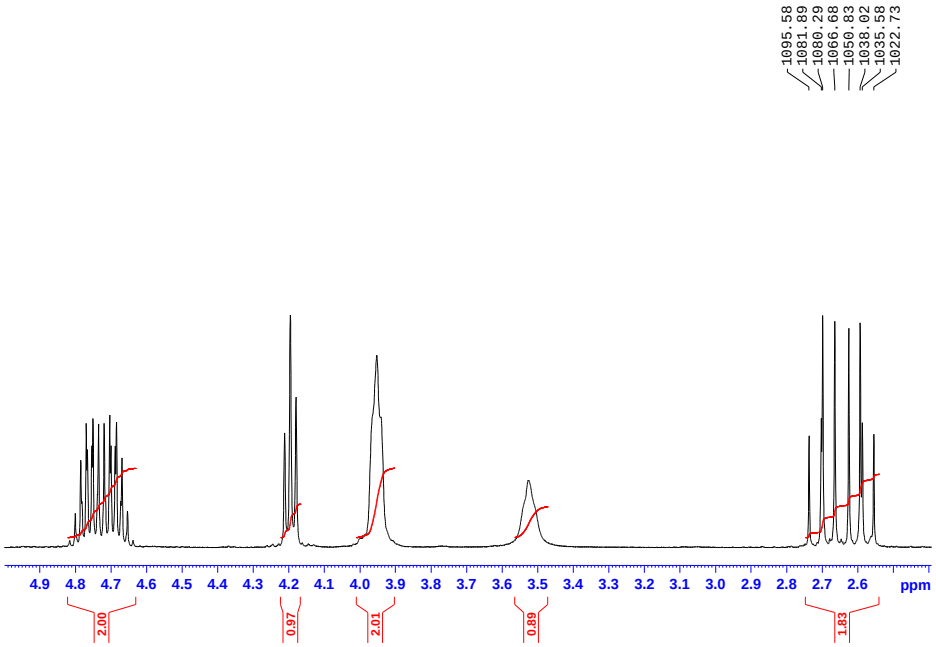
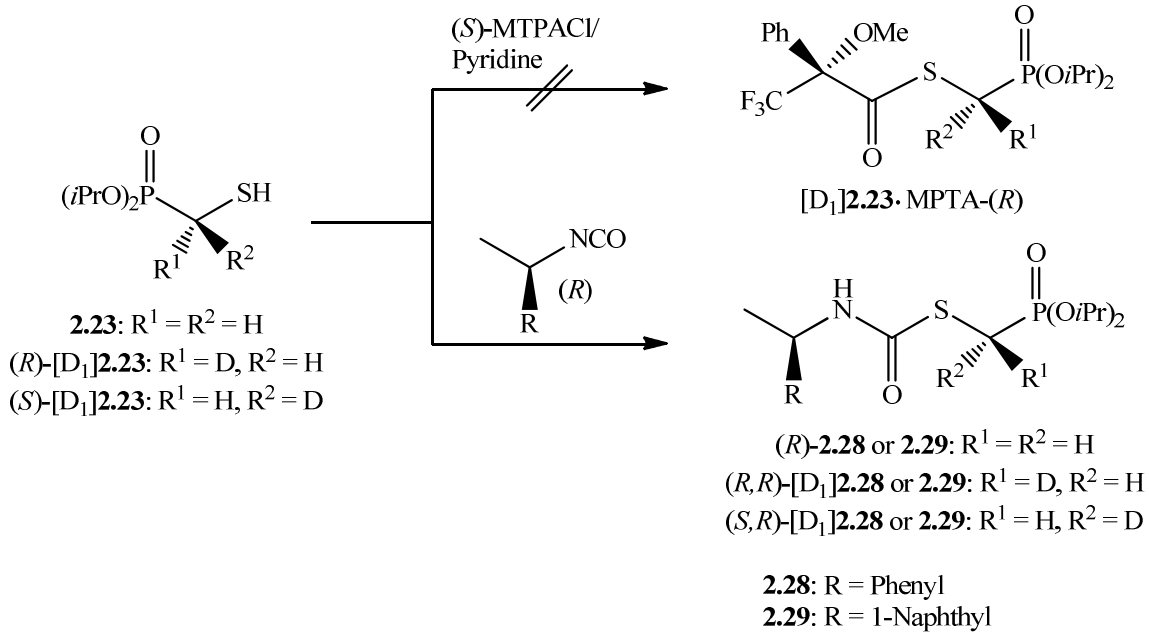


Figure 2.4. Segment of ^{1}H NMR spectrum (400 MHz) of the product **2.25** obtained in the experiment with pyridine

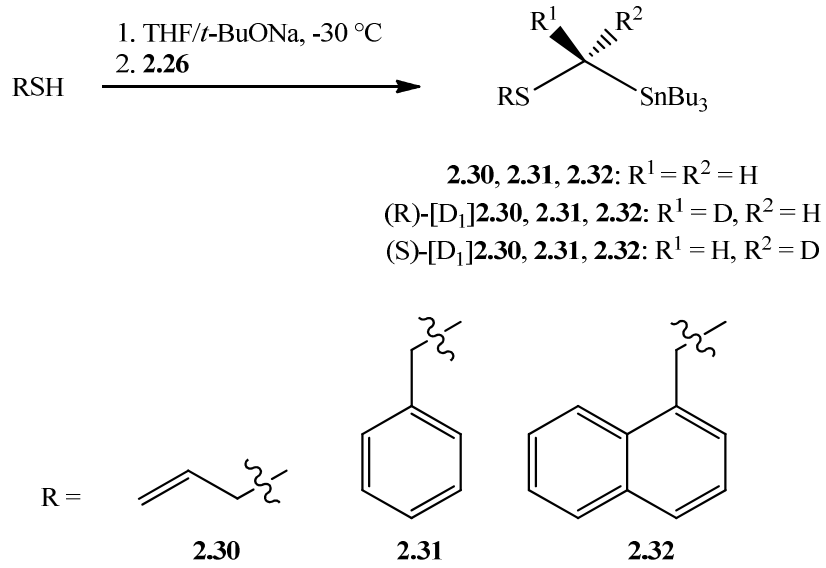
The ^{1}H NMR spectra of the isolated derivatives enabled quantification of H/D exchange. For the experiment performed with K_2CO_3 as a base, the integration for the SCH_2P group was 0.35 instead of 2.0 (Figure 2.3). It means that the exchange of protium for deuterium was high (82%). However, the H/D exchange with pyridine as base, although less basic than K_2CO_3, was significantly lowered, but still too high (9%) to be negligible. The integration for the SCH_2P group was 1.83 instead of 2.0 (Figure 2.4). These experiments revealed that the deuterium exchange occurred before derivatization and decreased by going from K_2CO_3 to the very weak base pyridine. It is unclear how a base could affect exchange of H for D in mercaptomethylphosphonate, but not in the derivatives **2.24** and **2.25**. With these findings in hand, this method for the determination of ee had to be abandoned. Popular Mosher chloride did not give a product in the reaction with mercaptomethylphosphonate for unknown reasons. Finally I tried (*R*)-(+)-1-phenylethyl and (*R*)-(–)-1-(1-naphthyl)ethyl isocyanates as chiral reagents to convert mercaptomethylphosphonate to thiocarbamates (Scheme 2.18). The latter reagent was more advantageous, as the resonances of the ABX system in the ^{1}H NMR spectrum were better separated.



Scheme 2.18. Derivatization of mercaptomethylphosphonate **2.23**

2.2.2. Chiral allylthio-[D_1]methyllithium − [2,3]-Wittig rearrangement

Allyl- and (arylmethylthio)methyllithiums were investigated for their configurational stability relative to the [2,3]-Wittig rearrangement. The three required stannanes were prepared by alkylation of sodium thiolates with stannylmethyl mesylates (Scheme 2.19).



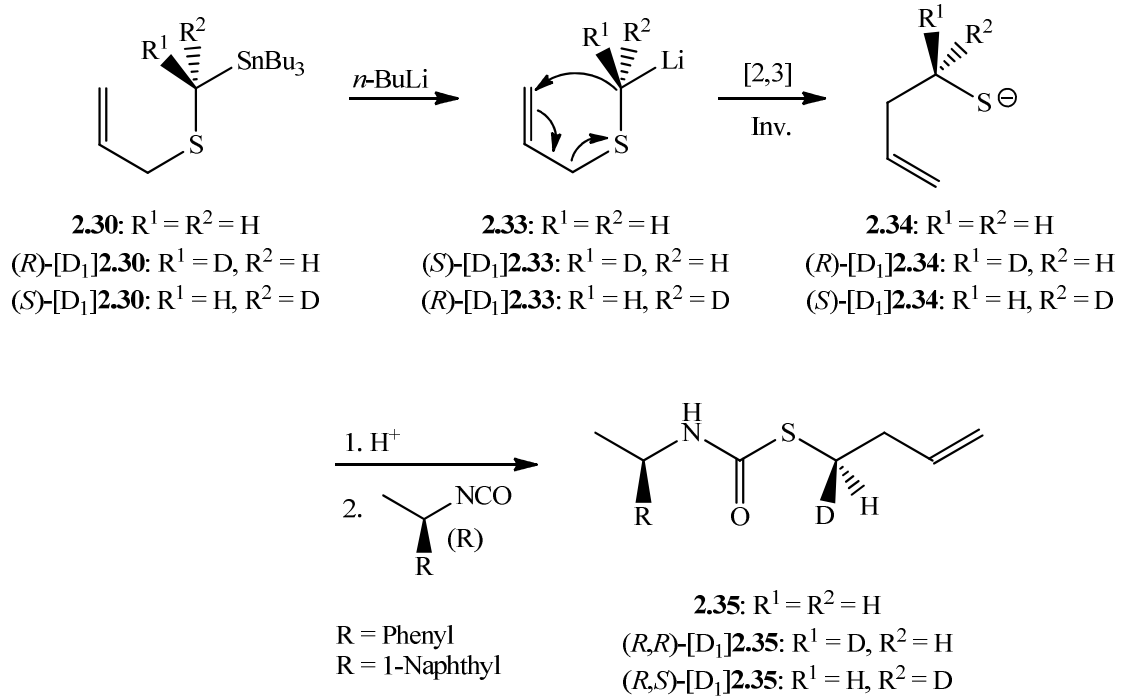
Scheme 2.19. Preparation of unlabeled thiomethylstannanes

The yields for the compounds **2.30**, **2.31**, **2.32** with a particular substituent are given in the Table 8.

Entry	Product	Yield (%)
1	**2.30**	84
2	**2.31**	92
3	**2.32**	82

Table 8. Preparation of the stannane precursors: results

At first the nondeuterated allylthiomethyllithium was prepared. The stannane **2.30** was transmetalated with excess *n*-BuLi to induce a [2,3]-sigmatropic rearrangement. Experiments in the unlabeled series revealed that transmetalation was complete. No starting material was detected after work-up. The crude product was immediately derivatized without purification because of its volatility. To determine the ee I tried (*R*)-(+)-1-phenylethyl and (*R*)-(–)-1-(1-naphthyl)ethyl isocyanate as chiral derivatizing agents. This time the former proved to be better, because the naphthyl-substituted isocyanate did not give a carbamate (Scheme 2.20).



Scheme 2.20. Rearrangement and derivatization of (allylthio-[D_1]methyl)tributylstannane **2.30**

Chiral allylthio-[D_1]methyllithium was prepared from stannane **2.30** by transmetalation to induce a [2,3]-sigmatropic rearrangement. The results with the deuterated precursors are compiled in Table 9. *n*-BuLi (1.2 eqiv.) was used for transmetalation in all cases.

Entry	Substrate/ Product[a]	Temp. (°C)	Time (min)	Solvent	Yield[b] (%)	ee (%)
1	(*S*)-**2.30**/(*S*)-**2.35**	−95	10	THF	83	≥95
2	(*S*)-**2.30**/(*S*)-**2.35**	−78	10	THF	95	91
3	(*S*)-**2.30**/(*S*)-**2.35**	−40	10	THF	99	83
4	(*S*)-**2.30**/(*S*)-**2.35**	0	3	THF	72	71
5	(*R*)-**2.30**/(*R*)-**2.35**	−78	10	Et_2O	62	50
6	(*R*)-**2.30**/(*R*)-**2.35**	0	3	Et_2O	45	20

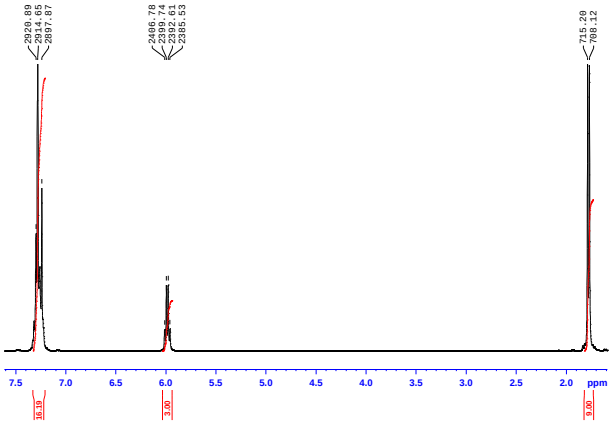
[a] Substrate and product are labeled

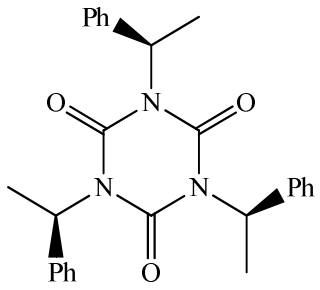
[b] Yield given for 2 steps

Table 9. Transmetalation and rearrangement of **2.30**: conditions and results

I assumed that the rearrangement proceeds with inversion of configuration at the carbanionic center as found for secondary allylthioalkyllithiums by Brückner.[91] The experiments performed in THF and Et_2O demonstrate that chiral allylthiomethyllithiums are configurationally labile and that their configurational stability increased with decreasing temperature. They were more stable in THF than Et_2O at the same temperature (entries 4 and 6, entries 2 and 5) However, they enantiomerized only very slowly at –95 °C (entry 1). In summary the chiral allylthio[D_1]methyllithiums are microscopically configurationally stable below –95 °C relative to the [2,3]-rearrangement.

Interestingly, a crystalline side product was also always isolated when the carbamate was purified by flash column chromatography. It took some time to solve the riddle which compound it was, since the ^{1}H NMR spectrum exhibited the resonances of a 1-phenylethyl group. After employing all analytical techniques I know, it turned out to be a compound **2.36** with a threefold axes of symmetry (Figure 2.5). It was formed from three molecules of isocyanate.



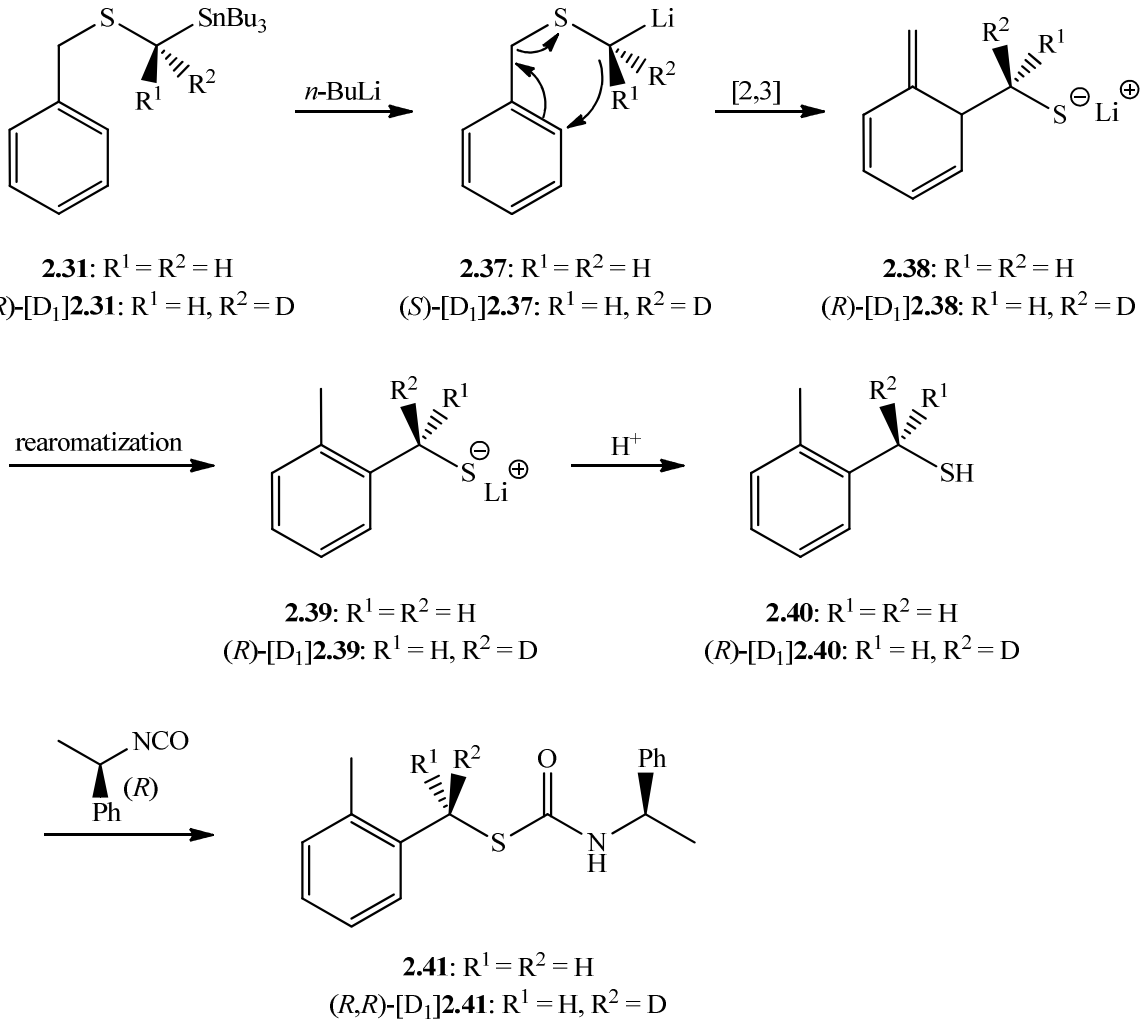


2.36

Figure 2.5. Side product **2.36** and its ^{1}H NMR spectrum

After the success with chiral allylthio-substituted [D_1]methyllithiums, I expanded the investigations to benzylthiomethyllithiums and their configurational stability. Again the microscopic configurational stability relative to the [2,3]-rearrangement was investigated. The unlabeled (benzylthiomethyl)tributylstannane was transmetalated and the thiomethyllithium **2.37** formed at –30 °C underwent a [2,3]-rearrangement. The dearomatized intermediate **2.38** was generated, which isomerized by a formal [1,3]-H-shift to the lithium 2-methylphenyl-methanethiolate (Scheme 2.21). The low boiling point of this thiol forced me to not isolate it

by flash chromatography, but instead to derivatize it with (*R*)-(+)-1-phenylethyl isocyanate immediately without purification.



Scheme 2.21. [2,3]-Rearrangement of (benzylthiomethyl)tributylsannane (**2.31**)

The experiments in the deuterated series were performed in THF, using *n*-BuLi for transmetalation (Table 10).

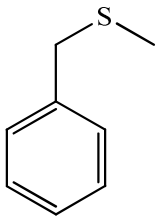
Entry	Substrate/ Product[a]	Temp. (°C)	Time (min)	Yield[b] (%)	ee (%)
1	(*R*)-**2.31**/(*R*)-**2.41**	–30	30	43	0
2	(*R*)-**2.31**/(*R*)-**2.41**	–50	25	59	0
3	(*R*)-**2.31**/(*R*)-**2.41**	–78	10	-	no [2,3] !

[a] Substrate and product are labeled

[b] Yield given for 2 steps

Table 10. Transmetalation and rearrangement of **2.31**: conditions and results

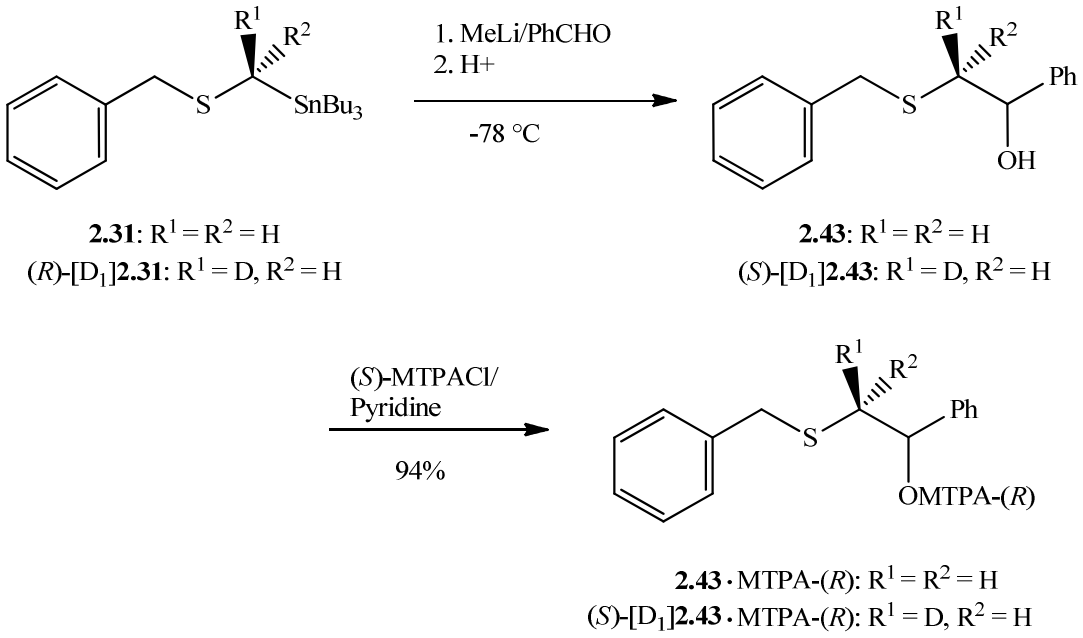
Surprisingly, benzylthio-[D_1]methyllithium rearranged down to –50 °C and gave a thiol racemic at the deuterium atom bearing carbon atom. When the reaction temperature was lowered to –78 °C, transmetalation occurred, but the [2,3]-rearrangement did not. The reaction was quenched with trifluoroacetic acid with no further work-up. The intermediate thiomethyllithium **2.37** was protonated and gave benzylmethylsulfide (**2.42**, Figure 2.6). The high activation energy needed to overcome the resonance energy of benzene ($36 \cdot kcal \cdot mol^{-1}$) blocked the [2,3]-rerrangement at –78 °C.



2.42

Figure 2.6. Benzylmethylsulfide

Inspired by these findings, I decided to study the microscopic configurational stability of benzylthiomethyllithiums relative to the addition to an electrophile. Unlabeled (benzylthiomethyl)tributylstannane was transmetalated at –78 °C for 10 minutes and after that time benzaldehyde was added (Scheme 2.22). The alcohol **2.43** was obtained in good yield and it was converted to the (*R*)-Mosher ester for the determination of the ee at the labeled carbon atom by ^{1}H NMR spectroscopy.



2.31: $R^1 = R^2 = H$
(*R*)-[D_1]**2.31**: $R^1 = D$, $R^2 = H$

2.43: $R^1 = R^2 = H$
(*S*)-[D_1]**2.43**: $R^1 = D$, $R^2 = H$

2.43 · MTPA-(*R*): $R^1 = R^2 = H$
(*S*)-[D_1]**2.43** · MTPA-(*R*): $R^1 = D$, $R^2 = H$

Scheme 2.22. Configurational stability test with **2.31**

Four experiments were performed with chirally deuterated (benzylthiomethyl)stannanes and one of them addressed the macroscopic configurational stability of thiomethyllithium. All experiments were carried out in THF using MeLi for transmetalation, because benzaldehyde was used as electrophile. The results are summarized in Table 11.

Entry	Substrate/ Product[a]	Temp (°C)	Yield (%)	ee (%)	Timescale
1	(*R*)-**2.31**/(*R*)-**2.43**	-78	72	0	macro 1 min
2	(*R*)-**2.31**/(*R*)-**2.43**	-78	24[b]	16	micro
3	(*R*)-**2.31**/(*R*)-**2.43**	-95	4[b]	21	micro
4[c]	(*R*)-**2.31**/(*R*)-**2.43**	-95	9[b]	26	micro

[a] Substrate and product are labeled

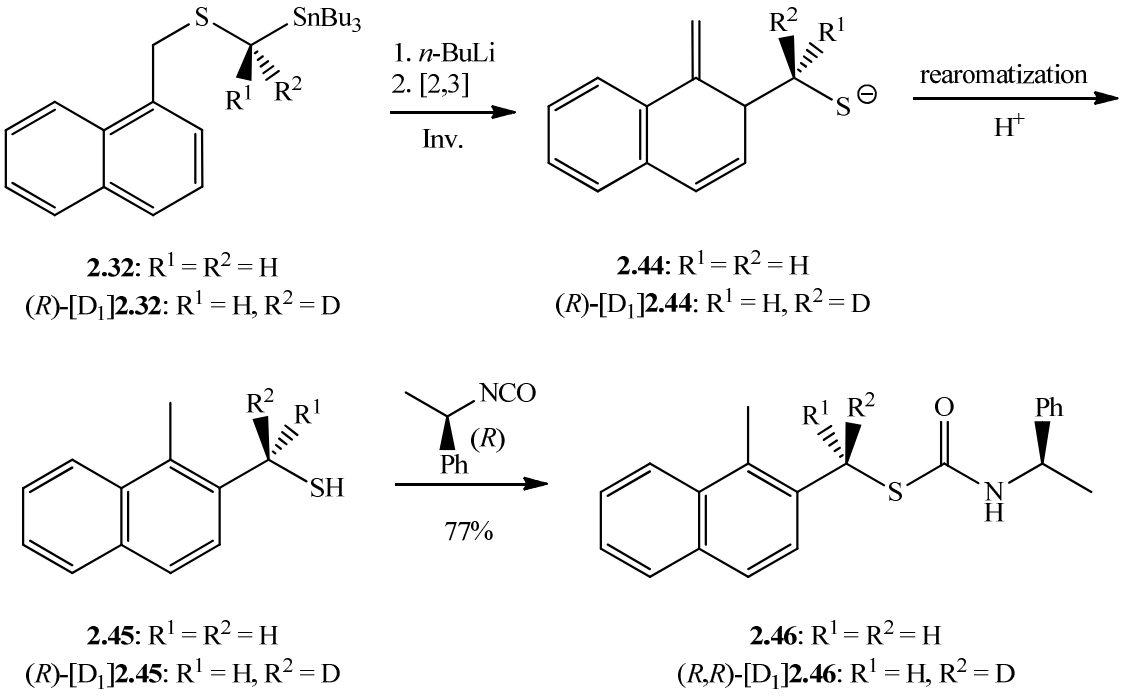
[b] Only small amount of stannane transmetalated

[c] Experiment performed with 2 equiv. of 12-crown-4

Table 11. Configurational stability test of **2.31**: conditions and results

As one can see, benzylthiomethyllithiums are microscopically configurationally unstable even at –95 °C (entries 3 and 4) and configurationally unstable on the macroscopic timescale (entry 1).

As the dearomatization of one ring of naphthalene is much more favorable than that of the benzene ring, I decided to investigate the naphthyl system as well. The protocol was similar to the previous studies on the configurational stability of benzylthiomethyllithium on the timescale of the [2,3]-rearrangement. In a preliminary experiment (1-naphthylmethylthiomethyl)tributylstannane was transmetalated at –78 °C for 10 minutes before quenching with trifluoroacetic acid. The rearrangement took place and the product was isolated in moderate yield (45%). Repetition of the experiment at –95 °C gave a similar result (Scheme 2.23).



Scheme 2.23. [2,3]-Rearrangement of (1-naphthylmethylthiomethyl)tributylstannane

For the estimation of the ee at the stereogenic center, thiol **2.45** was transformed into the thiocarbamate **2.46** with (*R*)-(+)-1-phenylethyl isocyanate. The CH_2S group displayed an AB system in the ^1H NMR spectrum, which allowed the determination of ee in the labeled series.

The [2,3]-rearrangement was assumed to follow an invertive course as for secondary *α*-thioalkyllithiums, based on the findings of Brückner.[91] The results for the deuterated series are presented below in Table 12.

Entry	Substrate/ Product[a]	Temp (°C)	Yield (%)	ee (%)
1[b]	(*R*)-**2.32**/(*R*)-**2.45**	-50	28[c]	60
2	(*R*)-**2.32**/(*R*)-**2.45**	-50	7[d]	67
3	(*R*)-**2.32**/(*R*)-**2.45**	-95	60	72

[a] Substrat and product are labeled

[b] 3 M MeLi in dimethoxymethane used for transmetalation

[c] no starting material recovered

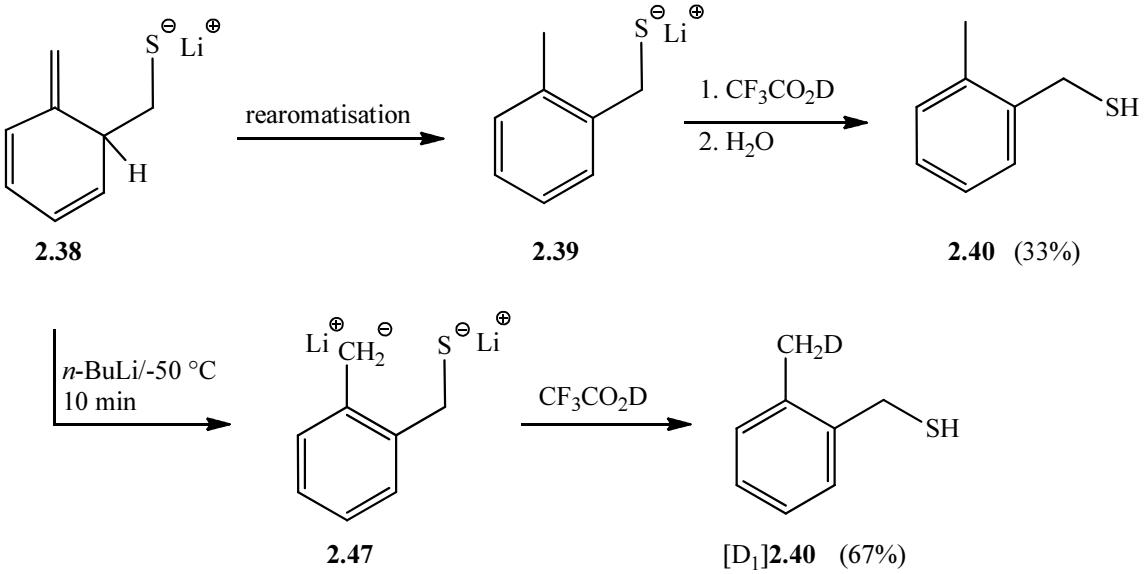
[d] 16% of starting material recovered

Table 12. Transmetalation and rearrangement of **2.32**: conditions and results

As expected 1-naphthylmethylthio-[D_1]methyllithium was found to be configurationally labile relative to the [2,3]-rearrangement. From the results it is obvious, that it is configurationally more stable than benzylthio-[D_1]methyllithium. The difference in results between benzyl and naphthyl-substituted species is probably caused by the various dearomatization energies. Rearomatization is highly exothermic and represents a strong driving force for the formal [1,3]-H-shift. The resonance stabilization energy for naphthalene is 61 kcal·mol, which is lower by 11 kcal·mol^{-1} than that for two benzene rings (2 x 36 kcal·mol^{-1}).[119] The energy of dearomatization of one ring of naphthalene will be about 25 kcal·mol^{-1} (61 kcal·mol^{-1} - 36 kcal·mol^{-1}), 11 kcal·mol^{-1} lower than for benzene with 36 kcal·mol^{-1}. Therefore the activation energy for the rearrangement of the naphthylmethylthiomethyllithium is lower than that for the phenyl analogue and it still proceeded at –95 °C, whereas the latter even did not rearrange at –78 °C.

2.3. Mechanism for formation of arylmethyllithium compounds as intermediates in [2,3]-rearrangement

When the [2,3]-rearrangements were performed, an interesting observation was made. During transmetalation of (benzylthiomethyl)tributylstannane the reaction mixture changed the color from colorless to intensive yellow. In the case of (1-naphthylmethylthiomethyl)tributylstannane the color changed to intensive red. A possible explanation for this was the formation of a conjugated organolithium, so I decided to study the mechanism of the [2,3]-thia-rearrangement in depth. Firstly, (benzylthiomethyl)tributylstannane was forced to undergo isomerization with excess of *n*-BuLi (1.5 equiv.). But this time the reaction was quenched with CF_3CO_2D instead of CF_3CO_2H. The reaction product, 2-methylphenylmethylthiol, contained a partially deuterated methyl group (67% D_1) as found by ^1H NMR spectroscopy (Scheme 2.24).



Scheme 2.24. Investigation of [2,3]-thia-rearrangement mechanism

The ^1H NMR spectrum displayed a singlet and a triplet at 2.38 and 2.37 ppm, respectively. The CH_3 group gave a singlet, whereas the CH_2D group, which was shifted to higher field, gave a triplet because of the small additional HD coupling (Figure 2.7).

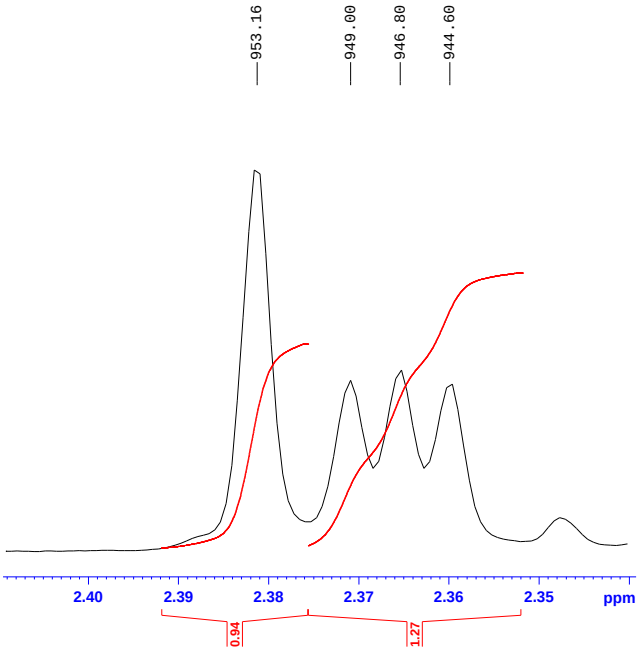
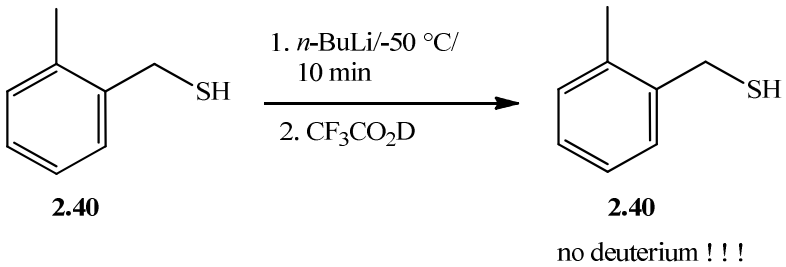


Figure 2.7. Segment of ^{1}H NMR spectrum (400 MHz) demonstrating content of deuterium in **2.40**

The integrations of the two well separated resonances (0.94 : 1.27) allowed evaluation of the ratio of the two isotopomers.

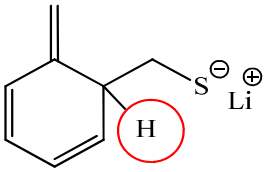
The deuterated compound could have been formed by metalation at the methyl group after rearomatization. To test this assumption, 2-methylphenylmethanethiol was stirred under the same conditions which were used for transmetalation (THF, –50 °C, 1.5 equiv. of *n*-BuLi, 10 min, then quenching with CF_3CO_2D) (Scheme 2.25). Surprisingly, the recovered starting material did not contain any deuterium.



Scheme 2.25. Investigation of deuterium exchange in **2.40**

These findings can be explained in the following way: the species formed by the [2,3]-rearrangement is the (6-methylene-2,4-cyclohexadienyl)methanethiolate **2.38**,[120] which can either rearomatize to furnish 2-methylphenylmethanthiolate **2.39** or be deprotonated at the

doubly allylic position by the excess of *n*-BuLi to produce benzyllithium **2.47** (Scheme 2.24 and Figure 2.8).

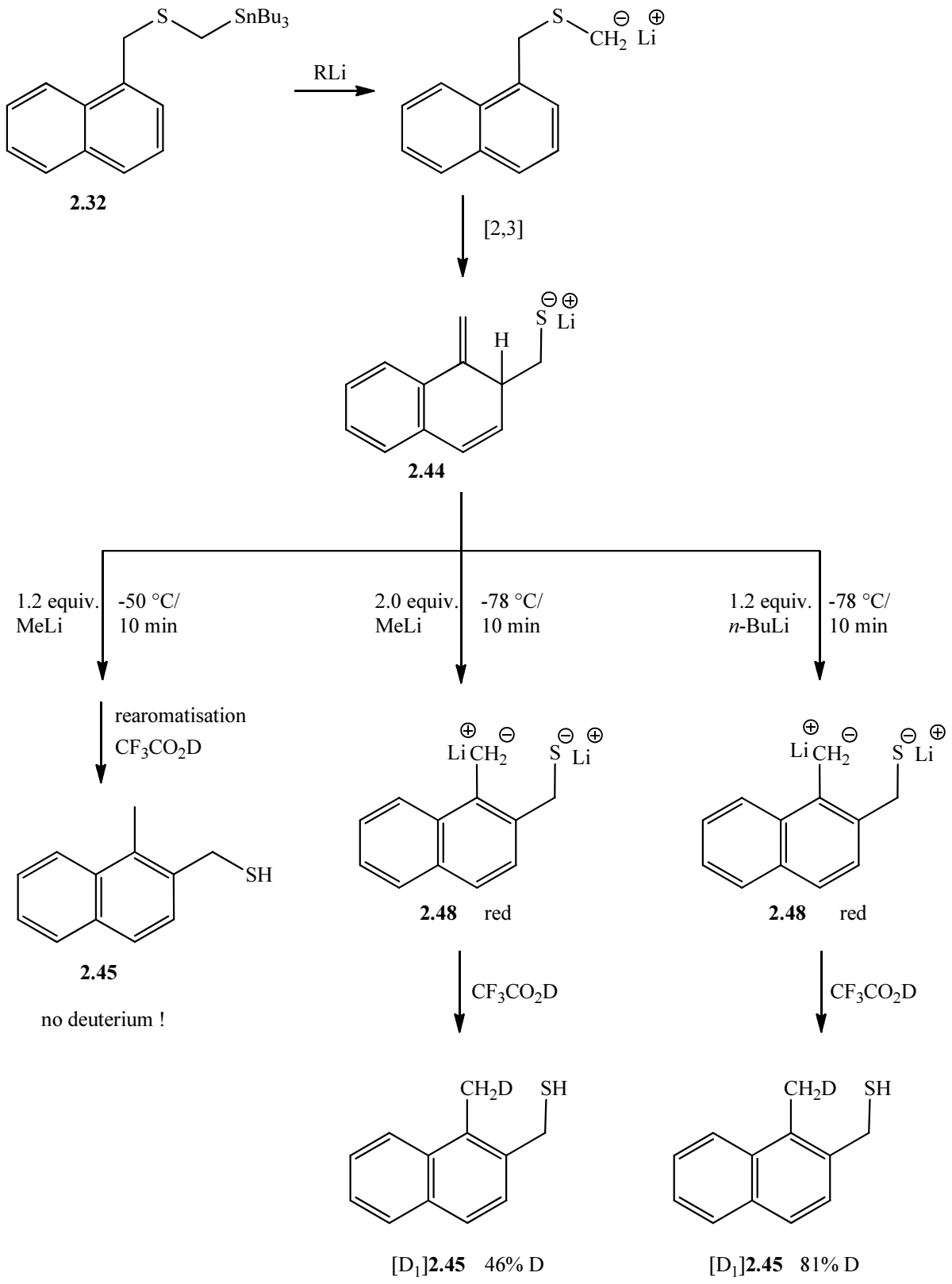


2.38

Figure 2.8. Intermediate **2.38**

Quenching with CF_3CO_2D deuterated the metalated species. The ratio of labeled and unlabeled 2-methylphenylmethanethiol reflects the ratio of **2.39** and **2.47**, which on the other side reflects the ratio of the two rates of their formation.

Analogous experiments were carried out for the ((1-methylnaphth-2-yl)methylthiomethyl)tributylstannane (**2.32**). It was transmetalated and the generated intermediate **2.44** was allowed to rearrange. CF_3CO_2D was added after 10 minutes (Scheme 2.26). The deuterium contents of the isolated (1-methyl-2-naphthyl)methanethiol (**2.45**) depended on the base (*n*-BuLi or MeLi) and its excess. When 1.2 equiv. of MeLi, a weaker base than *n*-BuLi, were used, only transmetalation and rearomatization occurred. No deuterium was incorporated into the product and no starting material was recovered (^{1}H NMR spectra of crude product). This means that tin-lithium exchange had to proceed faster than the deprotonation so that no base was left to perform the metalation.

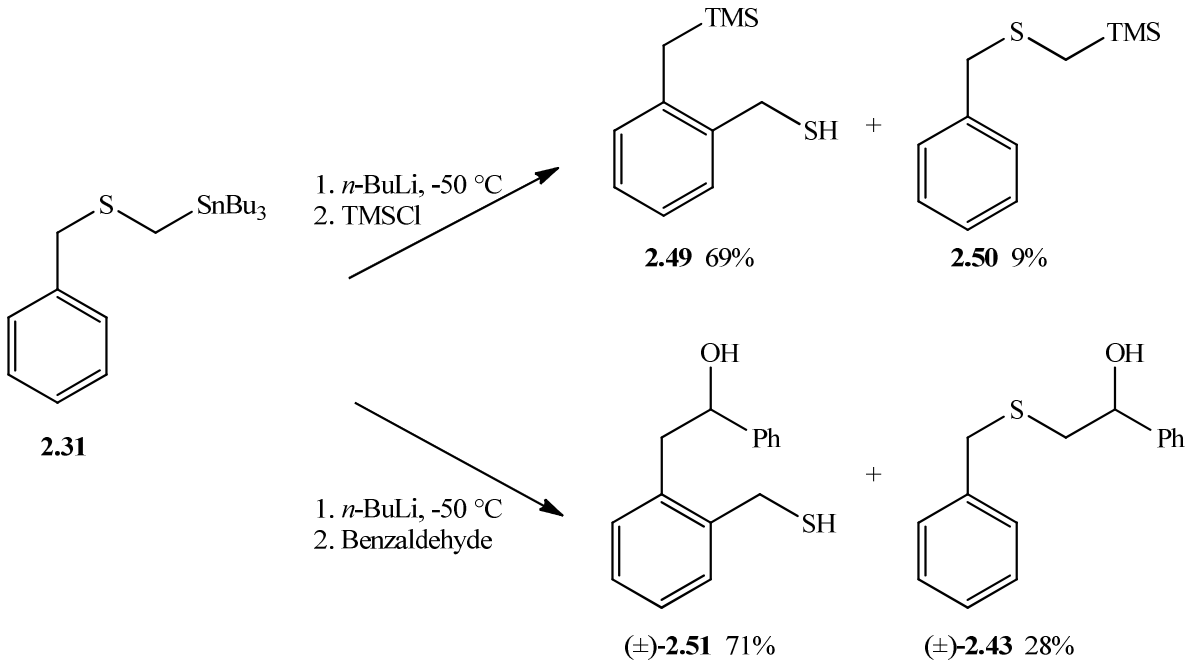


Scheme 2.26. Study of mechanism of [2,3]-thia-rearrangement

When 2.0 equiv. of MeLi were used at –78 °C, 46% of the molecules contained deuterium, indicating that a large excess of MeLi can indeed metalate **2.44**. When MeLi was replaced by 1.2 equiv. of *n*-BuLi under the same conditions, the deuterium contents of the product increased to 81%, indicating that metalation at the allylic position was faster than tin-lithium exchange. In the experiments with 1.2 equiv *n*-BuLi and 2.0 equiv. MeLi about 30% of starting material were recovered.

2.3.1. Formation and reactivity of (2-thiomethylaryl)methyllithiums

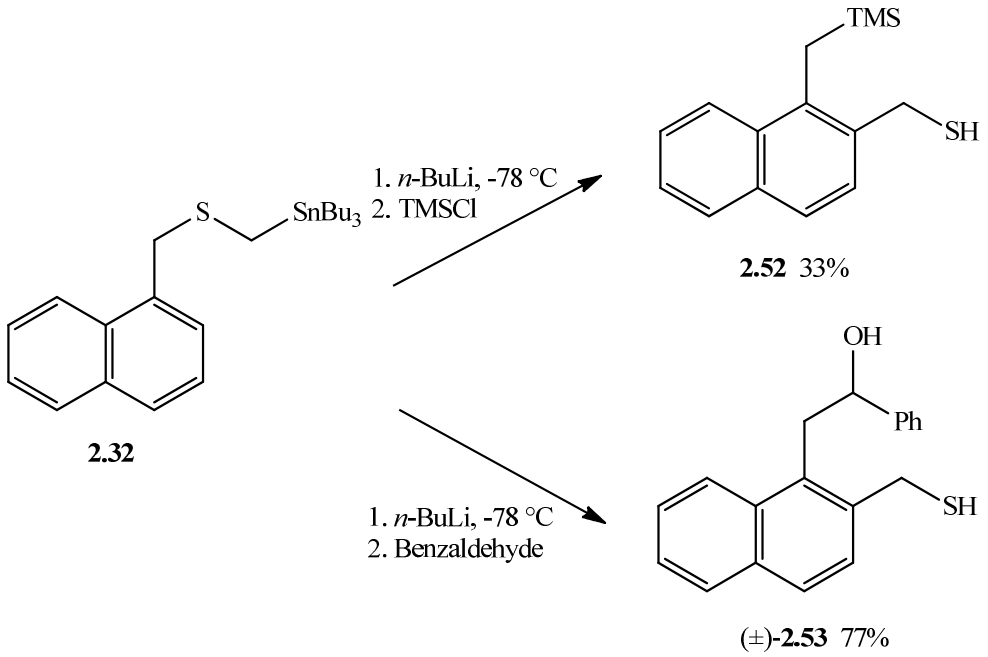
Inspired by this outcome, I reasoned that the dilithium compounds (**2.47** and **2.48**) should also react with benzaldehyde and chlorotrimethylsilane as electrophiles beside protons. (Benzylthiomethyl)tributylstannane (**2.31**) was transmetalated (2.5 equiv. *n*-BuLi) for 5 minutes at –50 °C and afterwards TMSCl was added (Scheme 2.27). Similarly, the experiment was repeated except that benzaldehyde replaced TMSCl (2.5 equiv. *n*-BuLi). In both cases the desired products **2.49** and (±)-**2.51** were isolated in good yields along with products **2.50** and (±)-**2.43** derived from the unrearranged intermediate.



Scheme 2.27. Products formed by transmetalation of **2.31** and reactions of intermediates with electrophiles

The experiment was repeated with (1-naphthylmethyl)thiomethyltributylstannane (**2.32**). The tin-lithium exchange was performed at –50 °C and the electrophile was added after some time

(5 minutes for TMSCl, 3 minutes for benzaldehyde) (Scheme 2.28). For this substrate the TMS-substituted product was obtained in low yield. However, the alcohol (±)-**2.53** derived from benzaldehyde was isolated in good yield (77%). In both cases no unrearranged products were observed.

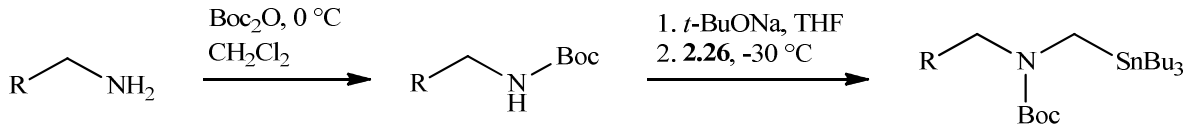


Scheme 2.28. Products formed by transmetalation of **2.32** and reactions of intermediates with electrophiles

2.3.2. Formation and reactivity of (2-aminomethylaryl)methyllithiums

Inspired by the results with phenylmethyl- and (naphthylmethylthio)methyllithiums, I wanted to expand this methodology to the oxygen- and nitrogen-substituted analogues. It would be interesting to generate arylmethyllithiums by the [2,3]-rearrangement of arylmethylthio-, arylmethoxy- and (arylmethylamino)methyllithiums followed by metalation, and quench them with various electrophiles.

The preparation of *N*-benzyl- and *N*-naphthyl carbamates **2.56** and **2.57** was quite simple and included protection of the arylmethylamine with Boc_2O (Scheme 2.29). The Boc-protected amines were alkylated with tributylstannylmethyl mesylate to yield the desired stannanes **2.58** and **2.59** respectively.



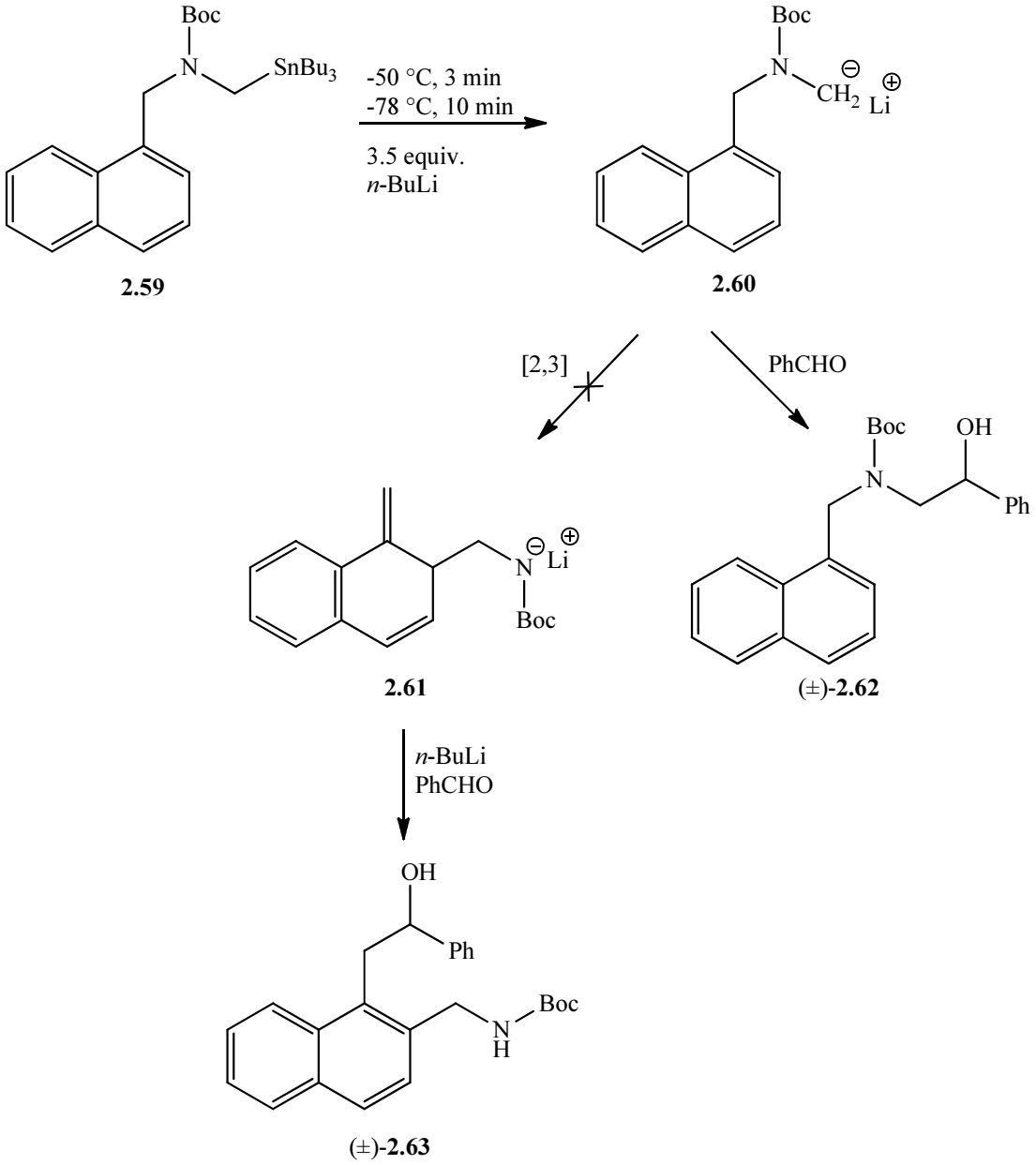
2.54: R = Phenyl
2.55: R = 1-Naphthyl

2.56: R = Phenyl, 80%
2.57: R = 1-Naphthyl, 77%

2.58: R = Phenyl, 53%
2.59: R = 1-Naphthyl, 68%

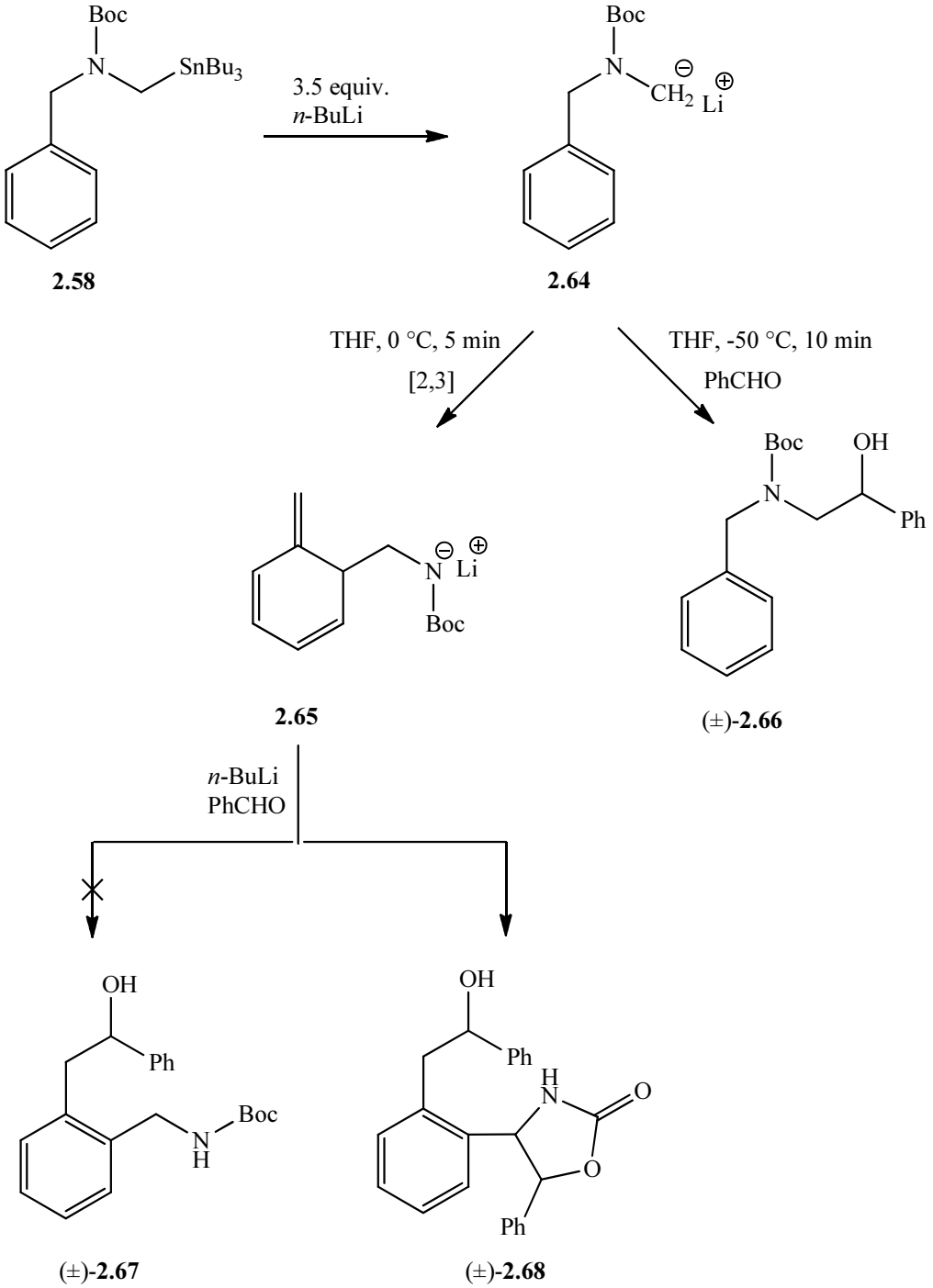
Scheme 2.29. Preparation of stannane precursors

Two experiments were performed with carbamate **2.59**. In the first one, transmetalation was carried out at –50 °C for 3 minutes and in the second one it was done at –78 °C for 10 minutes. After aging for the times given, benzaldehyde was added. In none of the experiments the desired product (±)-**2.63** was obtained. Only the addition product of the *N*-protected aminomethyllithium to benzaldehyde was found and the aminoalkohols (±)-**2.62** were isolated in good yields (52 and 59% respectively, Scheme 2.30).



Scheme 2.30. Products formed by transmetalation of **2.59** and reactions of intermediates with electrophiles

The *N*-benzyl-aminomethylstannane behaved similarly. At –50 °C the intermediate aminomethyllithium **2.64** did not rearrange and was added to benzaldehyde to give aminoalkohol (±)-**2.66** in 55% yield. When tin-lithium exchange occurred at 0 °C and benzaldehyde was added after 5 minutes, a small amount of the cyclic carbamate (±)-**2.68** was isolated. Its structure was assigned tentatively on the basis of the ^{13}C NMR spectrum, 2D NMR spectra and HRMS. The mechanism for its formation is unclear, but it is derived from the rearranged intermediate by addition of 2 molecules of benzaldehyde (Scheme 2.31).

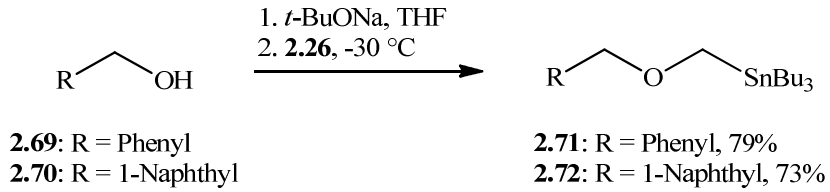


Scheme 2.31. Products formed by transmetalation of **2.58** and reactions of intermediates with electrophiles

I tried to optimize the temperature for the reaction to generate the desired product (±)-**2.67** in a good yield, but either the rearrangement did not take place or the side product (±)-**2.68** was obtained.

2.3.3. Formation and reactivity of (2-oxymethylaryl)methyllithiums

Finally, (arylmethoxy)methyllithiums were generated and investigated for their propensity to undergo a [2,3]-rearrangement. The starting tributylstannylmethyl ethers **2.71** and **2.72** were prepared by alkylation of phenyl- and 1-naphthylmethanol with tributylstannylmethyl mesylate (**2.26**) in the presence of *t*-BuONa as base in yields of 79 and 73%, respectively (Scheme 2.32).

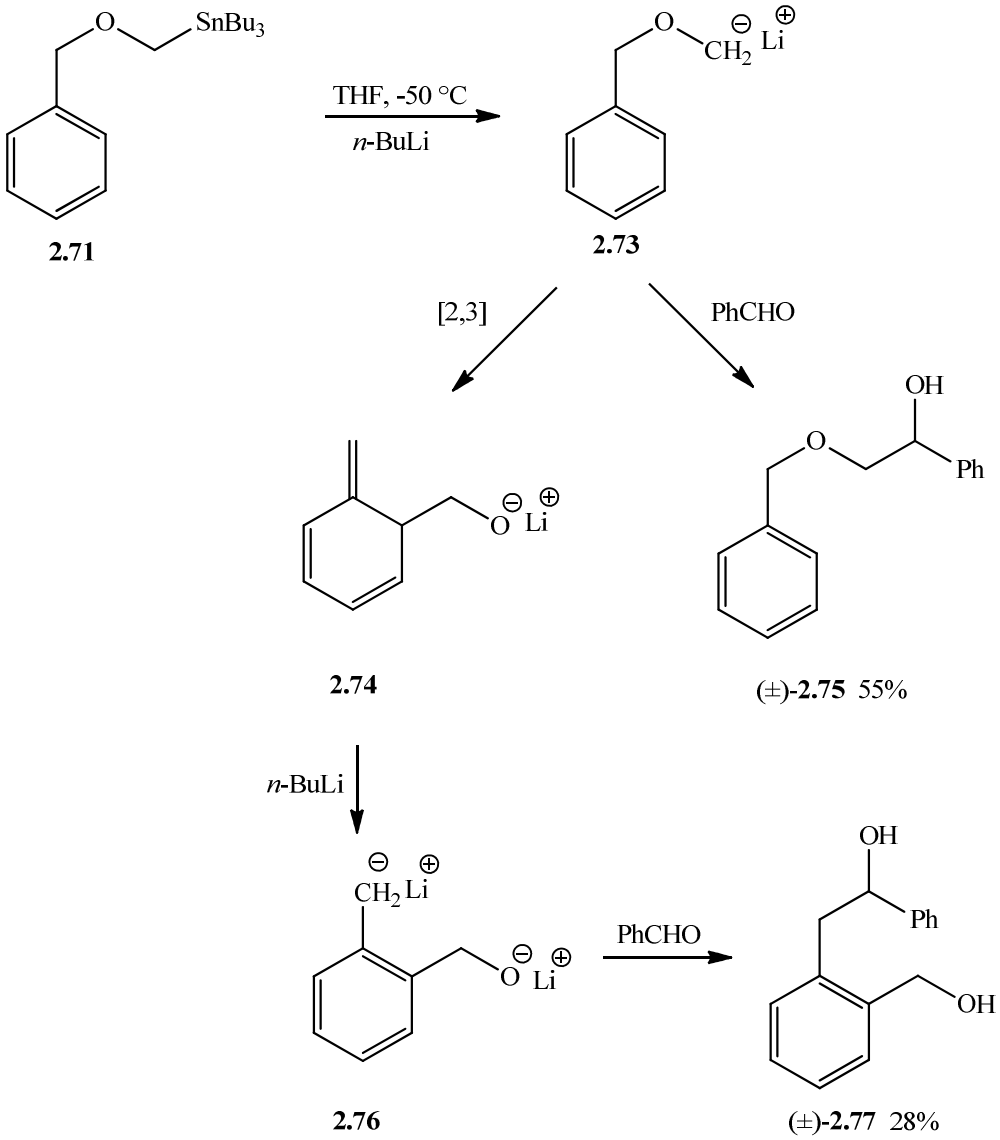


2.69: R = Phenyl
2.70: R = 1-Naphthyl

2.71: R = Phenyl, 79%
2.72: R = 1-Naphthyl, 73%

Scheme 2.32. Synthesis of **2.71** and **2.72**

(Benzyloxymethyl)tributylstannane (**2.71**) was transmetalated with 3.5 equiv. of *n*-BuLi at (–50 °C) for 3 minutes and then the intermediates formed were quenched with benzaldehyde. Two main products derived from the addition of the unrearranged and rearranged intermediates to benzaldehyde were obtained in yields of 55% and 28%, respectively (Scheme 2.33).

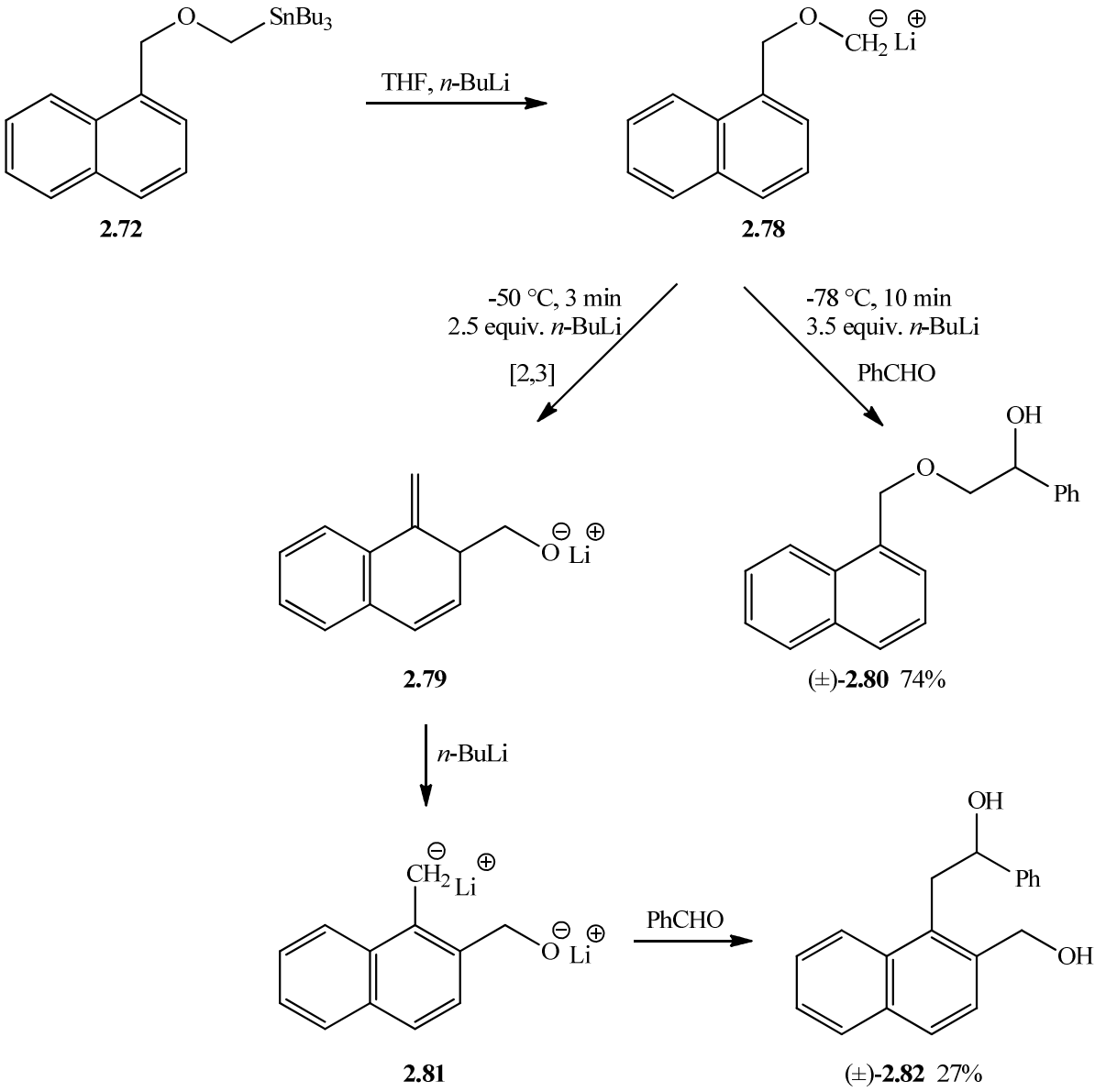


Scheme 2.33. Products formed by transmetalation of **2.71** and reactions of intermediates with electrophiles

When the experiment was repeated, with the difference that benzaldehyde was added 10 minutes after the addition of *n*-BuLi for transmetalation, the yield of (±)-**2.77** was similar (27%) to that in the previous experiment but the yield of (±)-**2.75** was lower (32%). Interestingly, the combined yields were lower in the latter case, possibly indicating chemical instability of the benzyllithium intermediate **2.73**.

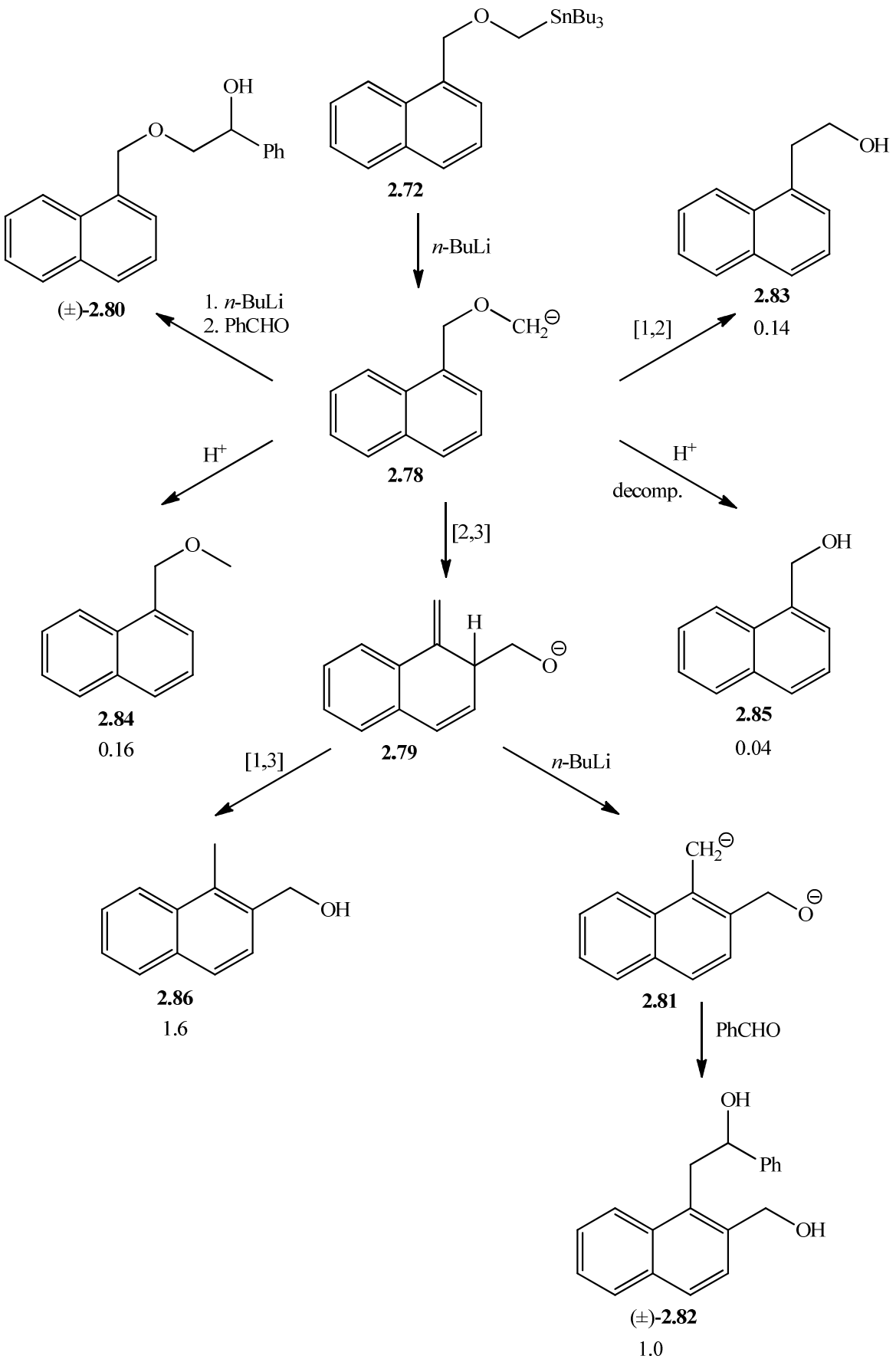
Two experiments were also conducted with (naphthylmethoxymethyl)tributylstannane (**2.72**). The first one was performed at –50 °C with 2.5 equiv. *n*-BuLi used for transmetalation. At this temperature the rearrangement of **2.72** was finished after 3 minutes because of the lower activation energy compared to that for the phenyl analogue. The (1-

naphthylmethoxy)methyllithium was added to benzaldehyde to give diol (±)-**2.82** (27%). When the temperature was lowered to –78 °C, the [2,3]-rearrangement did not take place, although 3.5 equiv. of *n*-BuLi were used. Instead of the diol only alcohol (±)-**2.80** was formed (74%, Scheme 2.34).



Scheme 2.34. Products formed by transmetalation of **2.72** and reactions of intermediates with electrophiles

Tin-lithium exchange with stannane **2.72** gave oxymethyllithium **2.78**, which can undergo a variety of reactions and therefore a mixture of products was obtained at –50 °C after addition of benzaldehyde (Scheme 2.35).



Scheme 2.35. Products formed by transmetalation of **2.72** and reactions of intermediates with electrophiles

The molar ratio of the products in the crude product was determined by ^{1}H NMR spectroscopy. Beside the already known compounds (±)-**2.80** and (±)-**2.82** some others were formed as well. 2-(1-Naphthyl)ethanol (**2.83**) was formed by the classic [1,2]-Wittig rearrangement of the oxymethyllithium **2.78**, methyl 1-naphthylmethyl ether (**2.84**) by protonation of **2.78**, 1-naphthylmethanol (**2.85**) by decomposition of **2.78** and 1-methyl-2-naphthylmethanol (**2.86**) in large amounts (50%) by a formal [1,3]-H-shift in **2.79**. Excess *n*-BuLi gave 1-phenylpentanol. Some benzaldehyde was recovered as 3.0 equiv. were used in the reaction.

In summary, phenyl- and naphthylmethoxymethyllithiums underwent a [2,3]-rearrangement at –50 °C, the latter also at –78 °C and even at –95 °C. The intermediate cyclohexadienyl systems with an exo-methylene group either rearomatized or were deprotonated by excess *n*-BuLi at the doubly allylic position and gave arylmethyllithiums, which could be quenched with benzaldehyde or TMSCl. The nitrogen analogues were transmetalated smoothly, but did not give the desired products. It follows that the feasibility of the [2,3]-rearrangement for the three heteroatom-substituted methyllithiums is given by the following sequence: S > O >>> N.

3. Experimental Part

3.1. General

All glassware was dried for several hours at 100 °C prior to use. For reactions at –78 °C acetone/dry ice bath was used, also with addition of liquid nitrogen to achieve –95 °C. Small quantities of reagents (µl) were measured out using analytical syringes from Hamilton. Normally, the reaction protocols for non-deuterated and deuterated compounds were identical and given for the former. The yields were averaged.

NMR spectroscopy

^{1}H, ^{13}C (*J* modulated) and ^{31}P NMR spectra were measured 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). 2D spectra were measured on DRX 400. The spectroscopic experiments were performed at 300K, unless otherwise specified. Chemical shifts were referenced either to residual $CHCl_3$ (δ_H = 7.24)/toluene-d_8 (CHD_2: δ_H = 2.09)/DMSO-d_6 (CD_3: δ_H = 2.50) or $CDCl_3$ (δ_C = 77.00)/toluene-d8 (CHD_2: δ_C = 21.04). All chemical shifts (δ) are given in ppm and *J* values in Hz. Following abbreviations are used to describe spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, sept = septet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, dsept = doublet of septets etc.

Infrared spectroscopy

IR spectra were run on a Perkin-Elmer 1600 FT-IR or 2000 FT-IR spectrometer or by using ATR on a Bruker VERTEX 70 IR spectrometer. Samples were measured as a film (usually obtained by applying several drops from NMR sample and evaporation of $CDCl_3$) on a silicon disc, or if the substance was crystalline, it was applied directly at the ATR. IR spectra are reported in wave numbers (cm^{-1}).

Mass Spectroscopy

Mass spectra were recorded on spectrometers from Micro Mass (Fissions Instrument, Trio2000) in EI mode (70 eV). HRMS were measured on Finnigan MAT 8230 with a resolution of 10000.

Chromatography

Flash column chromatography

Preparative flash column chromatography was performed with Merck silica gel (230-400 mesh).

Thin layer chromatography

All reactions were monitored using coated glass plates. TLC was carried out on 0.25 mm thick silica gel 60, F_{254} Merck plates. Detection of the spots was done by UV and/or by dipping the plate into a Molybdate reagent (a solution of 23.0 g of $(NH_4)_6Mo_7O_{24}$•4 H_2O and 1.0 g of $Ce(SO_4)_2$•4 H_2O in 500 ml of 10% aqueous H_2SO_4). Afterwards, the plate was heated with the heat gun. The reactions progress was controlled in the same way.

Polarimetry

Optical rotations were measured on a Perkin-Elmer 141 polarimeter. The length of the cell was 1 dm and the solution was kept at 20 °C. The optical rotations was measured with monochromatic sodium light (D-line, 598 nm). If the specific rotation was very low, it was also measured at 365 nm.

Melting points

Melting points were measured with a Reichert Thermovar instrument and were uncorrected.

Solvents

The solvents were purified and dried prior to use, according to the procedures as follows.

- **CH_2Cl_2** was dried by passing through aluminum oxide 90 active, neutral (0.063-0.200 mm, activity I) and stored over molecular sieves (3 Å).
- **Et_2O** was refluxed over $LiAlH_4$ and distilled prior to use.
- **Hexane** and **EtOAc** used for chromatography were purified by distillation
- **THF** was refluxed over potassium and freshly distilled prior to use.
- **TMEDA** and **pyridine** were refluxed over CaH_2, distilled and stored over molecular sieves (4 Å).

- **Toluene** was refluxed over sodium/benzophenone, then distilled and stored over molecular sieves (4 Å).

All other solvents were purified and dried by standard methods.

Chemicals

All commercially available reagents were supplied from Aldrich, Fluka, Merck or Acros in the best available quality and used without further purification.

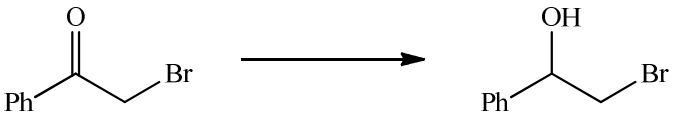
(*R*)-Mosher ester – General Procedure A

A solution of alcohol (0.10 mmol), dry pyridine (0.25 ml) and (*S*)-MTPACl (0.3 ml, 0.15 mmol, 0.5 M in dry CH_2Cl_2) was dissolved in dry CH_2Cl_2 (2 ml) and stirred at room temperature (for bromohydrines only 4 hours, for all other alcohols 4-18 hours). Afterwards CH_2Cl_2 (10 ml) and HCl (10 ml, 1 M) were added. The organic phase was separated, washed with a saturated aqueous solution of $NaHCO_3$, dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash chromatography.

3.2. Experimental procedures and compounds characterization

3.2.1. Chapter 2.1

(±)-2-Bromo-1-phenylethanol [(±)-2.6]



2.5 (±)-**2.6**

a) Reduction of *ω*-bromoacetophenone with borane

A solution of BH_3·THF (1.03 g, 1.1 ml, 12 mmol) was added to *ω*-bromoacetophenone (1.99 g, 10 mmol) in dry THF (20 ml) under argon at 0 °C. The reaction mixture was stirred for 2 hours at room temperature and 4 hours at 50 °C. Water (25 ml) was added and the solution was stirred for another 30 minutes at room temperature. The organic phase was separated and the aqueous one was extracted with CH_2Cl_2 (4 x 20 ml). The combined organic layers were washed with water, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography [hexane/EtOAc (5:1), R_f = 0.36] to yield (±)-2-bromo-1-phenylethanol [(±)-**2.6**] as a colorless oil (145 mg, 14%).

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 7.39-7.29 (m, 5H, H_{arom}), 4.92 (dd, X-part of an ABX-sys., J = 9.1, 3.5 Hz, 1H, CHO), 3.58 (AB-part of an ABX-sys., J_{AB} = 10.4 Hz, J = 9.1, 3.5 Hz, 2H, CH_2Br), 2.59 (br. s, 1H, OH).

a) Reduction of *ω* -bromoacetophenone with DIBAH

A solution of DIBAH (3.98 ml, 5.97 mmol, 1.5 M in toluene) was added dropwise to *ω*-bromoacetophenone (995 mg, 5.0 mmol) dissolved in dry Et_2O (25 ml) at –78 °C under argon. The reaction mixture was stirred for 2 hours at –78 °C and then 1 hour at –50 °C. The reaction was quenched with MeOH (0.5 ml) and water (2.5 ml) and stirred for another 30 minutes at room temperature. A solution of HCl (12 ml, 2 M) was added at 0 °C. The organic phase was separated and the aqueous one was extracted with Et_2O (3 x 10 ml). The combined organic layers were washed with water (15 ml) and a saturated aqueous solution of $NaHCO_3$ (15 ml), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by

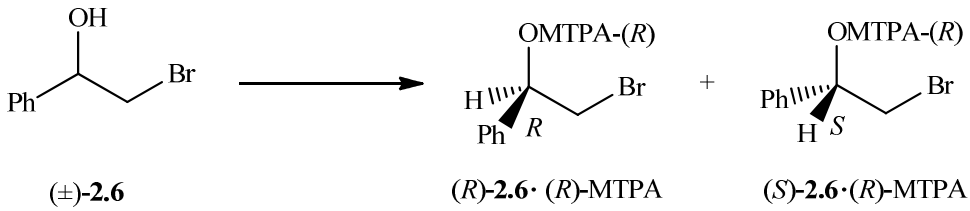
flash chromatography [hexane/EtOAc (7:1), R_f = 0.43] to yield (±)-2-bromo-1-phenylethanol [(±)-**2.6**] as a colorless oil (591 mg, 59%).

b) Reduction of ω-bromoacetophenone with (+)-DIP-chloride

A solution of (+)-DIP-chloride (1.8 g, 5.61 mmol) in dry THF (5 ml) was added to ω-bromoacetophenone (744 mg, 3.74 mmol) dissolved in dry THF (5 ml) under argon at 0 °C. The solution was stirred over night at room temperature. At 0 °C water (1 ml), pentaerythritol (916 mg, 6.73 mmol) and again water (15 ml) were added and the mixture was stirred for another 30 minutes at room temperature. The organic phase was separated and the aqueous one was extracted with Et_2O (3 x 15 ml). The combined organic layers were washed with water (2 x 10 ml), dried ($MgSO_4$), concentrated under reduced pressure and purified by flash chromatography [hexane/EtOAc (10:1)]. The still impure product was again dissolved in dry THF (10 ml) and pentaerythritol (680 mg, 5 mmol) dissolved in water (5 ml) was added. The solution was stirred overnight at room temperature. The organic phase was separated and the aqueous one was extracted with Et_2O (3 x 15 ml). The combined organic layers were washed with water (2 x 10 ml), dried ($MgSO_4$) and concentrated under reduced pressure. Ten drops of dry pyridine were added and the crude product was purified by flash chromatography [hexane/EtOAc (7:1)] to yield (*S*)-(+)-2-bromo-1-phenylethanol [(*S*)-(+)-**2.6**] as a colorless oil (193 mg, 26%), ee 94% (by ^{1}H NMR of (*R*)-Mosher ester), $[\alpha]_D^{20}$ = +39.24 (*c* = 1.975, CH_2Cl_2),{lit.[117]: $[\alpha]_D^{20}$ = +40.10, (*c* = 1.81, $CHCl_3$), ee 92%}. The ^{1}H NMR spectrum was identical to that of the racemate.

(*R*)-2.6·(*R*)-MTPA and (*S*)-2.6·(*R*)-MTPA

a) of racemate



(±)-**2.6** (*R*)-**2.6**· (*R*)-MTPA (*S*)-**2.6**·(*R*)-MTPA

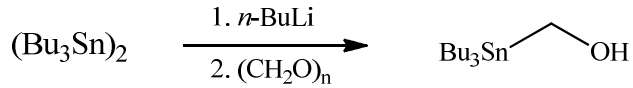
It was prepared according to General Procedure A from (±)-**2.6** (20 mg, 0.10 mmol) and purified by flash chromatography [hexane/EtOAc (10:1), R_f = 0.66] to give a mixture of diastereomeric Mosher esters (±)-**2.6**·(*R*)-MTPA (39 mg, 94%).

^{1}H NMR (400.13 MHz, toluene-d_8): δ = 7.59-7.55 (m, 2H, H_{arom}, (*R*,*S*)-diastereomer), 7.51-7.47 [m, 2H, H_{arom}, (*R*,*R*)], 7.08-6.91 [m, 14H, 8H_{arom} of (*R*,*S*), 6H_{arom} of (*R*,*R*)], 6.78-6.75 [m, 2H, H_{arom}, (*R*,*R*)], 6.04 [X-part of an ABX-sys., *J* = 8.8, 4.2 Hz, 1H, OCH, (*R*,*S*)], 5.90 [X-part of an ABX-sys., *J* = 9.6, 3.3 Hz, 1H, OCH, (*R*,*R*)], 3.58 [q, *J* = 1.0 Hz, 3H, OCH_3, (*R*,*R*)], 3.32 [q, *J* = 1.0 Hz, 3H, OCH_3, (*R*,*S*)], 3.07 [AB-part of an ABX-sys., J_{AB} = 11.1 Hz, *J* = 8.8, 4.2 Hz, 2H, CH_2Br, (*R*,*S*)], 3.01 [AB-part of an ABX-sys., J_{AB} = 11.4 Hz, *J* = 9.6, 3.3 Hz, 2H, CH_2Br, (*R*,*R*)]. Two diastereomers!

b) of (*S*)-**2.6**

The (*R*)-Mosher ester of (*S*)-(+)-2-bromo-1-phenylethanol (20 mg, 0.10 mmol) $[\alpha]_D^{20}$ = +39.24, (*c* = 1.975, CH_2Cl_2) was prepared similarly (40 mg, 96%); ee of alcohol: 94%. The ^{1}H NMR spectrum was identical to that of the racemic alcohol, except that the signals of the diastereomers differed in intensity.

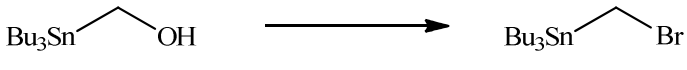
Tributylstannylmethanol (2.2)



2.1 **2.2**

A solution of *n*-BuLi (3.75 ml, 6 mmol, 1.6 M in hexane) was added to the hexabutyldistannane (2.9 g, 5 mmol) and TMEDA (0.9 ml, 6 mmol) dissolved in dry THF (20 ml) under argon at 0 °C. After 15 minutes paraformaldehyde (165 mg, 5.5 mmol) was added and the reaction mixture was stirred for 2 hours at 0 °C. Afterwards the reaction was quenched with CH_3CO_2H (6.25 ml, 1 M) and water (5 ml) was added. The organic phase was separated and the aqueous one was extracted with EtOAc (2 x 10 ml). The combined organic layers were washed with water (15 ml) and a saturated aqueous solution of NaCl (15 ml), dried ($MgSO_4$) and then concentrated under reduced pressure. The residue was purified by flash chromatography [hexane/EtOAc (10:1), R_f = 0.27] to give tributylstannylmethanol (787 mg, 49%) as a colorless oil.

(Bromomethyl)tributylstannane (2.3)



2.2 **2.3**

a) Prepared with NBS/ Ph_3P

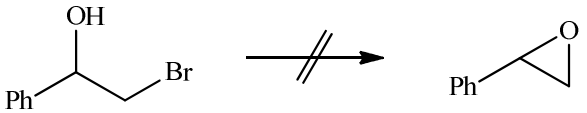
A solution of Ph_3P (772 mg, 2.94 mmol) in dry CH_2Cl_2 (3 ml) was added dropwise to NBS (523 mg, 2.94 mmol) dissolved in dry CH_2Cl_2 (5 ml) under argon at –78 °C. After 10 tributylstannylmethanol (787 mg, 2.45 mmol) dissolved in dry CH_2Cl_2 (4 ml) was added and the reaction mixture was stirred at room temperature for 30 minutes. After the addition of a few drops of MeOH the mixture was concentrated under reduced pressure and flash chromatographed [hexane/CH_2Cl_2 (1:1), R_f = 0.98] to yield (bromomethyl)tributylstannane (859 mg, 91%) as a colorless oil.

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 2.63 (s, $J(^{117/119}Sn)$ = 14.6 Hz, 2H, $SnCH_2Br$), 1.55-1.46 (m, 6H, 3 x $SnCH_2\underline{CH_2}$), 1.30 (sext, J = 7.3 Hz, 6H, 3 x $Sn(CH_2)_2\underline{CH_2}$, 1.00-0.95 (m, $J(^{117/119}Sn)$ = 51.4 Hz, 6H, 3 x $Sn\underline{CH_2}$), 0.88 (t, J = 7.3 Hz, 9H, 3 x $Sn(CH_2)_3\underline{CH_3}$)

b) Prepared by the Mitsunobu reaction with $Ph_3P{\cdot}HBr$

Ph_3P (109 mg, 0.62 mmol), $Ph_3P{\cdot}HBr$ (845 mg, 2.46 mmol) and tributylstannylmethanol (657 mg, 2.05 mmol) were dissolved in dry toluene (8.2 ml) under argon. After 5 minutes stirring at 0 °C DIAD (0.71 ml, 4.47 mmol) was added and the reaction mixture was stirred for another 90 minutes. The reaction was quenched with several drops of MeOH. The mixture was purified by flash chromatography [hexane/CH_2Cl_2 (1:1), R_f = 0.98] to give (bromomethyl)tributylstannane as a colorless oil (383 mg, 49%).

Test of stability of lithium alkoxide derived from (±)-2-bromo-1-phenylethanol towards formation of phenyloxirane at –78 °C

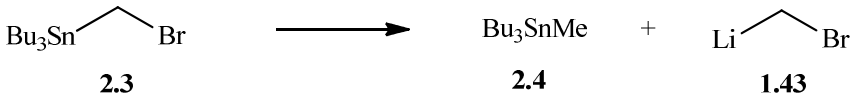


(±)-**2.6** (±)-**2.7**

A solution of MeLi (0.60 ml, 0.60 mmol, 1 M in cumene/THF) was added quickly at –78 °C to the (±)-2-bromo-1-phenylethanol [(±)-**2.6**] (100 mg, 0.5 mmol) dissolved in dry THF (2.5 ml) under argon atmosphere. After 5 minutes trifluoroacetic acid (75 mg, 0.65 ml, 0.65 mmol, 1.3 equiv., 1 M in dry CH_2Cl_2) and water (5 ml) 3 minutes later were added. The organic phase was separated and the aqueous one was extracted with Et_2O (3 x 15 ml). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The crude

product did not contain phenyloxirane as determined by ^{1}H NMR spectroscopy after spiking with an authentic sample. The crude product was purified by flash chromatography [hexane/EtOAc (7:1), R_f = 0.42] to yield (±)-2-bromo-1-phenylethanol (95 mg, 95%) as a colorless oil. The R_f value and to ^{1}H NMR spectrum were identical to that of the starting material.

Determination of ease of transmetalation of (bromomethyl)tributylstannane

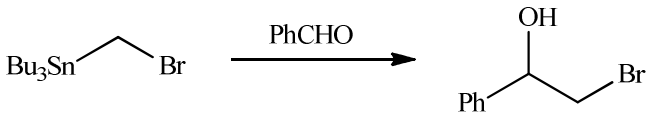


2.3 **2.4** **1.43**

A solution of MeLi (0.51 ml, 0.51 mmol, 1 M in cumene/THF) was added quickly at –78 °C to the (bromomethyl)tributylstannane (163 mg, 0.42 mmol) dissolved in dry THF (2 ml) under argon atmosphere. After 30 seconds trifluoroacetic acid (64 mg, 0.55 ml, 0.55 mmol, 1.3 equiv., 1 M in dry CH_2Cl_2) and water (5 ml) 1 minute later were added. The organic phase was separated and the aqueous one was extracted with CH_2Cl_2 (3 x 10 ml). The combined organic layers were washed with water (15 ml), dried (Na_2SO_4) and concentrated under reduced pressure. The crude product did not contain (bromomethyl)tributylstannane (**2.3**) but was virtually pure tributylmethylstannane (**2.4**) as determined by ^{1}H NMR spectroscopy.

Determination of chemical stability of bromomethyllithium under the conditions of evaluation of its macroscopic configurational stability

(±)-2-Bromo-1-phenylethanol [(±)-2.6]



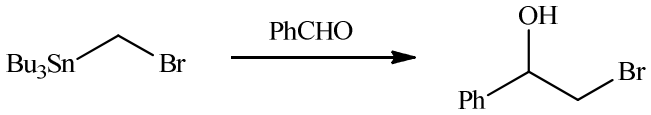
2.3 (±)-**2.6**

A solution of MeLi (0.63 ml, 0.63 mmol, 1 M in Cumene/THF) was added quickly at –78 °C to (bromomethyl)tributylstannane (203 mg, 0.529 mmol) dissolved in dry THF (2 ml) under argon atmosphere. After 30 seconds, benzaldehyde (84 mg, 0.4 ml, 0.793 mmol, 1.5 equiv., 2 M in dry THF) was added followed by trifluoroacetic acid (92 mg, 0.79 ml, 0.793 mmol, 1.5 equiv., 1 M in dry CH_2Cl_2) after 3 minutes. Water (5 ml) was added and the organic phase was separated and the aqueous one was extracted with CH_2Cl_2 (3 x 10 ml). The combined

organic layers were washed with water (15 ml), dried (Na_2SO_4) and concentrated under reduced pressure. The crude product (166 mg) did not contain neither bromomethylstannane nor 1-phenylethanol, but tributylmethylstannane and a small amount of bromhydrine as determined by ^1H NMR spectroscopy. The crude product was purified by flash chromatography [hexane/EtOAc (7:1)] to yield (±)-2-bromo-1-phenylethanol as colorless oil (about 10 mg).

Determination of chemical stability of bromomethyllithium under the conditions of evaluation of its microscopic configurtional stability

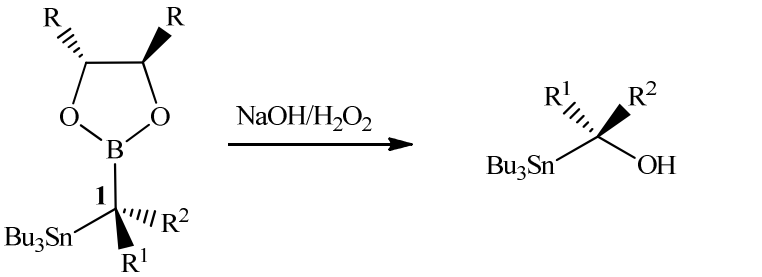
(±)-2-Bromo-1-phenylethanol [(±)-2.6]



2.3 (±)-**2.6**

A solution of MeLi (1.85 ml, 1.85 mmol, 1 M in Cumene/THF) was quickly added to a solution of (bromomethyl)tributylstannane (178 mg, 0.46 mmol) and benzaldehyde (194 mg, 0.93 ml, 1.85 mmol, 2 M in THF) in dry THF (2 ml) under argon atmosphere at –78 °C. After 5 minutes trifluoroacetic acid (232 mg, 2 ml, 2 mmol, 1 M in CH_2Cl_2) and water (5 ml) was added. The organic phase was separated and the aqueous one was extracted with CH_2Cl_2 (3 x 10 ml), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography [CH_2Cl_2, R_f = 0.46] to give (±)-2-bromo-1-phenyl-ethanol as a colorless oil (17 mg, 19%). The spectroscopic data was identical to those for (±)-**2.6**.

(*S*)- and (*R*)-Tributylstannyl-[D_1]methanol ([D_1]2.2)[41]



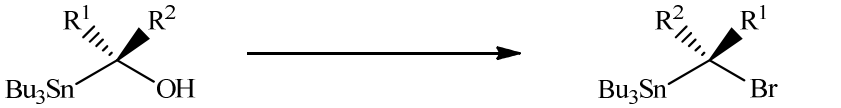
(1*S*)-[D_1]**boronate**: R^1 = H, R^2 = D
(1*R*)-[D_1]**boronate**: R^1 = D, R^2 = H

R = cyclohexyl

(*S*)-[D_1]**2.2**: R^1 = H, R^2 = D
(*R*)-[D_1]**2.2**: R^1 = D, R^2 = H

The two diasteromeric boronates were prepared and reduced with $LiEt_3BD$ (obtained from commercially available Et_3B (1M in THF) and LiD). The following procedure is an improved version of the literature one. An aqueous solution of NaOH (2.27 ml, 7.82 mmol, 3.44 M) and a solution of H_2O_2 (1.0 ml, 10.33 mmol, 30%) were added at 0 °C to the (4*R*,5*R*)-4,5-dicyclohexyl-2-[(*S*)-tributylstannyl-[D_1]methyl]-1,2-dioxaborolane (the less polar diastereomer) (1.689 g, 3.13 mmol) dissolved in dry THF (15.7 ml). After stirring the biphasic mixture vigorously for 1 hour, more NaOH (2.27 ml) and H_2O_2 (1.0 ml) were added. Stirring was continued for another hour and then water (18 ml) and pentaerythritol (600 mg) were added. The reaction mixture was stirred for 30 minutes. The organic phase was separated and the aqueous one was extracted with EtOAc (3 x 30 ml). The combined organic layers were washed with water (30 ml) and brine (30 ml), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography [hexane/EtOAc (10:1)] giving (*S*)-tributylstannyl-[D_1]methanol as a colorless oil (826 mg, 82%).
Similarly, (1*R*)-boronate (1.617 g, 2.99 mmol, the more polar diastereomer) was converted to (*R*)-tributylstannyl-[D_1]methanol (731 mg, 76%).

Preparation of (*R*)- and (*S*)-(bromo-[1-D_1]methyl)tributylstannane ([D_1]2.3)



2.2: $R^1 = R^2 = H$
(*S*)-[D_1]**2.2**: $R^1 = H$, $R^2 = D$
(*R*)-[D_1]**2.2**: $R^1 = D$, $R^2 = H$

2.3: $R^1 = R^2 = H$
(*R*)-[D_1]**2.3**: $R^1 = H$, $R^2 = D$
(*S*)-[D_1]**2.3**: $R^1 = D$, $R^2 = H$

1) Prepared with NBS

(*S*)-[D_1]**2.2** (197 mg, 0.61 mmol) was converted to (*R*)-[D_1]**2.3** (205 mg, 92%, ee 60%) by the procedure used for the preparation of the racemic bromide.

The spectroscopic data were identical to that of **2.3**, except for:

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 2.61 (t, J = 1.5 Hz, 1H, CHD).

2) with $Ph_3P{\cdot}HBr$ by the Mitsunobu reaction

Prepared in the same way as the racemic (bromomethyl)tributylstannane (**2.3**). To optimize reaction conditions several experiments were performed;

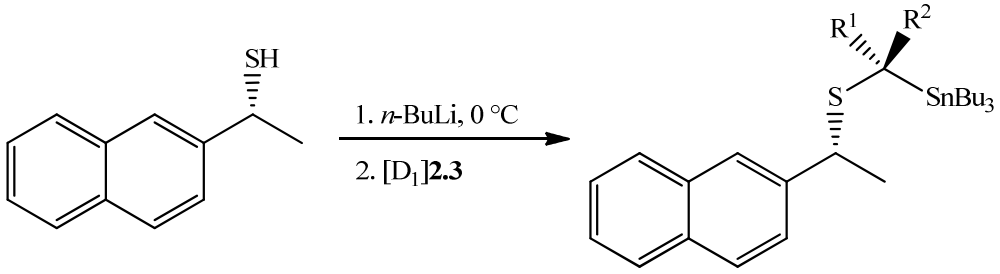
a) (*S*)-[D_1]**2.2** (471 mg, 1.46 mmol) was converted to (*R*)-[D_1]**2.3** (345 mg, 62%, ee 77%) by the procedure used for the preparation of the racemic bromide, except that the reaction was performed for 25 minutes.

b) (*R*)-[D_1]**2.2** (852 mg, 2.65 mmol) was converted to (*S*)-D_1]**2.3** (491 mg, 48%, ee 74%) by the procedure used for the preparation of the racemic bromide except that the reaction was performed for 10 minutes. After the addition of methanol, the reaction mixture was immediately applied to the column for the flash chromatography. The entire procedure (also flash chromatography) was performed in the cold room (3 °C). No bath was used during concentration of solutions under reduced pressure.

c) (*R*)-[D_1]**2.2** (958 mg, 2.98 mmol) was converted to (*S*)-[D_1]**2.3** (521 mg, 45%, ee 94%) by procedure b), except that the reaction was performed at –10 °C for 10 minutes.

d) (*R*)-[D_1]**2.2** (417 mg, 1.30 mmol) was converted to (*S*)-[D_1]**2.3** (179 mg, 35%, ee ≥ 99%) by procedure b), except that the reaction was performed at –25 °C for 10 minutes.

Determination of the enantiomeric excess of chiral, nonracemic bromide



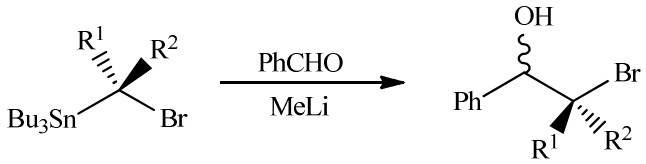
(*R*)-**2.8**

(1*S*,2*R*)-[D_1]**2.9**: R^1 = D, R^2 = H
(1*R*,2*R*)-[D_1]**2.9**: R^1 = H, R^2 = D

n-BuLi (0.064 ml, 0.10 mmol) was added at 0 °C to the (*R*)-[D_1]**2.8** in dry THF (0.5 ml) under argon atmosphere, followed by (bromo-[D_1]methyl)tributylstannane (26 mg, 0.068 mmol) after 15 minutes. After stirring at room temperature for 2 hours water (1 ml) was added. The

organic phase was separated and the aqueous one was extracted with EtOAc (3 x 5 ml). The combined organic layers were dried (Mg_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography [hexane/CH_2Cl_2 (10:1), R_f = 0.37] to give sulfide [D_1]**2.9** (31 mg, 93%) as a colorless oil. The ^{1}H NMR spectrum was identical to the literature one.[47]

Investigation of microscopic configurational stability of chiral bromo[D_1]methyllthium – Preparation of 2-bromo-1-phenyl-[2-D_1]ethanol ([D_1]2.6)



(*R*)-[D_1]**2.3**: R^1 = H, R^2 = D
(*S*)-[D_1]**2.3**: R^1 = D, R^2 = H

(2*S*)-[2-D_1]**2.6**: R^1 = H, R^2 = D
(2*R*)-[2-D_1]**2.6**: R^1 = D, R^2 = H

Following experiments were performed:

1) A solution of benzaldehyde (198 mg, 0.94 ml, 1.87 mmol, 2 M in THF) was added at – 78 °C to the (*R*)-bromo-[1-D_1]methyl)tributylstannane (180 mg, 0.47 mmol) in dry THF (2 ml) under argon atmosphere, followed by MeLi (1.87 ml, 1.87 mmol, 1 M in cumene/THF) dropwise. After 10 minutes the reaction was quenched with trifluoroacetic acid (240 mg, 2.07 ml, 2.07 mmol, 1 M in THF). Water (5 ml) was added and the organic phase was separated and the aqueous one was extracted with CH_2Cl_2 (3 x 5 ml). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography (CH_2Cl_2, R_f = 0.43) to give homogenous title product (2*S*)-[D_1]**2.6** (7 mg, 11%) as a colorless oil; impure fractions (estimated product about 10 mg) were discarded.

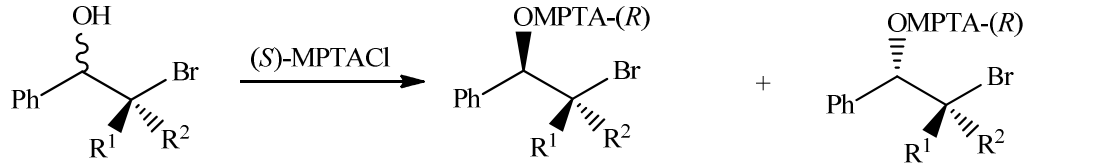
2) (*R*)-[D_1]**2.3** (157 mg, 0.41 mmol) was converted to (2*S*)-[D_1]**2.6** (15 mg, 18%, ee 76%) by procedure 1), except using 2 equiv. of benzaldehyde and MeLi (1 M solution obtained by dilution of 3 M MeLi in dimethoxymethane with dry THF) which was added dropwise every 5 seconds. If 3 M MeLi in dimethoxymethane was used or it was added more rapidly, no product or only product traces were obtained.

3) (*R*)-[D_1]**2.3** (161 mg, 0.42 mmol) was converted to (2*S*)-[D_1]**2.6** (11 mg, 12%, ee 75%) by procedure 2), except that acetophenone was used as electrophile.

4) (*S*)-[D_1]**2.3** (179 mg, 0.46 mmol) was converted to (2*R*)-[D_1]**2.6** (13 mg, 14%, ee ≥ 99%) by procedure 2).

5) (*S*)-[D_1]**2.3** (259 mg, 0.67 mmol) was converted to (2*R*)-[D_1]**2.6** (45 mg, 31%, ee 93%) by procedure 2), except that the reaction was performed with acetophenone as electrophile at – 95 °C.

Determination of enantiomeric excess at C-2 of deuterated bromohydrines (±)-2.6 · (*R*)-MTPA



(2*S*)-[2-D_1]**2.6** (1*S*,2*S*)-[2-D_1]**2.6**·MPTA-(*R*) (1*R*,2*S*)-[2-D_1]**2.6**·MPTA-(*R*)

It was prepared in quantitative yield form (±)-2-bromo-1-phenyl-[2-D_1]ethanol according to general procedure A and was purified by flash chromatography [hexane/EtOAc (10:1), R_f = 0.78]. The two diastereomers could be separated by preparative TLC chromatography [hexane/CH_2Cl_2 (3:1), R_{fA} = 0.56, R_{fB} = 0.35] giving diastereomers (1*R*,2*S*) (56% ee) and diastereomer (1*S*,2*S*) (57% ee) in quantitative yield.

Diastereomer (1*R*,2*S*)-[2-D_1]**2.6** · (*R*)-MTPA:

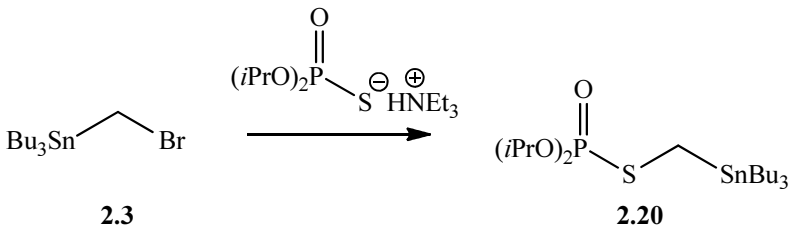
^{1}H NMR (400.13 MHz, toluene-d_8): δ = 5.89 (br. d, *J* = 2.5 Hz, 1H, CHO), 2.89 (d, *J* = 2.5 Hz, 1H, CHD).

Diastereomer (1*S*,2*S*)-[2-D_1]**2.6** · (*R*)-MTPA:

^{1}H NMR (400.13 MHz, toluene-d_8): δ = 5.94 (d, *J* = 8.8 Hz, 1H, CHO), 3.05 (d, *J* = 8.8 Hz, 1H, CHD).

3.2.2. Chapter 2.2.

Diisopropyl *S*-tributylstannylmethyl thiophosphate (2.20)



2.3 **2.20**

(Bromomethyl)tributylstannane (383 mg, 1.0 mmol) was added to a solution of the triethylammonium salt of the diisopropyl thiophosphoric acid (0.4 M in isopropanol, 4.17 ml, 1.5 mmol) and stirred over night at room temperature. After concentration on a rotary evaporator, water (20 ml) was added and the aqueous phase was extracted with CH_2Cl_2 (2 x 10 ml). The combined organic layers were washed with water (10 ml), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography [hexane/EtOAc (7:1), R_f = 0.59] to yield thiophosphate **2.20** as a colorless oil (463 mg, 92%).

IR (Si): ν = 2958, 2927, 1253, 979 cm^{-1}.

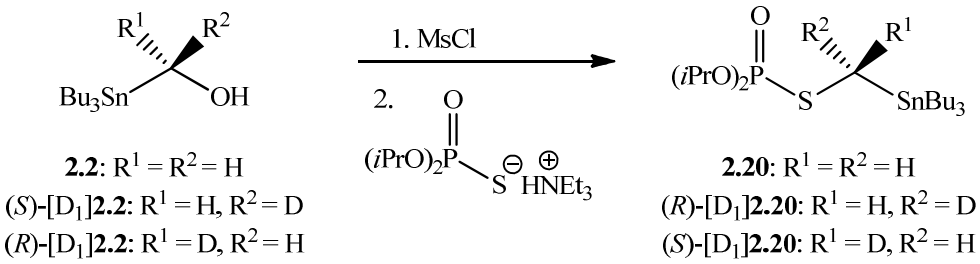
^{1}H NMR (400.27 MHz, $CDCl_3$): δ = 4.72 (dsept, $J(^{31}P)$ = 8.9 Hz, J = 6.2 Hz, 2H, 2 x $\underline{CH}(CH_3)_2$), 2.04 (d, $J(^{31}P)$ = 9.0 Hz, $J(^{117/119}Sn)$ = 35.4 Hz, 2H, SCH_2Sn), 1.60-1.38 (m, 6H, 3 x $SnCH_2\underline{CH_2}$), 1.36 (d, J = 6.3 Hz, 6H, 2 x $CH(\underline{CH_3})_2$), 1.33 (d, J = 6.3 Hz, 6H, 2 x $CH(\underline{CH_3})_2$), 1.29 (sext, J = 7.3 Hz, 6H, 3 x $Sn(CH_2)_2\underline{CH_2}$), 1.04-0.87 (m, $J(^{117/119}Sn)$ = 50.8 Hz, 6H, 3 x $Sn\underline{CH_2}$), 0.87 (t, J = 7.3 Hz, 9H, 3x $Sn(CH_2)_3\underline{CH_3}$)

^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 72.1 (d, $J(^{31}P)$ = 6.0 Hz, 2C, 2 x $\underline{CH}(CH_3)_2$), 28.9 (s, $J(^{117/119}Sn)$ = 21.8 Hz, 3C, 3 x $SnCH_2\underline{CH_2}$), 27.2 (s, $J(^{117/119}Sn)$ = 56.5 Hz, 3C, $Sn(CH_2)_2\underline{CH_2}$), 23.9 (d, $J(^{31}P)$ = 4.2 Hz, 2C, 2 x $CH(\underline{CH_3})_2$), 23.7 (d, $J(^{31}P)$ = 5.6 Hz, 2C, 2 x $CH(\underline{CH_3})_2$), 13.6 (s, 3C, 3 x $Sn(CH_2)_3\underline{CH_3}$), 9.7 (s, $J(^{117/119}Sn)$ = 323.4 Hz, 3C, 3 x $Sn\underline{CH_2}(CH_2)_2$), 4.5 (d, $J(^{31}P)$ = 4.9 Hz, 1C, SCH_2Sn).

^{31}P NMR (161.98 MHz, $CDCl_3$): δ = 29.5.

Anal. calculated for $C_{19}H_{43}O_3PSSn$ (501.29): C 45.52%, H 8.65%, S 6.40%; found: C 45.93%, H 8.85%, S 6.10%.

Diisopropyl *S*-tributylstannylmethyl thiophosphate (2.20)

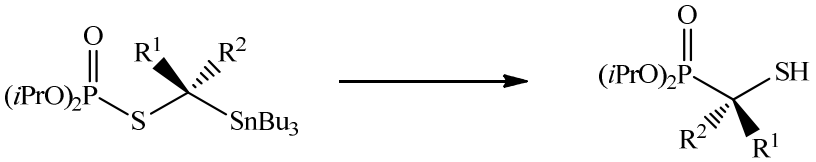


2.2: $R^1 = R^2 = H$
(*S*)-[D_1]**2.2**: $R^1 = H$, $R^2 = D$
(*R*)-[D_1]**2.2**: $R^1 = D$, $R^2 = H$

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

TMP (432 mg, 3.07 mmol) was dissolved in dry THF (12.4 ml) under argon and cooled to –10 °C. *n*-BuLi (1.93 ml, 3.07 mmol) was added and the solution was stirred for 15 minutes. Afterwards it was cooled to –78 °C and tributylstannylmethanol (826 mg, 2.56 mmol) in dry THF (4.2 ml) was added and the solution was stirred for 15 minutes. MsCl (258 µl, 3.33 mmol) was added and the solution was stirred for another 20 minutes, then freshly prepared triethylammonium salt of diisopropylthiophosphoric acid in isopropanol (10.68 ml, 3.84 mmol) was added. Then stirring was continued overnight at room temperature. The mixture was concentrated under reduced pressure and water (26 ml) was added. The aqueous phase was extracted with CH_2Cl_2 (2 x 30 ml). The combined organic phases were washed with water (30 ml), dried (Na_2SO_4), concentrated under reduced pressure and purified by flash chromatography [hexane/EtOAc (7:1), R_f = 0.38] to yield thiophosphate as a colorless oil (1.014 g, 79% for 2 steps).

Diisopropyl mercaptomethylphosphonate (2.23)[121]



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

2.23: $R^1 = R^2 = H$
(*S*)-[D_1]**2.23**: $R^1 = D$, $R^2 = H$
(*R*)-[D_1]**2.23**: $R^1 = H$, $R^2 = D$

1) *S*-Stannylmethyl thiophosphate **2.20** (217 mg, 0.43 mmol) was dissolved in dry THF (3 ml) under argon. The solution was cooled to –78 °C and MeLi (0.52 ml, 0.52 mmol, 1 M in THF/cumene) was added dropwise every 3 seconds. After 2 minutes CH_3CO_2D was added

and the solution was warmed up and concentrated under reduced pressure. Water was added (4 ml) and the aqueous phase was extracted with EtOAc (3 x 10 ml). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography [hexane/EtOAc (1:1), R_f = 0.14] to yield mercaptophosphonate **2.23** as a colorless oil (55 mg, 60%).

2) *S*-Stannylmethyl thiophosphate **2.20** (202 mg, 0.40 mmol) was converted to mercaptophosphonate **2.23** (28 mg, 33%) by procedure 1), except that the experiment was performed at 0 °C for 1 minute and the MeLi was added dropwise every second.

^{1}H NMR (400.27 MHz, $CDCl_3$): δ = 4.74 (dsept, $J(^{31}P)$ = 7.7 Hz, J = 6.3 Hz, 2H, 2 x $\underline{CH}(CH_3)_2$), 2.62 (dd, $J(^{31}P)$ = 13.3 Hz, J = 8.0 Hz, 2H, CH_2S), 1.80 (dt, $J(^{31}P)$ = 9.5 Hz, J = 8.0 Hz, 1H, SH), 1.33 (d, J = 6.3 Hz, 6H, 2 x $CH(\underline{CH_3})_2$), 1.32 (d, J = 6.3 Hz, 6H, 2 x $CH(\underline{CH_3})_2$)

^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 71.4 (d, $J(^{31}P)$ = 6.8 Hz, 2C, $\underline{CH}(CH_3)_2$), 24.1 (d, $J(^{31}P)$ = 3.8 Hz, 2C, 2 x $CH(\underline{CH_3})_2$), 23.9 (d, $J(^{31}P)$ = 5.0 Hz, 2C, 2 x $CH(\underline{CH_3})_2$), 18.7 (d, $J(^{31}P)$ = 156.9 Hz, 1C, $\underline{CH_2}SH$).

^{31}P NMR (161.98 MHz, $CDCl_3$): δ = 23.9 (s, P=O).

For diisopropyl mercapto-[D_1]methylphosphonate ([D_1]2.23)

1) (*S*)-*S*-tributylstannyl-[D_1]methyl thiophosphate (*S*)-[D_1]**2.20** (227 mg, 0.45 mmol) was converted to deuterated (*R*)-mercaptophosphonate (*R*)-[D_1]**2.23** (58 mg, 60%, ee 62%) by the procedure 1) used for the preparation of the racemic mercaptomethylphosphonate, except that the reaction was quenched with acetic acid 1 minute after the addition of MeLi.

2) (*S*)-*S*-tributylstannyl-[D_1]methyl thiophosphate (*S*)-[D_1]**2.20** (280 mg, 0.56 mmol) was converted to deuterated (*R*)-mercaptophosphonate (*R*)-[D_1]**2.23** (48 mg, 41%, ee 23%) by the procedure 1), except that the experiment was performed at 0 °C and the reaction was quenched with acetic acid 15 seconds after the addition of MeLi, added dropwise every second.

3) (*S*)-*S*-tributylstannyl-[D_1]methyl thiophosphate (*S*)-[D_1]**2.20** (229 mg, 0.46 mmol) was converted to deuterated (*R*)-mercaptophosphonate (*R*)-[D_1]**2.23** (22 mg, 22%, ee 77%) by the procedure 1), except that the reaction was performed in Et_2O at –95 °C and 1.05 equiv. MeLi were used.

4) (*S*)-*S*-tributylstannyl-[D_1]methyl thiophosphate (*S*)-[D_1]**2.20** (218 mg, 0.43 mmol) was converted to deuterated (*R*)-mercaptophosphonate (*R*)-[D_1]**2.23** (52 mg, 56%, racemic) by the procedure 3), except that the reaction was performed in dry Et_2O at 0 °C.

5) (*R*)-*S*-tributylstannyl-[D_1]methyl thiophosphate (*R*)-[D_1]**2.20** (286 mg, 0.57 mmol) was converted to deuterated (*S*)-mercaptophosphonate (*S*)-[D_1]**2.23** (31 mg, 25%, ee 61%) by the procedure 3), except that the experiment was performed in dry THF and the reaction was quenched with acetic acid 3 minutes after the addition of MeLi.

6) (*R*)-*S*-tributylstannyl-[D_1]methyl thiophosphate (*R*)-[D_1]**2.20** (249 mg, 0.50 mmol) was converted to deuterated (*S*)-mercaptophosphonate (*S*)-[D_1]**2.23** (73 mg, 68%, ee 52%) by the procedure 5), except that the reaction was performed with *n*-BuLi.

7) (*R*)-*S*-tributylstannyl-[D_1]methyl thiophosphate (*R*)-[D_1]**2.20** (132 mg, 0.26 mmol) was converted to deuterated (*S*)-mercaptophosphonate (*S*)-[D_1]**2.23** (20 mg, 36%, ee 52%) by the procedure 5), except that the reaction was quenched with acetic acid 20 minutes after the addition of MeLi (3M in dimethoxymethane).

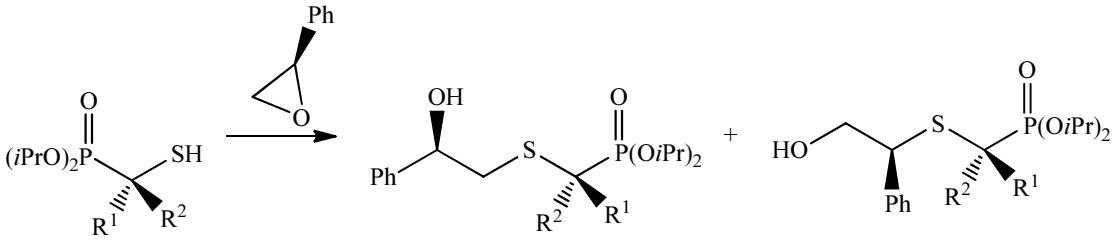
8) (*R*)-*S*-tributylstannyl-[D_1]methyl thiophosphate (*R*)-[D_1]**2.20** (250 mg, 0.50 mmol) was converted to deuterated (*S*)-mercaptophosphonate (*S*)-[D_1]**2.23** (no product isolated) by the procedure 3), except that the experiment was performed in a Trapp solvent mixture (THF:Et_2O:pentane = 4:1:1) at –110 °C and the reaction was quenched with acetic acid 15 minutes after the addition of MeLi (1.6M in Et_2O).

The spectroscopic data were identical to that of **2.23**, except for:

^{1}H NMR (400.27 MHz, $CDCl_3$): δ = 2.60 (tdd, $J(^{31}P)$ = 13.4 Hz, J = 8.2 Hz, J(D)= 2.1 Hz, 1H, CHD), 1.79 (dd, $J(^{31}P)$ = 8.5 Hz, J = 8.2 Hz, 1H, SH).

^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 71.5 (d, $J(^{31}P)$ = 6.9 Hz, 2C, 2 x $\underline{CH}(CH_3)_2$), 24.1 (d, $J(^{31}P)$ = 3.8 Hz, 2C, 2 x $CH(\underline{CH_3})_2$), 23.9 (d, $J(^{31}P)$ = 4.8 Hz, 2C, 2 x $CH(\underline{CH_3})_2$), 18.3 (dt, $J(^{31}P)$ = 151.8 Hz, J(D) = 21.2 Hz, 1C, CHD).

(*R*)-(–)-Diisopropyl [(2-hydroxy-2-phenylethyl)thio]methylphosphonate (2.24) and (*S*)-(+)-diisopropyl [(2-phenyl-2-hydroxyethyl)thio]methylphosphonate (2.25)



2.23: $R^1 = R^2 = H$
(*R*)-[D_1]**2.23**: R^1 = D, R^2 = H
(*S*)-[D_1]**2.23**: R^1 = H, R^2 = D

2.24: $R^1 = R^2 = H$
(*R*)-[D_1]**2.24**: R^1 = D, R^2 = H
(*S*)-[D_1]**2.24**: R^1 = H, R^2 = D

2.25: $R^1 = R^2 = H$
(*R*)-[D_1]**2.25**: R^1 = D, R^2 = H
(*S*)-[D_1]**2.25**: R^1 = H, R^2 = D

(*R*)-(+)-Phenyloxirane [0.12 ml, 1.02 mmol, ee 97% (GLC)] was added to a mixture of mercaptomethylphosphonate **2.23** (54 mg, 0.25 mmol) and K_2CO_3 (70 mg, 0.51 mmol) in isopropanol (2 ml) under argon. The mixture was stirred for 2 hours at room temperature. Afterwards it was concentrated under reduced pressure. Water was added (5 ml) and the mixture was extracted with EtOAc (3 x 10 ml), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography [hexane/EtOAc (1:2), R_{fA} = 0.37, R_{fB} = 0.22] to yield *S*-alkylated mercaptomethylphosphonates **2.24** and **2.25** (A: 44 mg, 52%; B: 19 mg, 24%) as colorless oils.

2.24: $[\alpha]_D^{20}$ = –25.65 (c = 3.15, acetone).

2.25: $[\alpha]_D^{20}$ = +83.36 (c = 1.40, acetone).

Anal. calculated for $C_{15}H_{25}O_4PS$ (332.40): C 54.20%, H 7.58%; found for **2.24**: C 54.27%, H 7.61%; found for **2.25**: C 54.09%, H 7.54%.

2.24:
IR (Si): ν = 3369, 2979, 1238, 990 cm^{-1}.

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 7.38-7.29 (m, 4H, H_{arom}), 7.27-7.21 (m, 1H, H_{arom}), 4.88 (X-part of ABX-sys., J = 9.1, 3.0 Hz, 1H, CHOH), 4.77 (dsept, $J(^{31}P)$ = 7.6 Hz, J = 6.2 Hz, 2H, 2 x $CH(CH_3)_2$), 3.08 (A-part of ABX-sys., J_{AB} = 14.3 Hz, J = 3.0 Hz, 1H, SCH_2CH), 2.89 (B-part of ABX-sys., J_{AB} = 14.3 Hz, J = 9.1 Hz, 1H, SCH_2CH), 2.75 (AB-sys., J_{AB} = 15.6 Hz, $J(^{31}P)$ = 12.9 Hz, 2H, PCH_2S), 1.34 (d, J = 6.2 Hz, 3H, $CH(CH_3)_2$), 1.33 (d, J = 6.2 Hz, 9H, 3 x $CH(CH_3)_2$).

^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 142.9 (s, 1C, $C_{q\ arom}$), 128.4 (s, 2C, 2x C_{arom}), 127.6 (s, 1C, C_{arom}), 125.7 (s, 2C, 2 x C_{arom}), 73.0 (s, 1C, CHOH), 71.7 (d, $J(^{31}P)$ = 6.1 Hz, 1C, $CH(CH_3)_2$), 71.6 (d, $J(^{31}P)$ = 6.9 Hz, 1C, $CH(CH_3)_2$), 43.3 (d, $J(^{31}P)$ = 1.8 Hz, 1C, $CHCH_2S$), 26.5 (d, $J(^{31}P)$ = 151.3 Hz, 1C, SCH_2P), 24.1 (d, $J(^{31}P)$ = 3.8 Hz, 1C, $CH(CH_3)_2$), 24.0 (d, $J(^{31}P)$ = 3.8 Hz, 1C, $CH(CH_3)_2$), 23.9 (d, $J(^{31}P)$ = 5.4 Hz, 2C, $CH(CH_3)_2$).

^{31}P NMR (161.98 MHz, $CDCl_3$): δ = 24.7 (P=O).

2.25:

IR(Si): ν = 3383, 2978, 2932, 1386, 1374, 1234, 1179, 1105, 1066, 985 cm^{-1}.

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 7.36-7.28 (m, 4H, H_{arom}), 7.27-7.22 (m, 1H, H_{arom}), in 4.75 and 4.68 (two dsept, $J(^{31}P)$ = 7.7 Hz, J = 6.2 Hz, 2H, 2 x $CH(CH_3)_2$), 4.20 (X-part of ABX-sys. ≈ t, J = 6.8 Hz, J = 6.1 Hz, 1H, $SCHCH_2$), 3.95 (AB-part of ABX-sys., J_{AB} = 11.9 Hz, J = 6.8, 6.1 Hz, 2H, $CHCH_2OH$), 3.04 (br. s, 1H, CH_2OH), 2.64 (AB-sys., J_{AB} = 15.2, $J(^{31}P)$ = 13.6 Hz, 2H, PCH_2S), 1.32 (d, J = 6.3 Hz, 3H, $CH(CH_3)_2$), 1.31 (d, J = 6.3 Hz, 3H, $CH(CH_3)_2$), 1.30 (d, J = 6.3 Hz, 3H, $CH(CH_3)_2$), 1.29 (d, J = 6.3 Hz, 3H, $CH(CH_3)_2$).

^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 138.9 (s, 1C, $C_{q\ arom}$), 128.7 (s, 2C, 2x C_{arom}), 128.1 (s, 2C, 2 x C_{arom}), 127.8 (s, 1C, C_{arom}), 71.7 (d, $J(^{31}P)$ = 6.8 Hz, 1C, $CH(CH_3)_2$), 71.4 (d, $J(^{31}P)$ = 7.0 Hz, 1C, $CH(CH_3)_2$), 65.9 (s, 1C, CH_2OH), 53.9 (d, $J(^{31}P)$ = 3.1 Hz, CH_2CHS), 25.3 (d, $J(^{31}P)$ = 151.4 Hz, 1C, PCH_2S), 24.1 (d, $J(^{31}P)$ = 3.8 Hz, 1C, $CH(CH_3)_2$), 24.0 (d, $J(^{31}P)$ = 3.8 Hz, 1C, $CH(CH_3)_2$), 23.9 (d, $J(^{31}P)$ = 5.4 Hz, 2C, $CH(CH_3)_2$).

^{31}P NMR (161.98 MHz, $CDCl_3$): δ = 24.5 (P=O).

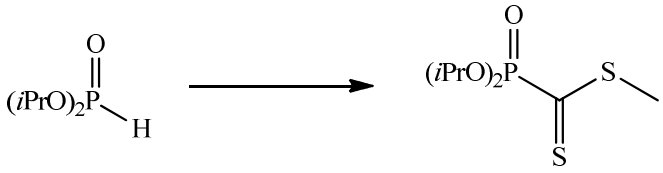
Diisopropyl *S*-tributylstannyl-[D_1]methyl thiophosphate

Prepared in the same way as the racemic compound **2.20**. The spectroscopic data were identical to **2.20**, except for:

^{1}H NMR (400.27 MHz, $CDCl_3$): δ = 2.04 (br. d, $J(^{31}P)$ = 9.0 Hz, $J(^{117/119}Sn)$ = 35.4 Hz, 1H, SCHD).

Preparation of 2.23 as a reference substance

1) *S*-Methyl (diisopropoxyphosphinyl)dithioformate[122]



Diisopropyl phosphite (1.67 ml, 10 mmol) was dissolved in dry THF (20 ml) under argon and cooled to –78 °C. *n*-BuLi (6.88 ml, 11 mmol) was added and the solution was stirred for 5 minutes. Then CS_2 (0.72 ml, 12 mmol) was added and the solution was stirred for another 15 minutes. MeI (0.75 ml, 12 mmol) was added and then stirring was continued at room temperature for another 2 hours. Again MeI (0.75 ml, 12 mmol) was added and the solution was stirred for another 2 hours. Afterwards the reaction mixture was concentrated under reduced pressure and a saturated aqueous solution of $NaHCO_3$ (20 ml) was added. The mixture was extracted with EtOAc (2 x 20 ml). The combined organic phases were washed with aqueous $NaHCO_3$ (20 ml), dried ($MgSO_4$), concentrated under reduced pressure and purified by bulb-to-bulb distillation (70 °C, 0.5 mbar) (lit.[111]: 116-117 °C/0.4 mm) to yield a dark red colored oil (858 mg, 33%).

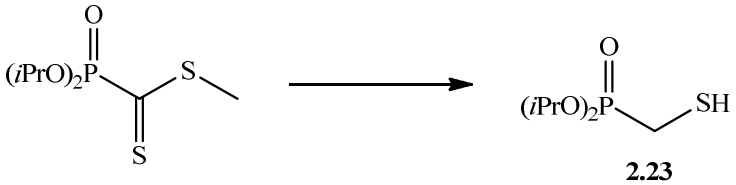
n_D^{20} = 1.5220 (lit.[111]: n_D^{25} =1.5168).

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 4.82 (dsept, J = 6.2 Hz, $J(^{31}P)$ = 7.3 Hz, 2H, 2 x $\underline{CH}(CH_3)_2$), 2.66 (s, 3H, SCH_3), 1.37 (d, J = 6.2 Hz, 6H, 2 x $CH(\underline{CH_3})_2$), 1.32 (d, J = 6.2 Hz, 6H, 2 x $CH(\underline{CH_3})_2$).

^{13}C NMR (100.61 MHz, $CDCl_3$): δ = CS_2 n. d., 73.7 (d, J(^{31}P) = 6.8 Hz, 2C, CH$(CH_3)_2$), 24.1 (d, J(^{31}P) = 3.9 Hz, 2C, 2 x CH(CH_3)$_2$), 23.6 (d, J(^{31}P) = 5.4 Hz, 2C, 2 x CH(CH_3)$_2$), 19.3 (d, J(^{31}P) = 3.0 Hz, 1C, SCH_3).

^{31}P NMR (161.98 MHz, $CDCl_3$): δ = -2.7 (s, P=O).

2) Reduction of *S*-methyl (diisopropoxyphosphinyl)dithioformate to mercaptomethylphosphonate (2.23)



2.23

S-Methyl (diisopropoxyphosphinyl)dithioformate (769 mg, 3 mmol) was dissolved in dry acetonitrile (30 ml) under argon and a solution of $NaBD_4$ (454 mg, 12 mmol in mixture of 1.5 ml of 1M NaOH and 1.5 ml of MeOH) was added. The reaction mixture was refluxed for 30 minutes, water (1 ml) was added and refluxing was continued for another 60 minutes. Afterwards the reaction mixture was cooled to room temperature and Et_2O (30 ml) and 2M HCl (22 ml) were added. The phases were separated and the aqueous one was extracted with Et_2O (3 x 25 ml). The combined organic layers were washed with water (3 x 25 ml), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography [hexane/EtOAc (1:1), R_f = 0.37] to yield mercaptomethylphosphonate as a colorless oil (301 mg, 47%).
Surprisingly, no deuterium was found in the product. The spectroscopic data were identical to that of the compound prepared by rearrangement (**2.23**).

Attemped preparation of deuterated (*R*)-(–)-Diisopropyl [(2-hydroxy-2-phenylethyl)thio]-[D_1]methylphosphonate (2.24) and (*S*)-(+)-diisopropyl [(2-phenyl-2-hydroxyethyl)thio]-[D_1]methylphosphonate (2.25)

Mercapto[D_1]methylphosphonate [D_1]**2.23** (44 mg, 0.21 mmol) was converted to *S*-alkylated mercaptomethylphosphonates [D_1]**2.24** and [D_1]**2.25** (**2.24**: 35 mg, 48%; **2.25**: 16 mg, 25%) as colorless oils by the procedure used before (K_2CO_3/isopropanol). No deuterium was found in the products!

Investigation of the deuterium exchange in products 2.24 and 2.25

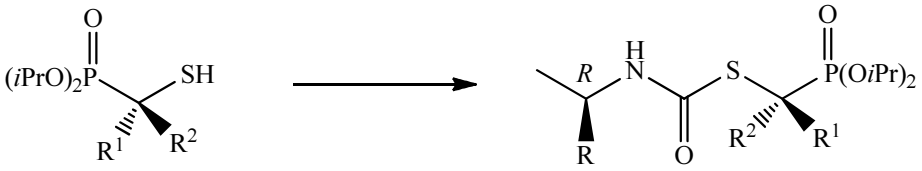
A mixture of *S*-alkylated mercaptomethylphosphonate **2.25** (112 mg, 0.34 mmol) and K_2CO_3 (92 mg, 0.67 mmol) in 2-propanol-OD (3 ml) were stirred for 3 hours at room temperature under argon. Afterwards it was concentrated under reduced pressure. Water (2 ml) was added and the mixture was extracted with EtOAc (3 x 10 ml), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography [hexane/EtOAc (1:2), R_f = 0.35] to yield *S*-alkylated mercaptomethylphosphonate **2.25** (63 mg, 56%) as colorless oil containing no deuterium (by ^{1}H NMR).
An analogous experiment was performed with *S*-alkylated mercaptomethylphosphonate **2.24** and the same result was obtained.

Deuterium exchange in mercaptomethylphosphonate 2.23 during the derivatization

1) (*R*)-(+)-Phenyloxirane [0.22 ml, 1.88 mmol, ee 97% (GLC)] was added to a mixture of mercaptomethylphosphonate **2.23** (100 mg, 0.47 mmol) and K_2CO_3 (130 mg, 0.94 mmol) in 2-propanol-OD (1.5 ml) under argon. The mixture was stirred for 2 hours at room temperature and concentrated under reduced pressure. Water was added (10 ml) and the mixture was extracted with EtOAc (3 x 15 ml), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography [hexane/EtOAc (1:2), R_{fA} = 0.33, R_{fB} = 0.18] to yield *S*-alkylated mercaptomethylphosphonates **2.24** and **2.25** (**2.24**: 95 mg, 61%; **2.25**: 23 mg, 15%) as colorless oils. The integration in the ^{1}H NMR spectrum for the two diastereotopic protons of the CH_2P group corresponded to 0.36 hydrogens instead of 2.0 for both diastereomers.

2) Mercaptomethylphosphonate **2.23** (92 mg, 0.43 mmol) was converted to *S*-alkylated mercaptomethylphosphonates **2.24** and **2.25** (**2.24**: 90 mg, 63%; **2.25**: 33 mg, 23%) by the procedure 1) except that pyridine (70 µl, 0.87 mmol) was used as a base. The integration in the ^{1}H NMR spectrum for the two diastereotopic protons of the CH_2P group corresponded to 1.83 hydrogens instead of 2.0 for both diastereomers.

_S_-(Diisopropoxyphosphinyl)methyl (_R_)-1-phenylethylthiocarbamate (2.28)



2.23: $R^1 = R^2 = H$
(*R*)-[D_1]**2.23**: $R^1 = D$, $R^2 = H$
(*S*)-[D_1]**2.23**: $R^1 = H$, $R^2 = D$

(*R*)-**2.28**: $R^1 = R^2 = H$
(*R,R*)-[D_1]**2.28**: $R^1 = D$, $R^2 = H$
(*S,R*)-[D_1]**2.28**: $R^1 = H$, $R^2 = D$

R = Phenyl

2.23 (30 mg, 0.14 mmol) and (*R*)-(+)-1-Phenylethyl isocyanate (39 µl, 0.28 mmol, ee 99%) were dissolved in dry THF (2 ml) under argon. The reaction mixture was stirred for 2.5 hours at room temperature. Afterwards water (1 ml) was added and the mixture was concentrated under reduced pressure and purified by flash chromatography [hexane/EtOAc (1:2), $R_f = 0.29$] to yield the thiocarbamate **2.28** (48 mg, 100%) as a colorless oil

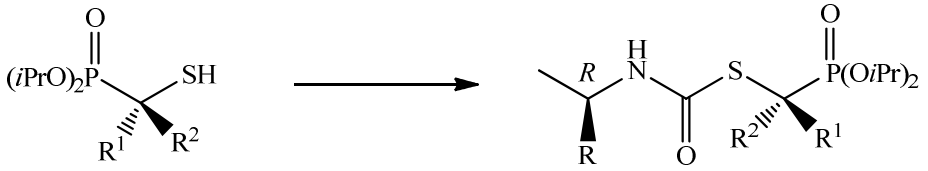
IR (Si): ν = 3230, 2981, 2930, 1679, 1534, 1265, 1239, 994 cm^{-1}.

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 7.28-7.14 (m, 5H, H_{arom}), 6.56 (br. s, 1H, NH), 4.99 (br. s, 1H, $\underline{CH}CH_3$), 4.63 (dsept, $J(^{31}P)$ = 7.6 Hz, J = 6.2 Hz, 2H, 2 x $\underline{CH}(CH_3)_2$), 3.13 (AB-sys., J_{AB} = 15.2 Hz, $J(^{31}P)$ = 13.2 Hz, 2H, CH_2S), 1.43 (d, J = 7.0 Hz, 3H, $CH\underline{CH_3}$), 1.24 (d, J = 6.2 Hz, 3H, $CH(\underline{CH_3})_2$), 1.23 (d, J = 6.2 Hz, 3H, $CH(\underline{CH_3})_3$, 1.22 (d, J = 6.5 Hz, 3H, $CH(\underline{CH_3})_2$, 1.20 (d, J = 6.5 Hz, 3H, $CH(\underline{CH_3})_2$.

^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 164.3 (br. s, 1C, C=O), 142.8 (s, 1C, $C_{q\ arom}$), 128.5 (s, 2C, C_{arom}), 127.3 (s, 1C, C_{arom}), 126.0 (s, 2C, C_{arom}), 71.4 (d, J = 6.9 Hz, 2C, 2 x $\underline{CH}(CH_3)_2$), 51.5 (s, 1C, $\underline{CH}CH_3$), 24.0 (d, $J(^{31}P)$ = 3.7 Hz, 1C, $CH(\underline{CH_3})_2$), 23.9 (d, $J(^{31}P)$ = 3.7 Hz, 1C, $CH(\underline{CH_3})_2$), 23.9 (d, $J(^{31}P)$ = 152.2 Hz, 1C, CH_2S), 23.8 (d, $J(^{31}P)$ = 5.2 Hz, 2C, $CH(\underline{CH_3})_2$), 29.9 (br. s, 1C, $CH\underline{CH_3}$).
^{31}P NMR (161.98 MHz, $CDCl_3$): δ = 22.6 (s, P=O).

Anal. calculated for $C_{16}H_{26}NO_4PS$ (359.42): C 53.47%, H 7.29%, N 3.90%, S 8.92%; found: C 54.19%, H 7.59%, N 3.80%, S 8.41%

_S_-(Diisopropoxyphosphinyl)methyl (_R_)-1-(1-naphthyl)ethylthiocarbamate (2.29)



2.23: $R^1 = R^2 = H$
(*R*)-[D_1]**2.23**: $R^1 = D$, $R^2 = H$
(*S*)-[D_1]**2.23**: $R^1 = H$, $R^2 = D$

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

R = 1-Naphthyl

Mercaptomethylphoshonate **2.23** (76 mg, 0.36 mmol) and (*R*)-(−)-1-(1-naphthyl)ethyl isocyanate (0.62 ml, 0.72 mmol, ee 95%) were dissolved in dry THF (3 ml) under argon. The solution was stirred for 5 hours at room temperature. Afterwards water (0.25 ml) was added) and the mixture was stirred for another 2.5 h. Then it was concentrated under reduced pressure and purified by flash chromatography [hexane/EtOAc (1:2), R_f = 0.61] to yield thiocarbamate **2.29** (136 mg, 97%) as a colorless oil.

IR (Si): ν = 3222, 2980, 2931, 1675, 1533, 1238, 1216, 994 cm^{-1}.

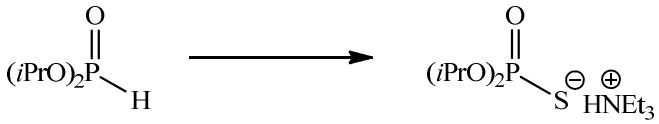
^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 8.04 (d, J = 8.3 Hz, 1H, H_{arom}), 7.85-7.75 (m, 1H, H_{arom}), 7.74 (d, J = 7.9 Hz, 1H, H_{arom}), 7.55-7.35 (m, 4H, H_{arom}) 6.59 (br. s, 1H, NH), 5.85 (br. s, 1H, $\underline{CH}CH_3$), 4.61 (dsept, $J(^{31}P)$ = 7.7 Hz, J = 6.3 Hz, 2H, 2 x $\underline{CH}(CH_3)_2$), 3.18 (AB-sys., J_{AB} = 15.0 Hz, $J(^{31}P)$ = 12.9 Hz, 2H, CH_2S), 1.63 (d, J = 6.8 Hz, 3H, $CH\underline{CH_3}$), 1.27 (d, J = 6.0 Hz, 3H, $CH(\underline{CH_3})_2$), 1.26 (d, J = 5.7 Hz, 3H, $CH(\underline{CH_3})_3$, 1.23 (d, J = 6.2 Hz, 3H, $CH(\underline{CH_3})_2$, 1.21 (d, J = 6.2 Hz, 3H, $CH(\underline{CH_3})_2$.

^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 164.3 (br. s, 1C, C=O), 137.9 (s, 1C, $C_{q\ arom}$), 133.8 (s, 1C, $C_{q\ arom}$), 130.7 (s, 1C, $C_{q\ arom}$), 128.8 (s, 1C, C_{arom}), 128.8 (s, 1C, C_{arom}), 128.3 (s, 1C, C_{arom}), 126.4 (s, 1C, C_{arom}), 125.7 (s, 1C, C_{arom}), 125.2 (s, 1C, C_{arom}), 123.0 (s, 1C, C_{arom}), 122.6 (s, 1C, C_{arom}), 71.40 (d, $J(^{31}P)$ = 6.7 Hz, 1C, $\underline{CH}(CH_3)_2$), 71.38 (d, $J(^{31}P)$ = 6.7 Hz, 1C, $\underline{CH}(CH_3)_2$), 60.31 (s, 1C, $\underline{CH}CH_3$), 24.0 (d, $J(^{31}P)$ = 153.2 Hz, 1C, CH_2S), 23.94 (d, $J(^{31}P)$ = 4.5 Hz, 1 x $CH(\underline{CH_3})_2$), 23.91 (d, $J(^{31}P)$ = 4.4 Hz, 1 x $CH(\underline{CH_3})_2$), 23.79 (d, $J(^{31}P)$ = 4.8 Hz, 1 x $CH(\underline{CH_3})_2$), 23.77 (d, $J(^{31}P)$ = 5.2 Hz, 1 x $CH(\underline{CH_3})_2$), 21.1 (br. s, 1C, $CH\underline{CH_3}$).

^{31}P NMR (161.98 MHz, $CDCl_3$): δ = 22.5 (s, P=O).

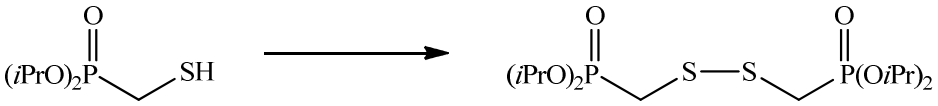
Anal. calculated for $C_{20}H_{28}NO_4PS$ (409.48): C 58.66%, H 6.89%, N 3.42%, S 7.83%; found: C 59.05%, H 7.14%, N 3.80%, S 8.41%.

Triethylammonium salt of diisopropyl thiophosphoric acid



Diisopropyl phosphite (1.66 g, 10 mmol), sulfur (0.32 g, 10 mmol) and triethylamine (1.39 ml, 10 mmol) were dissolved in isopropanol (25 ml) and stirred for 2 hours at 50 °C. Then it was cooled and stored in the refrigerator.

Preparation of disulfide derived from mercaptomethylphosphonate, as a reference sample



2.23

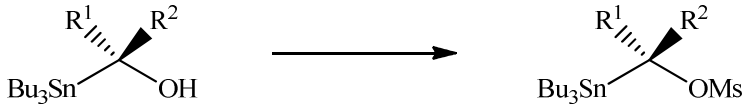
Triethylamine (0.12 ml, 0.84 mmol) was added to the solution of **2.23** (152 mg, 0.72 mmol) in dry THF (3.6 ml). After cooling to 0 °C a solution of iodine (108 mg, 0.43 mmol) in dry THF (1.8 ml) was added dropwise. The reaction mixture was stirred for 2 hours at room temperature and then concentrated under reduced pressure. CH_2Cl_2 was added and after washing with water and an aqueous solution of $Na_2S_2O_3$ the organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc, R_f = 0.25) to yield disulfide as a colorless oil (134 mg, 88%).
IR (Si): ν = 2978, 2933, 1386, 1375, 1253, 1179, 1142, 1106, 982, cm^{-1}.

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 4.72 (dsept, $J(^{31}P)$ = 7.7 Hz, J = 6.2 Hz, 4H, 2 x $\underline{CH}(CH_3)_2$), 3.17 (d, $J(^{31}P)$ = 13.3 Hz, 4H, 2 x CH_2S), 1.32 (d, J = 6.1 Hz, 12H, 4 x $CH(\underline{CH_3})_2$), 1.31 (d, J = 6.1 Hz, 12H, 4 x $CH(\underline{CH_3})_2$).

^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 71.4 (d, $J(^{31}P)$ = 6.8 Hz, 4C, $\underline{CH}(CH_3)_2$), 35.4 (d, $J(^{31}P)$ = 146.2 Hz, 2C, 2 x CH_2S), 24.0 (d, $J(^{31}P)$ = 4.5 Hz, 4C, 4 x $CH(\underline{CH_3})_2$), 23.9 (d, $J(^{31}P)$ = 5.3 Hz, 4C, 4 x $CH(\underline{CH_3})_2$).

^{31}P NMR (161.98 MHz, $CDCl_3$): δ = 21.6 (s, P=O).

Tributylstannylmethyl methanesulfonate (2.26)



2.2: $R^1 = R^2 = H$
(*S*)-[D_1]**2.2**: $R^1 = H$, $R^2 = D$
(*R*)-[D_1]**2.2**: $R^1 = D$, $R^2 = H$

2.26: $R^1 = R^2 = H$
(*S*)-[D_1]**2.26**: $R^1 = H$, $R^2 = D$
(*R*)-[D_1]**2.26**: $R^1 = D$, $R^2 = H$

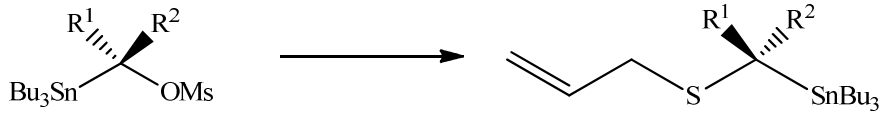
To the solution of TMP (0.41 ml, 2.44 mmol) in dry THF (9.5 ml) under argon *n*-BuLi was added at –10 °C. After stirring for 10 minutes the reaction mixture was cooled down to –78 °C and **2.2** (655 mg, 2.03 mmol) dissolved in dry THF (3.5 ml) was added. After stirring for 15 minutes mesyl chloride (0.20 ml, 2.64 mmol) was added and stirring was continued for another 20 minutes. Afterwards water (13 ml) and 2M HCl (13 ml) were added. The mixture was extracted with EtOAc (3 x 20 ml) and the combined organic phases were washed with a saturated aqueous solution of $NaHCO_3$ (30 ml) and H_2O (30 ml), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography [hexane/EtOAc (7:1), R_f = 0.56] to yield mesylate **2.26** (697 mg, 92%) as a colorless oil.

^{1}H NMR (400.27 MHz, $CDCl_3$): δ = 4.31 (s, $J(^{117/119}Sn)$ = 14.1 Hz, 2H, CH_2O), 2.93 (s, 3H, CH_3), 1.61-1.40 (m, 6H, 3 x $\underline{CH_2}CH_2Sn$), 1.30 (sext, J = 7.1 Hz, 6H, 3 x $\underline{CH_2}(CH_2)_2Sn$), 1.09-0.89 (m, $J(^{117/119}Sn)$ = 51.5 Hz, 6H, 3 x $\underline{CH_2}Sn$), 0.88 (t, J = 7.3 Hz, 9H, 3x $\underline{CH_3}(CH_2)_3Sn$).

Tributylstannyl-[D_1]methyl methanesulfonate ([D_1]2.26)

The spectroscopic data were identical to that of **2.26**, except for:
^{1}H NMR (400.27 MHz, $CDCl_3$): δ = 4.31 (s, $J(^{117/119}Sn)$ = 14.1 Hz, J(D) = 1.2 Hz, 1H, CHDO).

(Allylthiomethyl)tributylstannane (2.30)



2.26: $R^1 = R^2 = H$
(*S*)-[D_1]**2.26**: $R^1 = H$, $R^2 = D$
(*R*)-[D_1]**2.26**: $R^1 = D$, $R^2 = H$

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

Allylmercaptane (0.20 ml, 2.37 mmol) was added to a solution of *t*-BuONa (228 mg, 2.37 mmol) in THF (5.0 ml) and stirred under argon for 10 minutes. Afterwards the reaction mixture was cooled down to –30 °C and tributylstannylmethyl mesylate **2.26** (632 mg, 1.58 mmol) in dry THF (3 ml) was added. After stirring for 15 minutes, 1M HCl (8 ml) and hexanes (8 ml) were added. The organic phase was separated and washed with brine (20 ml), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography [hexane/CH_2Cl_2 (30:1), R_f = 0.54] to yield tributylstannylmethyl sulfide **2.30** (500 mg, 84%) as a colorless oil.

IR (Si): ν = 2956, 2926, 2853, 1635, 1464, 1376, 911 cm^{-1}.

^{1}H NMR (400.27 MHz, $CDCl_3$): δ = 5.74 (tdd, J_{trans} = 17.2 Hz, J_{cis} = 10.0 Hz, J = 7.3 Hz, 1H, $\underline{CH}$=CH_2), 5.07 (tdd, J_{cis} = 10.0 Hz, J = 1.7, 0.8 Hz, 1H, CH=$\underline{CH_2}$, H_{cis}), 5.03 (tdd, J_{trans} = 17.2 Hz, J = 1.7, 1.2 Hz, 1H, CH=$\underline{CH_2}$, H_{trans}), 3.06 (ddd, J = 7.3, 1.2, 0.8 Hz, 2H, $\underline{CH_2}$S), 1.80 (s, J($^{117/119}$Sn) = 41.3 Hz, 2H, Sn-$\underline{CH_2}$), 1.60-1.38 (m, 6H,3 x $\underline{CH_2}$-CH_2-Sn), 1.30 (sext, J = 7.3 Hz, 6H, 3 x $\underline{CH_2}(CH_2)_2$Sn), 1.10-0.82 (m, J($^{117/119}$Sn) = 50.6 Hz, 6H, 3 x $\underline{CH_2}$Sn), 0.87 (t, J = 7.3 Hz, 9H, 3x $\underline{CH_3}(CH_2)_3$Sn).

^{13}C NMR (100.61MHz, $CDCl_3$): δ = 133.9 (s, 1C, $\underline{CH}$=CH_2), 116.7 (s, 1C, $\underline{CH_2}$=CH), 41.0 (s, 1C, $\underline{CH_2}$S), 29.0 (s, J($^{117/119}$Sn) = 20.9 Hz, 3C, 3 x $\underline{CH_2}(CH_2)_2$Sn), 27.3 (s, J($^{117/119}$Sn) = 55.2 Hz, 3C, 3 x $\underline{CH_2}CH_2$Sn), 13.7 (s, 3C, 3 x $\underline{CH_3}(CH_2)_3$), 9.5 (s, J($^{117/119}$Sn) = 334.7, 319.6 Hz, 3C, 3 x Sn$\underline{CH_2}(CH_2)_2$), 7.5 (s, 1C, S$\underline{CH_2}$Sn).

Anal. calculated for $C_{16}H_{34}SSn$ (377.22): C 50.94%, H 9.08%; found: C 51.16%, H 9.14%

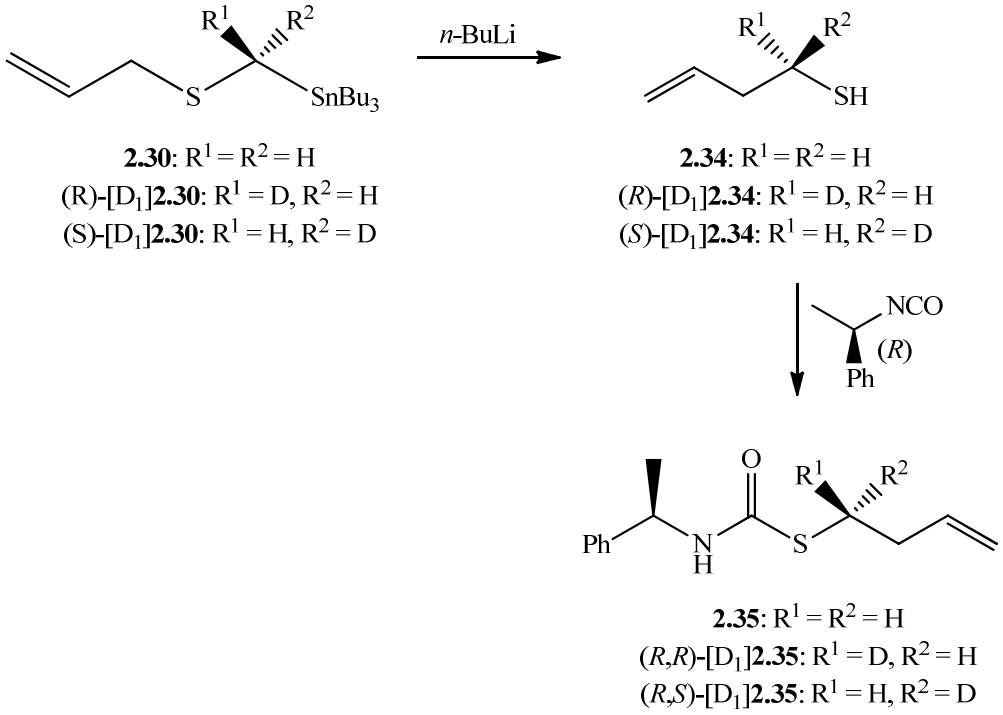
(Allylthio-[D_1]methyl)tributylstannane ([D_1]2.30)

Allylmercaptane (0.22 ml, 2.58 mmol) was converted to tributylstannyl-[D_1]methyl sulfide (*R*)- and (*S*)-[D_1]**2.30** (537 mg, 83%) as a colorless oil.

The spectroscopic data were identical to **2.30**, except for:

^{1}H NMR (400.27 MHz, $CDCl_3$): δ = 1.78 (br. s, $J(^{117/119}Sn)$ = 40.7 Hz, 1H, CHDS).

[2,3]-Rerrangement of (allylthiomethyl)tributylstannane and derivatization of 3-butenethiol to thiocarbamate (2.35)



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

2.34: $R^1 = R^2 = H$
(*R*)-[D_1]**2.34**: R^1 = D, R^2 = H
(*S*)-[D_1]**2.34**: R^1 = H, R^2 = D

2.35: $R^1 = R^2 = H$
(*R*,*R*)-[D_1]**2.35**: R^1 = D, R^2 = H
(*R*,*S*)-[D_1]**2.35**: R^1 = H, R^2 = D

Step 1

n-BuLi (0.25 ml, 0.39 mmol) was added to the solution of sulfide **2.30** (131 mg, 0.33 mmol) in dry THF (2.5 ml) at –95 °C under argon. After 10 minutes 2M CF_3COOH (70 μl, 0.13 mmol) was added and the mixture was used immediately for the derivatization - the thiol **2.34** cannot be isolated because of its low boiling point.

Step 2

(*R*)-(+)-1-Phenylethyl isocyanate (0,10 ml, 0.66 mmol, ee 99%) was added to the reaction mixture of **2.34** at –95 °C under argon. The cooling bath was removed and stirring was continued at room temperature. After 45 minutes a saturated aqueous solution of $NaHCO_3$ (10 ml) was added and the mixture was extracted with EtOAc (2 x 20 ml). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by two flash chromatographies [first: hexane/EtOAc (10:1), R_f = 0.38, side product 0.45; second: hexane/CH_2Cl_2 (1:1), R_f = 0.29, side product 0.68) to yield thiocarbamate **2.35** (64 mg, 83%) as colorless crystals; m.p. = 46-47 °C (hexane).

$[\alpha]_D^{20}$ = –97.78 (c = 0.90, acetone).

IR (Si): ν = 3293, 2977, 1652, 1520, 1495, 1217, 699 cm^{-1}.

^{1}H NMR (400.27 MHz, $CDCl_3$): δ = 7.37-7.18 (m, 5H, H_{arom}), 5.77 (tdd, J_{trans} = 17.0 Hz, J_{cis} = 10.2 Hz, J = 6.7 Hz, 1H, $\underline{CH}$=CH_2), 5.54 (br. s, 1H, NH), 5.06 (qd, J_{trans} = 17.0 Hz, J = 1.6 Hz, 1H, CH=$\underline{CH_2}$), 5.05 (br. s, 1H, $\underline{CH}CH_3$), 5.01 (tdd, J_{cis} = 10.2 Hz, J = 1.6, J = 1.2 Hz, 1H, CH=$\underline{CH_2}$), 2.95 (AB-sys, J_{AB} = 13.4 Hz, J = 7.1 Hz, 2H, $\underline{CH_2}S$), 2.35 (tddd, J = 7.1, 6.7, 1.6, 1.2 Hz, 2H, $\underline{CH_2}CH_2S$), 1.49 (d, J = 6.9 Hz, 3H, $\underline{CH_3}CH$).

^{13}C NMR (100.61MHz, $CDCl_3$): δ = 142.8 (s, 1C, $C_{q\ arom}$), 136.3 (s, 1C, $\underline{CH}CH_2$), 128.7 (s, 2C, C_{arom}), 127.5 (s, 2C, C_{arom}), 126.0 (s, 1C, C_{arom}), 116.3 (s, 1C, $\underline{CH_2}$=CH), 51.1 (s, 1C, $\underline{CH}CH_3$), 34.5 (s, 1C, $\underline{CH_2}CH_2S$), 29.2 (s, 1C, $\underline{CH_2}S$), 22.0 (s, 1C, $\underline{CH_3}CH$).

Anal. calculated for $C_{13}H_{17}NOS$ (235.35): C 66.16%, H 7.25%, N 6.04%, S 13.40%; found: C 66.34%, H 7.28%, N 5.95%, S 13.62%

Rerrangement of (allylthio-[D_1]methyl)tributylstannanes, derivatization of [D_1]but-3-enethiols formed and determination of ee.

1) Allylthio-[D_1]methylstannane (*S*)-[D_1]**2.30** (174 mg, 0.46 mmol) was converted to deuterated 3-butenethiol (*S*)-[D_1]**2.34** and derivatized to (*S*)-[D_1]**2.35** (90 mg, 83%, ee ≥95%) by the procedure used for the preparation of the racemic 3-butenethiol.

2) Allylthio-[D_1]methylstannane (*S*)-[D_1]**2.30** (161 mg, 0.43 mmol) was converted to deuterated 3-butenethiol (*S*)-[D_1]**2.34** and derivatized to (*S*)-[D_1]**2.35** (95 mg, 95%, ee 91%) by the procedure 1), except that the experiment was performed at –78 °C.

3) Allylthio-[D_1]methylstannane (*S*)-[D_1]**2.30** (172 mg, 0.45 mmol) was converted to deuterated 3-butenethiol (*S*)-[D_1]**2.34** and derivatized to (*S*)-[D_1]**2.35** (104 mg, 99%, ee 83%) by the procedure 1), except that the experiment was performed at –40 °C.

4) Allylthio-[D_1]methylstannane (*S*)-[D_1]**2.30** (164 mg, 0.43 mmol) was converted to deuterated 3-butenethiol (*S*)-[D_1]**2.34** and derivatized to (*S*)-[D_1]**2.35** (73 mg, 72%, ee 71%) by the procedure 1), except that the experiment was performed at 0 °C and the reaction was quenched with trifluoroacetic acid 3 minutes after the addition of *n*-BuLi.

5) Allylthio-[D_1]methylstannane (*R*)-[D_1]**2.30** (189 mg, 0.50 mmol) was converted to deuterated 3-butenethiol (*R*)-[D_1]**2.34** and derivatized to (*R*)-[D_1]**2.35** (74 mg, 62%, ee 50%) by the procedure 2), except that the experiment was performed in dry Et_2O.

6) Allylthio-[D_1]methylstannane (*R*)-[D_1]**2.30** (184 mg, 0.49 mmol) was converted to deuterated 3-butenethiol (*R*)-[D_1]**2.34** and derivatized to (*R*)-[D_1]**2.35** (51 mg, 45%, ee 20%) by the procedure 4), except that the experiment was performed in dry Et_2O.

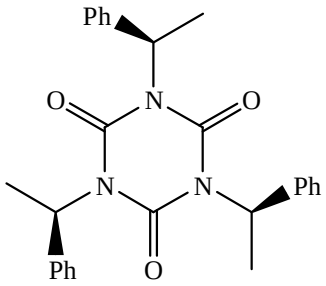
The spectroscopic data were identical to **2.35**, except for:

^{1}H NMR (400.27 MHz, $CDCl_3$): δ = 2.95 (t, J = 7.2 Hz, 1H, CHD), 2.34 (t, J = 6.9 Hz, $\underline{CH_2}$CHD).

To determinate the enantiomeric excesses of derivatives [D_1]**2.35** the ^{1}H NMR experiments were performed in d_6-DMSO with irradiation at 2.24 ppm (decoupling of SCHD$\underline{CH_2}$). Two broad singlets were observed for the two diastereotopic protons of the SCHD group.

^{1}H NMR (600.13 MHz, DMSO): δ = 2.83 (br. s, CHD) and 2.80 (br. s, CHD).

Byproduct **2.36** was also found.



Colorless crystals (132 mg, 70%), m.p. = 149-150 °C (ethanol).

$[\alpha]_D^{20}$ = –234.9 (c = 1.10, acetone).
$[\alpha]_D^{20}$ = –258.8 (c = 0.37, ethanol).

IR (Si): ν = 3032, 2984, 1687, 1429, 1370, 1349, 1214 cm^{-1}.

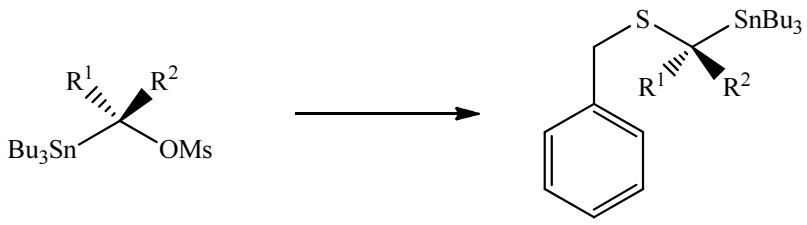
^{1}H NMR (400.27 MHz, $CDCl_3$): δ = 7.39-7.12 (m, 15H, H_{arom}), 5.99 (q, J = 7.1 Hz, 3 x CH), 1.78 (d, J = 7.1 Hz, 9H, 3 x CH_3).

^{13}C NMR (100.61MHz, $CDCl_3$): δ = 148.5 (s, 3C, C=O), 139.6 (s, 3C, $C_{q\ arom}$), 128.3 (s, 6C, 6 x C_{arom}), 127.4 (s, 3C, 3x C_{arom}), 126.9 (s, 6C, 6 x C_{arom}), 52.9 (s, 3C, 3 x CH), 16.4 (s, 3C, 3 x CH_3).

MS (EI, 70 eV): m/z (%) = 441 (13, M^+), 337 (25, M^+-C_6H_8), 233 [100, M^+-2(C_6H_8)].

Anal. calculated for $C_{27}H_{27}N_3O_3$ (441.52): C 73.45%, H 6.16%, N 9.52%; found: C 73.46%, H 5.99%, N 9.49%.

(Benzylthiomethyl)-, (*R*)- and (*S*)-benzylthio-[D_1]methyltributylstannane (2.31)



2.26: $R^1 = R^2 = H$
(*S*)-[D_1]**2.26**: $R^1 = H$, $R^2 = D$
(*R*)-[D_1]**2.26**: $R^1 = D$, $R^2 = H$

2.31: $R^1 = R^2 = H$
(*R*)-[D_1]**2.31**: $R^1 = D$, $R^2 = H$
(*S*)-[D_1]**2.31**: $R^1 = H$, $R^2 = D$

Benzylmercaptane (0.35 ml, 3.0 mmol) was added to a mixture of *t*-BuONa (289 mg, 3.0 mmol) in dry THF (6.3 ml) and stirred under argon for 10 minutes. Afterwards the reaction mixture was cooled to –30 °C and **2.26** (798 mg, 2.0 mmol) in dry THF (3.5 ml) was added. Stirring was continued for 15 minutes and then 1M HCl (10 ml) and hexane (10 ml) were added. The organic phase was separated and washed with brine (20 ml), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified first by bulb-to-bulb distillation (45 °C, 0.5 mbar) to remove excess benzylmercaptane and then by flash chromatography [hexane/CH_2Cl_2 (30:1), R_f = 0.33] to yield benzylthiomethylstannane **2.31** (786 mg, 92%) as a colorless oil.

IR (Si): ν = 2955, 2923, 2851, 1493, 1453, 1376 1071cm^{-1}.

^{1}H NMR (400.27 MHz, $CDCl_3$): δ = 7.35-7.15 (m, 5H, H_{arom}), 3.64 (s, 2H, CH_2S), 1.77 (s, $J(^{117/119}Sn)$ = 41.6 Hz, 2H, CH_2Sn), 1.57-1.33 (m, 6H, 3 x $\underline{CH_2}CH_2Sn$), 1.30 (sext, J = 7.3 Hz, 6H, 3 x $\underline{CH_2}(CH_2)_2Sn$), 0.97-0.80 (m, $J(^{117/119}Sn)$ = 49.6 Hz, 6H, 3 x $\underline{CH_2}Sn$), 0.85 (t, J = 7.3 Hz, 9H, 3x $\underline{CH_3}(CH_2)_3Sn$).

^{13}C NMR (100.61MHz, $CDCl_3$): δ = Cq not detected, 129.0 (s, 2C, C_{arom}), 128.3 (s, 2C, C_{arom}), 126.6 (s, 1C, C_{arom}), 42.5 (s, 1C, CH_2S), 29.0 (s, $J(^{117/119}Sn)$ = 20.6 Hz, 3C, 3 x $\underline{CH_2}(CH_2)_2Sn$), 27.2 (s, $J(^{117/119}Sn)$ = 55.2 Hz, 3C, 3 x $\underline{CH_2}$-CH_2Sn), 13.7 (s, 3C, 3 x $\underline{CH_3}(CH_2)_3$), 9.5 (s, $J(^{117/119}Sn)$ = 334.4 Hz, 3C, 3 x $Sn\underline{CH_2}(CH_2)_2$), 8.3 (t, $J(^{117/119}Sn)$ = 223.0 Hz, 1C, $S\underline{CH_2}Sn$).

Anal. calculated for $C_{20}H_{36}SSn$ (427.27): C 56.22%, H 8.49%, S 7.50%; found: C 56.48%, H 8.45%, S 7.26%

[D$_1$]2.31

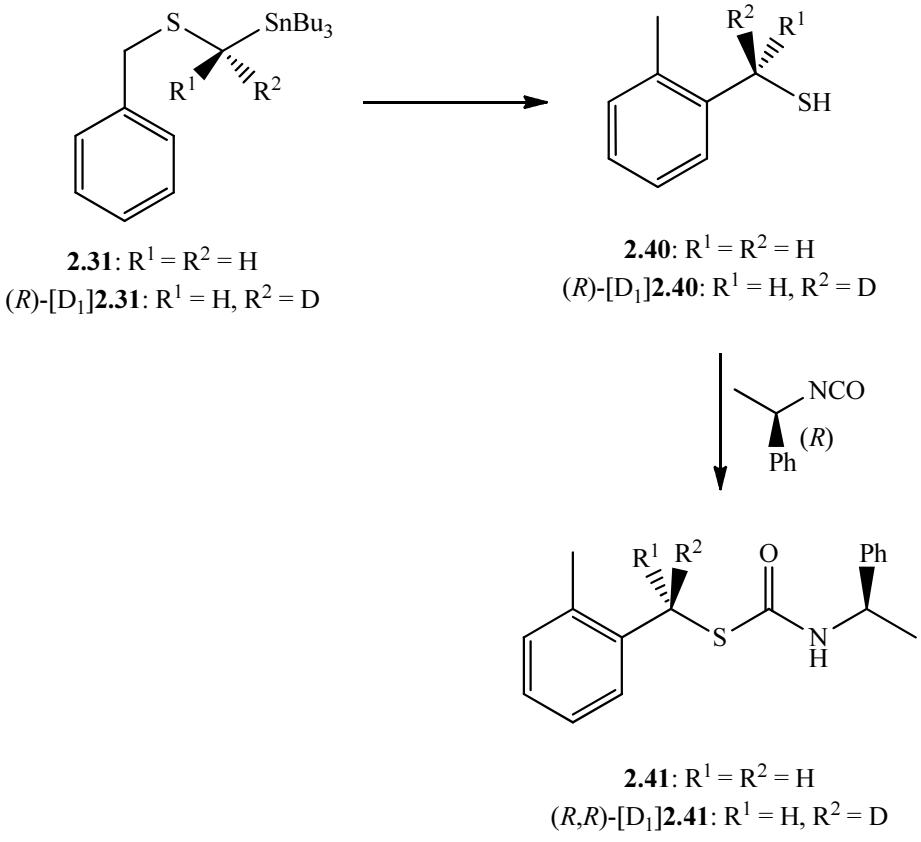
Similarly, (*S*)-tributylstannyl-[D$_1$]methyl mesylate [(*S*)-[D$_1$]**2.26**] (1.690 g, 4.22 mmol) was converted to (*R*)-benzylthio-[D$_1$]methylstannane [(*R*)-[D$_1$]**2.31**] (1.535 g, 85%) as a colourless oil.

Similarly, (*R*)-tributylstannyl-[D$_1$]methyl mesylate [(*R*)-[D$_1$]**2.26**] (1.0 g, 2.49 mmol) was converted to (*S*)-benzylthio-[D$_1$]methylstannane [(S)-[D$_1$]**2.31]** (870 mg, 82%) as a colourless oil.

The ^{1}H NMR spectra of (*R*)- and (*S*)-benzylthio-[D$_1$]methylstannane [(*R*)- and (*S*)-[D$_1$]**2.31**] were identical to that of the unlabeled spezies, except for the resonance of the CHDSn group:

^{1}H NMR (400.27 MHz, $CDCl_3$): δ = 1.77 (s, $J(^{117/119}Sn)$ = 41.6 Hz, 1H, CHDSn).

[2,3]-Rearrangement of (*R*)-(benzylthio-[D$_1$]methyl)tributylstannane, derivatization of 2-methylphenyl-[D$_1$]methanethiol formed and determination of ee.



2.31: R^1 = R^2 = H
(*R*)-[D$_1$]**2.31**: R^1 = H, R^2 = D

2.40: R^1 = R^2 = H
(*R*)-[D$_1$]**2.40**: R^1 = H, R^2 = D

2.41: R^1 = R^2 = H
(*R*,*R*)-[D$_1$]**2.41**: R^1 = H, R^2 = D

Step 1

n-BuLi (0.41 ml, 0.65 mmol) was added to a solution of **2.31** (231 mg, 0.54 mmol) in dry THF (3.8 ml) at –30 °C under argon. After 30 minutes 2M CF_3COOH (0.11 ml, 0.22 mmol) was added and the mixture was used directly for the derivatization. The 2-methylphenylmethanethiol (**2.40**) [detectable by TLC: hexane/CH_2Cl_2 (10:1), R_f = 0.54] was not isolated because of its volatility.

Step 2

This step was optimized using commercially available (2-methylphenyl)methanethiol. (*R*)-(+)-1-Phenylethyl isocyanate (0.17 ml, 1.08 mmol) was added to the above mixture containing (2-methylphenyl)methanethiol under argon. After stirring for 1.5 hours at room temperature water (1 ml) was added and the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography [hexane/CH_2Cl_2 (1:1), R_f = 0.43] to yield thiocarbamate **2.41** (91 mg, 59%) as colorless crystals; m.p. = 92-93 °C (diisopropyl ether).

IR (ATR): ν = 3277, 2972, 2926, 1643, 1527, 1493, 1446, 1216 cm^{-1}.

^{1}H NMR (400.27 MHz, $CDCl_3$): δ = 7.41-7.20 (m, 6H, H_{arom}), 7.19-7.05 (m, 3H, H_{arom}), 5.52 (br. s, 1H, $\underline{CH}CH_3$), 5.08 (br. s, 1H, NH), 4.16 (AB-sys, J_{AB} = 13.7 Hz, 2H, $\underline{CH_2}S$), 2.33 (s, 3H, $\underline{CH_3}Ph$), 1.49 (d, J = 6.9 Hz, 3H, $\underline{CH_3}CH$).

^{13}C NMR (100.61MHz, $CDCl_3$): δ = CO n. d., 142.7 (s, 1C, $C_{q\ arom}$), 136.6 (s, 1C, $C_{q\ arom}$), 136.1 (s, 1C, $C_{q\ arom}$), 130.4 (s, 1C, C_{arom}), 129.9 (s, 1C, C_{arom}), 128.7 (s, 2C, C_{arom}), 127.6 (s, 2C, C_{arom}), 127.5 (s, 1C, C_{arom}), 126.2 (s, 1C, C_{arom}), 126.0 (s, 1C, C_{arom}), 51.2 (s, 1C, $\underline{CH}CH_3$), 32.4 (s, 1C, $\underline{CH_2}S$), 22.0 (br. s, 1C, $\underline{CH_3}CH$), 19.4 (s, 1C, $\underline{CH_3}Ph$).

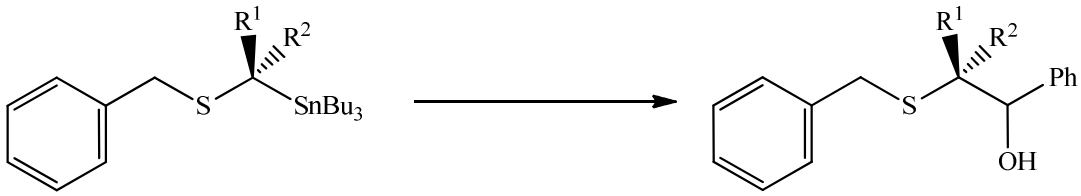
Anal. calculated for $C_{17}H_{19}NOS$ (285.40): C 71.54%, H 6.71%, N 4.91%, S 11.23%; found: C 71.29%, H 6.77%, N 4.92%, S 11.06%.

(*S*)-(Benzylthio-[D_1]methyl)tributylstannane [(*R*)-[D_1]**2.31**] (232 mg, 0.54 mmol) was converted to thiocarbamate (*R*,*S*)-[D_1]**2.41** (92 mg, 59%) as colorless crystals.

The 1H NMR spectrum was identical to that of the unlabeled species **2.41**, except for:

^{1}H NMR (400.27 MHz, $CDCl_3$): δ = 4.17 (s, 1H, CHD), 4.13 (s, 1H, CHD) (thiol was racemic).

2-Benzylthio-1-phenylethanol and benzylthio-1-phenyl-[2-D_1]ethanol (2.43)[123,124]



2.31: $R^1 = R^2 = H$
(*R*)-[D_1]**2.31**: R^1 = D, R^2 = H

2.43: $R^1 = R^2 = H$
(*S*)-[D_1]**2.43**: R^1 = D, R^2 = H

n-BuLi (0.17 ml, 0.26 mmol) was added to a solution of thiomethylstannane **2.31** (92 mg, 0.22 mmol) in dry THF (1.6 ml) at –78 °C under argon. After 10 minutes 2M benzaldehyde in dry THF (0.17 ml, 0.33 mmol) was added, followed by a saturated aqueous solution of $NaHCO_3$ (3 ml) 5 minutes later. The mixture was extracted with EtOAc (3 x 15 ml). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography [hexane/EtOAc (10:1), R_f =0.26] to yield alcohol **2.43** (42 mg, 77%) as a colorless oil.

^{1}H NMR (400.27 MHz, $CDCl_3$): δ = 7.40-7.18 (m, 10H, H_{arom}), 4.66 (X-part of ABX-sys. J = 9.2, 3.7 Hz, 1H, CHOH), 3.71 (s, 2H, CH_2S), 2.78 (A-part of ABX-sys., J_{AB} = 14.0 Hz, J = 3.7 Hz, 1H, SCH_2CH), 2.65 (B-part of ABX-sys., J_{AB} = 14.0 Hz, J = 9.2 Hz, 1H, SCH_2CH), 2.47 (br. s, 1H, OH).

^{13}C NMR (100.61MHz, $CDCl_3$): δ = 142.5 (s, 1C, $C_{q\ arom}$), 137.9 (s, 1C, $C_{q\ arom}$), 128.9 (s, 2C, C_{arom}), 128.6 (s, 2C, C_{arom}), 128.5 (s, 2C, C_{arom}), 127.8 (s, 1C, C_{arom}), 127.2 (s, 1C, C_{arom}), 125.8 (s, 2C, C_{arom}), 71.7 (s, 1C, CHOH), 40.9 (s, 1C, SCH_2), 36.2 (s, 1C, SCH_2CH).

(*S*)-[D_1]2.43

Similarly, the experiments with labeled compounds were performed:

1) (*R*)-benzylthio-[D_1]methylstannane [(*R*)-[D_1]**2.31**] (233 mg, 0.54 mmol) was transformed into alcohol (*S*)-[D_1]**2.43** (95 mg, 72%) by the procedure used for the preparation of the racemic alcohols, except that the benzaldehyd was added 1 minute after the addition of MeLi.
2) (*R*)-benzylthio-[D_1]methylstannane [(*R*)-[D_1]**2.31**] (213 mg, 0.50 mmol) was transformed into alcohol (*S*)-[D_1]**2.43** (30 mg, 24%, ee 16%) by the procedure used for the preparation of the racemic alcohols, except that the benzaldehyd was present in the reaction mixture while adding dropwise every 3 seconds MeLi.

3) (*R*)-benzylthio-[D_1]methylstannane [(*R*)-[D_1]**2.31**] (217 mg, 0.51 mmol) was transformed into alcohol (*S*)-[D_1]**2.43** (5 mg, 4%, ee 21%) by the procedure 2), except that the experiment was performed at –95 °C.

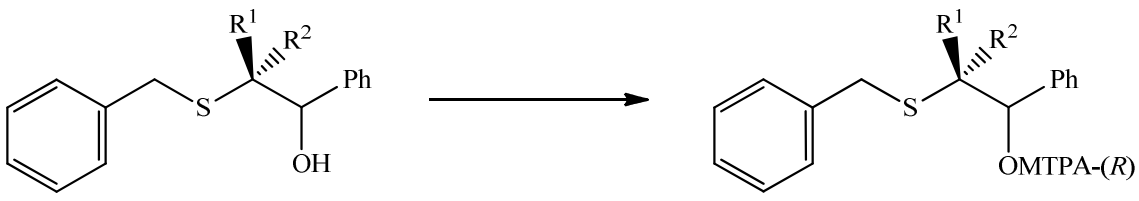
4) (*R*)-benzylthio-[D_1]methylstannane [(*R*)-[D_1]**2.31**) (228 mg, 0.53 mmol) was transformed into alcohol (*S*)-[D_1]**2.43** (11 mg, 9%, ee 26%) by the procedure 3), except that the experiment was performed with 2 equiv. of 12-Crown-4.

The spectroscopic data were identical to that **2.43**, except for:

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 4.59 (2 overlapping d, J = 9.2, 3.7 Hz, 1H, CHOH), 2.82 (br. s, 1H, OH), 2.68 (br. s, 1H, SCHDCH), 2.58 (br. d, J = 9.2 Hz, 1H, SCHDCH).

^{13}C NMR (100.61MHz, $CDCl_3$): δ = 40.4 (t, J = 21.5 Hz, 1C, SCHDCH).

(*R*)-Mosher esters of unlabeled and labeled alcohol 2.43



2.43: $R^1 = R^2 = H$
(*S*)-[D_1]**2.43**: R^1 = D, R^2 = H

2.43 · MTPA-(*R*): $R^1 = R^2 = H$
(*S*)-[D_1]**2.43** · MTPA-(*R*): R^1 = D, R^2 = H

Unlabeled racemic alcohol (±)-**2.43** (mg, mmol) was converted to a 1:1 mixture of diastereomeric (*R*)-Mosher esters according to general procedure A. The product was purified

by flash chromatography [hexane/EtOAc (10:1), R_f =0.51] to yield esters **2.43**·(*R*)-MTPA (28 mg, 94%) as a colorless oil.

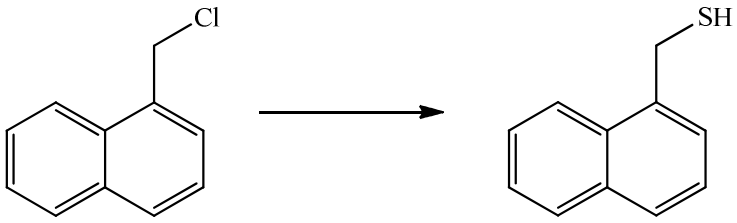
^{1}H NMR (600.13 MHz, $CDCl_3$): δ = 7.48-7.07 (m, 30H, H_{arom}), 5.97 (X-part of ABX-sys., *J* = 8.2, 5.7 Hz, 1H, CHOH, diastereomer A), 5.86 (X-part of ABX-sys., *J* = 9.0, 4.8 Hz, 1H, CHOH, diastereomer B), 3.66 (AB-sys., J_{AB} = 13.5 Hz, 2H, CH_2S), 3.60 (t, *J* = 1.2 Hz, 3H, OCH_3), 3.52 (s, 2H, CH_2S), 3.45 (t, *J* = 1.2 Hz, 3H, OCH_3), 2.87 (A-part of ABX-sys., J_{AB} = 14.4 Hz, *J* = 9.0 Hz, 1H, SCH_2CH, B), 2.83 (A-part of ABX-sys., J_{AB} = 14.4 Hz, *J* = 8.2 Hz, 1H, SCH_2CH, A), 2.70 (B-part of ABX-sys., J_{AB} = 14.4 Hz, *J* = 4.8 Hz, 1H, SCH_2CH, B), 2.69 (B-part of ABX-sys., J_{AB} = 14.4 Hz, *J* = 5.7 Hz, 1H, SCH_2CH, A).

Similarly, the deuterated alcohol (*S*)-[D_1]**2.43** (11 mg, 0.045 mmol), obtained by determination of microscopic configurational stability of chiral benzylthiomethyllithium by procedure 4 was converted to (*R*)-Mosher esters (*S*)-[D_1]**2.43**·(*R*)-MTPA (18 mg, 87%).

The spectroscopic data were identical to that of **2.43**·(*R*)-MTPA, except for:

^{1}H NMR (600.13 MHz, $CDCl_3$): δ = 2.85 (d, *J* = 9.0 Hz, 0.42H, CHD), 2.81 (d, *J* = 8.2 Hz, 0.67H, CHD), 2.68 (2 overlapping d, 1H, CHD).

1-Naphthylmethanethiol[125,126]

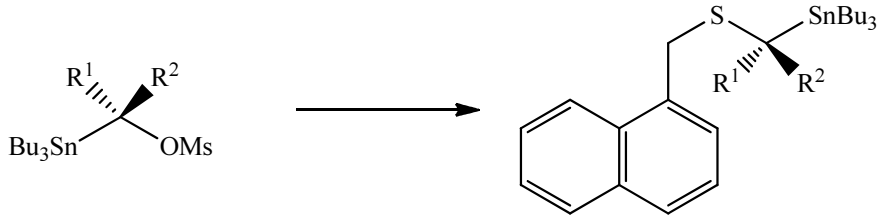


1-Chloromethylnaphthalene (3.0 g, 16.98 mmol, 97%) and thiourea (1.292 g, 16.98 mmol) were dissolved in dry ethanol (10 ml) and refluxed for 2 hours and stirred for another hour at room temperature. An aqueous solution of NaOH (2.83 ml, 9.5 M) was added to the reaction mixture under argon and refluxing was continued for another hour. Water (5 ml) and 8 M H_2SO_4 (37.5 ml) were added and the aqueous phase was extracted with Et_2O (3 x 30 ml). The combined organic phases were dried ($MgSO_4$), concentrated under reduced pressure and purified by flash chromatography [hexane/CH_2Cl_2 (8:1), R_f =0.45] to yield 1-naphthylmethanethiol (2.387 g, 81%) as a colorless oil.

^{1}H NMR (400.27 MHz, $CDCl_3$): δ = 8.10 (d, J = 8.4 Hz, 1H, H_{arom}), 7.89 (d, J = 8.1 Hz, 1H, H_{arom}), 7.78 (d, J = 8.0 Hz, 1H, H_{arom}), 7.62-7.37 (m, 4H, H_{arom}), 4.20 (d, J = 7.2 Hz, 2H, CH_2S), 1.90 (t, J = 7.2 Hz, 1H, SH).

^{13}C NMR (100.61MHz, $CDCl_3$): δ = 136.9 (s, 1C, $C_{q\ arom}$), 134.1 (s, 1 C, $C_{q\ arom}$), 130.7 (s, 1C, $C_{q\ arom}$), 128.9 (s, 1C, C_{arom}), 128.1 (s, 1C, C_{arom}), 126.3 (s, 1C, C_{arom}), 126.1 (s, 1C, C_{arom}), 125.9 (s, 1C, C_{arom}), 125.5 (s, 1C, C_{arom}), 123.6 (s, 1C, C_{arom}), 26.6 (s, 1C, CH_2S).

(1-Naphthylmethyl)thiomethyl- and (*S*)-(1-naphthylmethylthio-[D_1]methyl)-tributylstannane (2.32)



2.26: $R^1 = R^2 = H$
(*S*)-[D_1]**2.26**: $R^1 = H$, $R^2 = D$

2.32: $R^1 = R^2 = H$
(*R*)-[D_1]**2.32**: $R^1 = D$, $R^2 = H$

1-Naphthylmethylthiol (745 mg, 4.66 mmol) dissolved in dry THF (5 ml) was added to a mixture of *t*-BuONa (450 mg, 4.66 mmol) in dry THF (10.0 ml) and stirred under argon for 10 minutes. Afterwards the reaction mixture was cooled to –30 °C and tributylstannylmethyl mesylate **2.26** (1.240 g, 3.11 mmol) in dry THF (3.5 ml) was added. After stirring for 15 minutes 1M HCl (15 ml) and Et_2O (15 ml) was added. The organic phase was washed with brine (25 ml) and 2 M NaOH (3 x 25 ml), dried ($MgSO_4$), and concentrated under reduced pressure. The residue and purified by flash chromatography [hexane/CH_2Cl_2 (30:1), R_f = 0.33] to yield thiomethylstannane **2.32** (1.219 g, 82%) as a colorless oil.

IR (Si): ν = 2954, 2922, 2851, 1510, 1462, 1376, 1074, 1016 cm^{-1}.

^{1}H NMR (400.27 MHz, $CDCl_3$): δ = 8.19-8.11 (d, J = 8.5 Hz, 1H, H_{arom}), 7.85-7.68 (m, 2H, H_{arom}), 7.55-7.42 (m, 2H, H_{arom}), 7.41-7.33 (m, 2H, H_{arom}), 4.12 (s, 2H, CH_2S), 1.83 (s, $J(^{117/119}Sn)$ = 40.1 Hz, 2H, CH_2Sn), 1.49-1.33 (m, 6H, 3 x $\underline{CH_2}CH_2Sn$), 1.21 (sext, J = 7.3 Hz, 6H, 3 x $\underline{CH_2}(CH_2)_2Sn$), 0.98-0.83 (m, 6H, 3 x $\underline{CH_2}Sn$), 0.81 (t, J = 7.3 Hz, 9H, 3x $\underline{CH_3}(CH_2)_3Sn$).

^{13}C NMR (100.61MHz, $CDCl_3$): δ = 134.1 (s, 1C, $C_{q\ arom}$), 133.7 (s, 1C, $C_{q\ arom}$), 131.6 (s, 1C, $C_{q\ arom}$), 128.6 (s, 1C, C_{arom}), 127.7 (s, 1C, C_{arom}), 127.2 (s, 1C, C_{arom}), 125.8 (s, 1C, C_{arom}), 125.6 (s, 1C, C_{arom}), 125.0 (s, 1C, C_{arom}), 124.3 (s, 1C, C_{arom}), 40.4 (s, 1C, $\underline{CH_2}S$), 28.9 (s, J($^{117/119}$Sn) = 20.9 Hz, 3C, 3 x $\underline{CH_2}(CH_2)_2Sn$), 27.2 (s, J($^{117/119}$Sn) = 55.1 Hz, 3C, 3 x $\underline{CH_2}CH_2Sn$), 13.6 (s, 3C, 3 x $\underline{CH_3}(CH_2)_3$), 9.5 (s, J($^{117/119}$Sn) = 319.6 Hz, 3C, 3 x $Sn\underline{CH_2}(CH_2)_2$), 9.1 (s, J($^{117/119}$Sn) = 214.4 Hz, 1C, $S\underline{CH_2}Sn$).

Anal. calculated for $C_{24}H_{38}SSn$ (477.33): C 60.39%, H 8.02%; found: C 60.34%, H 7.76%.

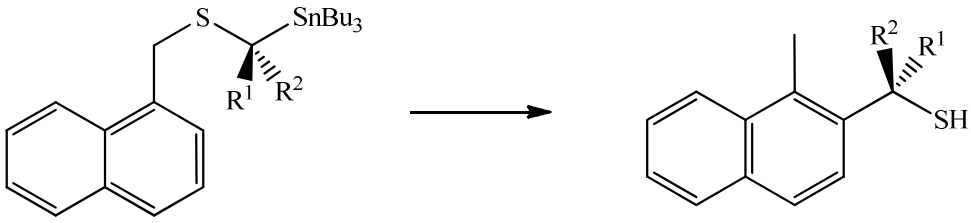
Similarly, (*S*)-tributylstannyl-[D_1]methyl mesylate (*S*)-[D_1]**2.26** (678 mg, 1.69 mmol) was converted to thiomethylstannane (*R*)-[D_1]**2.32** (642 mg, 79%).

The spectroscopic data were identical to that of **2.32**, except for:

^{1}H NMR (400.27 MHz, $CDCl_3$): δ = 1.81 (s, J($^{117/119}$Sn) = 41.0 Hz, 1H, CHDSn)

^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 8.8 (t, J = 21.0 Hz, 1C, S$\underline{CHD}$Sn).

(1-Methylnaphth-2-yl)methanethiol and (1-methylnaphth-2-yl)-[D_1]methanethiol (2.45)



2.32: $R^1 = R^2 = H$
(*R*)-[D_1]**2.32**: R^1 = H, R^2 = D

2.45: $R^1 = R^2 = H$
(*R*)-[D_1]**2.45**: R^1 = H, R^2 = D

n-BuLi (0.50 ml, 0.79 mmol) was added to the solution of thiomethylstannane **2.32** (314 mg, 0.66 mmol) in dry THF (4.6 ml) at –78 °C under argon. After 10 minutes 2M CF_3COOH (0.43 ml, 0.87 mmol) was added and the mixture was extracted with EtOAc (3 x 10 ml). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography [hexane/CH_2Cl_2 (10:1), R_f =0.32] to yield thiol **2.45** (57 mg, 45%) as a colorless oil.

IR (Si): ν = 3050, 2924, 1597, 1510, 1382, 1264, 1248, 1210, 1060 cm^{-1}.

^{1}H NMR (400.27 MHz, $CDCl_3$): δ = 8.04 (d, , J = 8.5 Hz, 1H, H_{arom}), 7.79 (d, J = 8.1 Hz, 1H, H_{arom}), 7.67 (d, J = 8.4 Hz, 1H, H_{arom}), 7.55-7.40 (m, 2H, H_{arom}), 7.38-7.33 (m, 1H, H_{arom}), 3.94 (d, J = 7.0 Hz, 2H, $\underline{CH_2}SH$), 2.69 (s, 3H, CH_3), 1.71 (t, J = 7.0 Hz, 1H, $CH_2\underline{SH}$).
^{13}C NMR (100.61MHz, $CDCl_3$): δ = 136.1 (s, 1C, $C_{q\ arom}$), 133.1 (s, 1C, $C_{q\ arom}$), 132.8 (s, 1C, $C_{q\ arom}$), 131.1 (s, 1C, $C_{q\ arom}$), 128.5 (s, 1C, C_{arom}), 127.3 (s, 1C, C_{arom}), 126.7 (s, 1C, C_{arom}), 126.1 (s, 1C, C_{arom}), 125.4 (s, 1C, C_{arom}), 124.1 (s, 1C, C_{arom}), 27.7 (s, 1C, $\underline{CH_2}SH$), 14.2 (s, 1C, CH_3).

Anal. calculated for $C_{12}H_{12}S$ (189.07): C 76.38%, H 6.39%, S 16.76%; found: C 76.55%, H 6.42%, S 17.03%.

Similarly, the experiments with labeled (*R*)-[D_1]**2.32** compound were performed:

1) Deuterated stannane (*R*)-[D_1]**2.32** (208 mg, 0.43 mmol) was rearranged to (*R*)-(1-methylnaphth-2-yl)-[D_1]methanethiol [(*R*)-[D_1]**2.45**] (49 mg, 60%, ee 72%) by the procedure used for the preparation of the racemic alcohols, except that the experiment was performed at –95 °C.

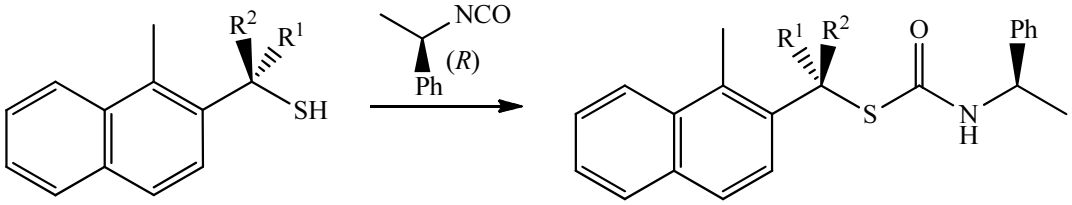
2) Deuterated stannane (*R*)-[D_1]**2.32** (212 mg, 0.44 mmol) was rearranged to (*R*)-(1-methylnaphth-2-yl)-[D_1]methanethiol [(*R*)-[D_1]**2.45**] (6 mg, 7%, ee 67%) by the procedure used for the preparation of the racemic alcohols, except that the experiment was performed at –50 °C.

3) Deuterated stannane (*R*)-[D_1]**2.32** (206 mg, 0.43 mmol) was rearranged to (*R*)-(1-methylnaphth-2-yl)-[D_1]methanethiol [(*R*)-[D_1]**2.45**] (22 mg, 28%, ee 60%) by the procedure 2), except that the experiment was performed using MeLi (3M in dimethoxymethane) .

The ^{1}H NMR spectrum was identical to that of **2.45**, except for:

^{1}H NMR (400.27 MHz, $CDCl_3$): δ = 3.92 (dt, J = 7.0, 1.8 Hz, 1H, $\underline{CHD}SH$), 1.69 (d, J = 7.0 Hz, 1H, $CHD\underline{SH}$).

_S_-(1-Methylnaphth-2-yl)methyl (_R_)-_N_-(1-phenylethyl)thiocarbamate and -(1-methylnaphth-2-yl)-[D_1]methyl (_R_)-_N_-(1-phenylethyl)thiocarbamate (2.46)



2.45: $R^1 = R^2 = H$
(*R*)-[D_1]**2.45**: $R^1 = H$, $R^2 = D$

2.46: $R^1 = R^2 = H$
(*R*,*R*)-[D_1]**2.46**: $R^1 = H$, $R^2 = D$

(*R*)-(+)-1-Phenylethyl isocyanate (67 µl, 0.48 mmol) was added to a solution of thiol **2.45** (46 mg, 0.24 mmol) in dry THF (1.2 ml) under argon at room temperature. After 1 hour water (1 ml) was added and the mixture was extracted with EtOAc (3 x 15 ml). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography [hexane/CH_2Cl_2 (1:1), R_f =0.37] to yield thiocarbamate **2.46** (39 mg, 50%) as colorless crystals; m.p. = 134-135 °C (diisopropyl ether).

IR (ATR): ν = 3284, 2975, 2925, 1640, 1509, 1446, 1204, 1179, 1101 cm^{-1}.

^{1}H NMR (400.27 MHz, $CDCl_3$): δ = 8.03 (d, J = 8.5 Hz, 1H, H_{arom}), 7.78 (d, J = 8.3 Hz, 1H, H_{arom}), 7.63 (d, J = 8.4 Hz, 1H, H_{arom}), 7.53-7.39 (m, 3H, H_{arom}), 7.38-7.19 (m, 5H, H_{arom}), 5.46 (br. s, 1H, NH), 5.10 (br. s, 1H, $\underline{CH}CH_3$), 4.38 (AB-sys, J_{AB} = 13.2 Hz, 2H, $\underline{CH_2}S$), 2.65 (s, 3H, $\underline{CH_3}$), 1.50 (d, J = 6.9 Hz, 3H, $\underline{CH_3}CH$).

^{13}C NMR (100.61 MHz, $CDCl_3$): δ = C=O (n. d.), 142.7 (s, 1C, $C_{q\ arom}$), 133.0 (s, 1C, $C_{q\ arom}$), 132.9 (s, 1C, $C_{q\ arom}$), 132.4 (s, 1C, $C_{q\ arom}$), 128.8 (s, 1C, C_{arom}), 128.5 (s, 1C, C_{arom}), 128.2 (s, 1C, C_{arom}), 127.6 (s, 1C, C_{arom}), 126.4 (s, 1C, C_{arom}), 126.0 (s, 1C, C_{arom}), 125.4 (s, 1C, C_{arom}), 124.1 (s, 1C, C_{arom}), 51.3 (s, 1C, $\underline{CH}CH_3$), 33.3 (s, 1C, CH_2S), 22.1 (br. s, 1C, $CH\underline{CH_3}$), 14.5 (s, 1C, $\underline{CH_3}$).

Anal. calculated for $C_{21}H_{21}NOS$ (335.46): C 75.19%, H 6.31%, N 4.18%, S 9.56%; found: C 74.89%, H 6.22%, N 4.05%, S 9.56%.

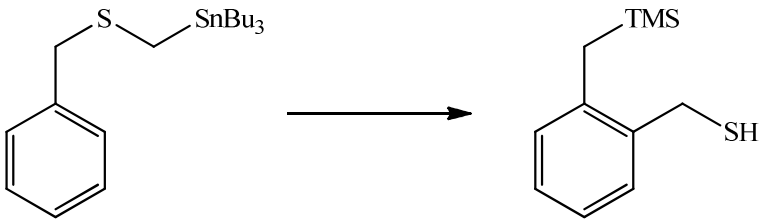
Similarly, deuterated thiol (*R*)-[D_1]**2.45** (49 mg, 0.26 mmol) obtained by rearrangement at –95 °C using *n*-BuLi) was converted to thiocarbamate (*R*,*R*)-[D_1]**2.46** (36 mg, 42%).
The spectroscopic data were identical to that of **2.46**, except for:

^{1}H NMR (400.27 MHz, $CDCl_3$): δ = 4.38 (br. s, 0.86H, CHD), 4.35 (br. s, 0.14H, CHD).

^{13}C NMR (100.61MHz, $CDCl_3$): δ = 33.1 (t, *J* = 21.9 Hz, 1C, CHDS).

3.2.3. Chapter 2.3.

(2-Trimethylsilylmethylphenyl)methanthiol (2.49)



2.31 **2.49**

n-BuLi (1.10 ml, 1.75 mmol) was added to a solution of **2.31** (297 mg, 0.70 mmol) in dry THF (5.0 ml) at –50 °C under argon. After 5 minutes TMSCl (0.27 ml, 2.1 mmol) was added and the reaction mixture was stirred for another 30 minutes. Then a saturated aqueous solution of $NaHCO_3$ (5 ml) and water (5 ml) were added and the mixture was extracted with EtOAc (3 x 15 ml). The combined organic phases were dried ($MgSO_4$), concentrated under reduced pressure and purified by flash chromatography [hexane/CH_2Cl_2 (30:1), R_f =0.60] to yield thiol **2.49** (102 mg, 69%) as a colorless oil.

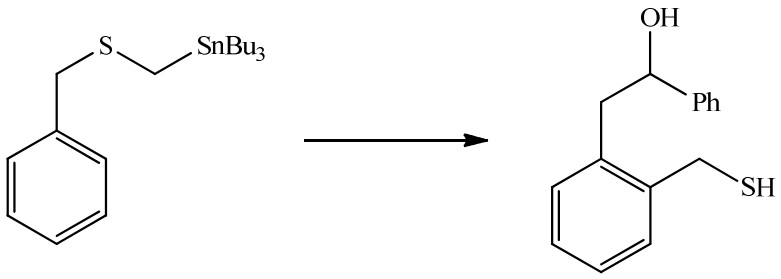
IR (Si): ν = 2953, 1489, 1248, 1153, 854 (with shoulder) cm^{-1}.

^{1}H NMR (400.27 MHz, $CDCl_3$): δ = 7.22 (dd, *J* = 7.5, 1.4 Hz, 1H, H_{arom}), 7.15-7.00 (m, 2H, H_{arom}), 6.96 (dd, *J* = 7.4, 1.3 Hz, 1H, H_{arom}), 3.66 (d, *J* = 7.0 Hz, 2H, $\underline{CH_2}SH$), 2.20 (s, 2H, $\underline{CH_2}Si$), 1.62 (t, *J* = 7.0 Hz, 1H, $CH_2\underline{SH}$), 0.10 (s, 9H, 3 x $Si\underline{CH_3}$)

^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 138.2 (s, 1C, $C_{q\ arom}$), 137.4 (s, 1C, $C_{q\ arom}$), 129.6 (s, 1C, C_{arom}), 129.2 (s, 1C, C_{arom}), 127.1 (s, 1C, C_{arom}), 124.7 (s, 1C, C_{arom}), 27.0 (s, 1C, $\underline{CH_2}SH$), 23.3 (s, 1C, $\underline{CH_2}Si$), –1.4 (s, 3C, 3 x Si$\underline{CH_3}$)

Anal. calculated for $C_{11}H_{18}SSi$ (210.41): C 62.79%, H 8.62%, S 15.24%; found: C 62.85%, H 8.92%, S 15.08%.

2-(2-Mercaptomethyl)phenyl-1-phenylethanol (2.51)



2.31 (±)-**2.51**

n-BuLi (1.10 ml, 1.75 mmol) was added to a solution of **2.31** (300 mg, 0.70 mmol) in dry THF (5.0 ml) at –50 °C under argon. After 5 minutes 2M benzaldehyde (1.05 ml, 2.1 mmol) was added and the reaction mixture was stirred for another 30 minutes. Then a saturated aqueous solution of $NaHCO_3$ (5 ml) and water (5 ml) were added and the mixture was extracted with EtOAc (3 x 15 ml). The combined organic phases were dried ($MgSO_4$), concentrated under reduced pressure and purified by flash chromatography [hexane/EtOAc (10:1), R_f =0.16] to yield alcohol (±)-**2.51** (124 mg, 71%) as a colorless oil.

IR (Si): ν = 3411, 3061, 3027, 2927, 1492, 1452, 1247, 1048 cm^{-1}.

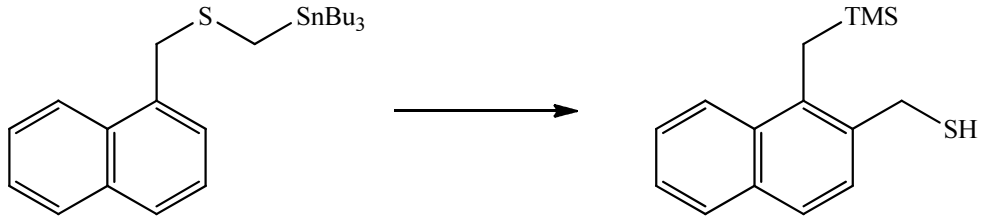
^{1}H NMR (400.27 MHz, $CDCl_3$): δ = 7.40-7.15 (m, 9H, H_{arom}), 4.98 (X-part of ABX-sys., J = 8.0, 5.4 Hz, 1H, $\underline{CH}OH$), 3.73 (AB-part of ABX-sys., J_{AB} = 13.2 Hz, J = 7.1 Hz, 2H, $\underline{CH_2}SH$), 3.10 (AB-part of ABX-sys., J_{AB} = 14.1 Hz, J = 8.0, 5.4 Hz, 2H, $\underline{CH_2}CH$), 1.73 (X-part = t, J = 7.1 Hz, 1H, $CH_2\underline{SH}$).

^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 144.1 (s, 1C, $C_{q\ arom}$), 140.0 (s, 1C, $C_{q\ arom}$), 135.8 (s, 1C, $C_{q\ arom}$), 130.9 (s, 1C, C_{arom}), 129.5 (s, 1C, C_{arom}), 128.5 (s, 2C, C_{arom}), 127.7 (s, 1C, C_{arom}),

127.5 (s, 1C, C_{arom}), 127.3 (s, 1C, C_{arom}), 125.8 (s, 2C, C_{arom}), 75.1 (s, 1C, CHOH), 42.4 (s, 1C, CH_2CH), 26.3 (s, 1C, CH_2SH).

Anal. calculated for $C_{15}H_{16}OS$ (244.35): C 73.73%, H 6.60%, S 13.12%; found: C 74.08%, H 6.78, S 12.94%.

(1-Trimethylsilylmethyl-2-naphthyl)methanthiol (2.52)



2.32 **2.52**

n-BuLi (1.24 ml, 1.99 mmol) was added to a solution of **2.32** (380 mg, 0.80 mmol) in dry THF (5.7 ml) at –78 °C under argon. After 5 minutes TMSCl (0.31 ml, 2.4 mmol) was added and the reaction mixture was stirred for another 30 minutes. Then a saturated aqueous solution of $NaHCO_3$ (5 ml) and water (5 ml) were added and the mixture was extracted with EtOAc (3 x 15 ml). The combined organic phases were dried ($MgSO_4$), concentrated under reduced pressure. The residue was purified by flash chromatography [hexane/CH_2Cl_2 (10:1), R_f = 0.29] to yield naphthylmethanthiol **2.52** (98 mg, 47%) as a colorless oil.

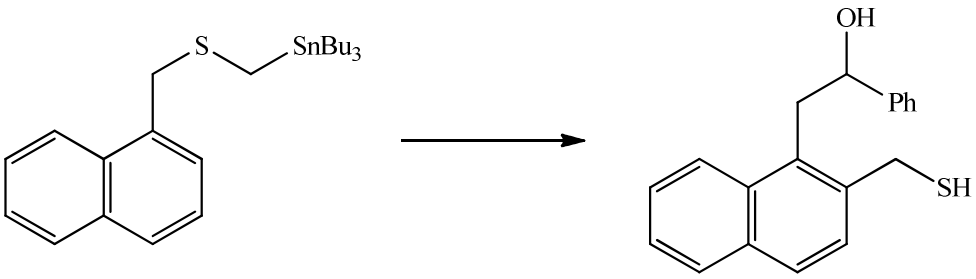
IR (Si): ν = 3050, 2952, 1511, 1417, 1382, 1248, 1155 cm^{-1}.

^{1}H NMR (400.27 MHz, $CDCl_3$): δ = 7.94 (d, *J* = 9.1 Hz, 1H, H_{arom}), 7.77 (dd, J = 7.6, 1.6 Hz, 1H, H_{arom}), 7.58 (d, *J* = 8.4 Hz, 1H, H_{arom}), 7.49-7.39 (m, 2H, H_{arom}), 7.38 (d, *J* = 8.4 Hz, 1H, H_{arom}), 3.88 (d, *J* = 6.8 Hz, 2H, CH_2SH), 2.70 (s, 2H, CH_2Si), 1.69 (t, *J* = 6.8 Hz, 1H, CH_2SH), 0.02 (s, 9H, 3 x SiCH_3).

^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 134.4 (s, 1C, $C_{q\ arom}$), 134.1 (s, 1C, $C_{q\ arom}$), 133.1 (s, 1C, $C_{q\ arom}$), 132.2 (s, 1C, $C_{q\ arom}$), 128.5 (s, 1C, C_{arom}), 127.5 (s, 1C, C_{arom}), 125.4 (s, 1C, C_{arom}), 125.23 (s, 1C, C_{arom}), 125.21 (s, 1C, C_{arom}), 125.1 (s, 1C, C_{arom}), 27.8 (s, 1C, CH_2SH), 19.0 (s, 1C, CH_2Si), –0.4 (s, 3C, 3 x SiCH_3).

Anal. calculated for $C_{15}H_{20}SSi$ (260.47): C 69.17%, H 7.74%, S 12.31%; found: C 69.82%, H 7.98, S 12.16%.

2-(2-Mercaptomethyl-1-naphthyl)-1-phenylethanol (2.53)



2.32 (±)-**2.53**

n-BuLi (1.10 ml, 1.75 mmol) was added to a solution of **2.53** (336 mg, 0.70 mmol) in dry THF (5.0 ml) at –78 °C under argon. After 3 minutes 2 M benzaldehyde (1.05 ml, 2.1 mmol) was added and the reaction mixture was stirred for another 30 minutes. Then a saturated aqueous solution of $NaHCO_3$ (5 ml) and water (5 ml) were added and the mixture was extracted with EtOAc (3 x 15 ml). The combined organic phases were dried ($MgSO_4$), concentrated under reduced pressure and purified by flash chromatography [hexane/EtOAc (10:1), R_f = 0.23] to yield alcohol (±)-**2.53** (158 mg, 77%) as colorless crystals; m.p. = 120-121 °C, (1,2-dichloroethane/diisopropyl ether).

IR (ATR): ν = 3422, 2995, 2919, 2850, 1779, 1759, 1383, 1245, 1052 cm^{-1}.

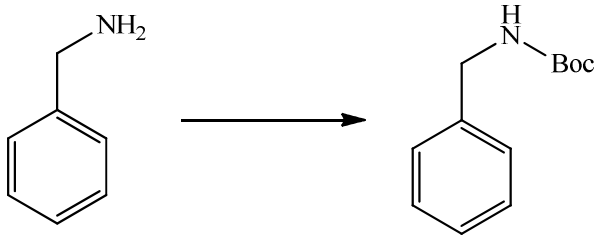
^{1}H NMR (400.27 MHz, $CDCl_3$): δ = 8.13 (d, J = 8.5 Hz, 1H, H_{arom}), 7.82 (d, J = 7.4 Hz, 1H, H_{arom}), 7.73 (d, J = 8.5 Hz, 1H, H_{arom}), 7.59-7.25 (m, 8H, H_{arom}), 5.11 (X-part of ABX-sys., J = 8.6, 4.7 Hz, 1H, CHOH), 3.95 (A-part of ABX-sys., J_{AB} = 13.1 Hz, J = 7.2 Hz, 1H, CH_2SH), 3.78 (B-part of ABX-sys., J_{AB} = 13.1 Hz, J = 7.2 Hz, 1H, CH_2SH), 3.62 (A-part of ABX-sys., J_{AB} = 14.5 Hz, J = 8.6 Hz, 1H, CH_2CH), 3.52 (B-part of ABX-sys., J_{AB} = 14.5 Hz, J = 4.7 Hz, 1H, CH_2CH), 2.0 (br. s, 1H, OH), 1.78 (X-part of ABX-sys. = t, J = 7.2 Hz, 1H, CH_2SH).

^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 144.3 (s, 1C, $C_{q\ arom}$), 138.2 (s, 1C, $C_{q\ arom}$), 133.2 (s, 1C, $C_{q\ arom}$), 132.6 (s, 1C, $C_{q\ arom}$), 130.9 (s, 1C, $C_{q\ arom}$), 128.9 (s, 1C, C_{arom}), 128.6 (s, 2C, C_{arom}), 128.0 (s, 1C, C_{arom}), 127.8 (s, 1C, C_{arom}), 127.6 (s, 1C, C_{arom}), 126.4 (s, C, C_{arom}), 125.6 (s, 2C,

C_{arom}), 125.5 (s, 1C, C_{arom}), 124.1 (s, 1C, C_{arom}), 74.8 (s, 1C, CHOH), 38.3 (s, 1C, CH_2CH), 27.0 (s, 1C, CH_2SH).

Anal. calculated for $C_{19}H_{18}OS$ (294.41): C 77.51%, H 6.16%, S 10.89%; found: C 76.38%, H 5.99, S 10.36%.

_t_-Butyl _N_-benzylcarbamate (2.56)



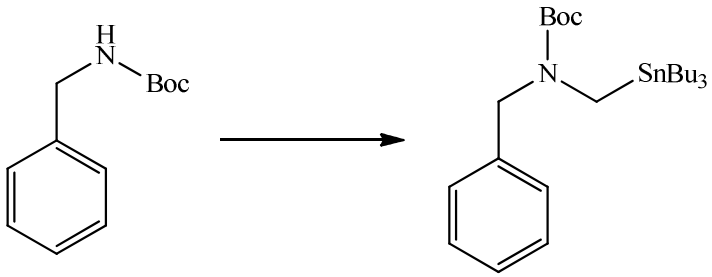
2.54 **2.56**

Di-*tert*-butyl dicarbonate (2.39 g, 11 mmol) was dissolved in dry CH_2Cl_2 (30 ml) and Et_3N (2.08 ml) and benzylamine (**2.54**, 1.10 ml, 1.072 g, 10 mmol) were added at 0 °C and the reaction mixture was stirred overnight. A solution of HCl (20 ml, 0.5 M) was added. The mixture was extracted with EtOAc (3 x 30 ml) and the combined organic phases were washed with H_2O (50 ml), dried ($MgSO_4$), concentrated under reduced pressure and crystallized from hexane to yield carbamate **2.56** (1.654 g, 80%) as colorless crystals; m.p. = 55-56 °C (Lit.[127]: 54-55 °C); TLC: hexane/EtOAc (5:1), R_f = 0.74.

^{1}H NMR (400.27 MHz, $CDCl_3$): δ = 7.40-7.17 (m, 5H, H_{arom}), 4.87 (br. s, 1H, NH), 4.29 (br. d, J = 5.1 Hz, 2H, CH_2), 1.45 (s, 9H, 3xCH_3).

^{13}C NMR (100.61MHz, $CDCl_3$): δ = 155.9 (s, 1C, C=O), 138.9 (s, 1C, $C_{q\ arom}$), 128.5 (s, 2C, C_{arom}), 127.4 (s, 1C, C_{arom}), 127.3 (s, 2C, C_{arom}), 79.4 (s, 1C, C_q), 44.7 (s, 1C, CH_2), 28.4 (s, 3C, 3xCH_3).

_t_-Butyl _N_-Benzyl-_N_-(tributylstannylmethyl)carbamate (2.58)

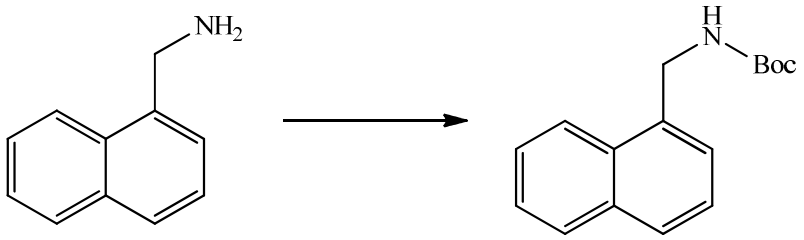


2.56 **2.58**

A solution of *t*-BuONa (268 mg, 2.48 mmol) and **2.56** (514 mg, 2.48 mmol) in dry THF (8.0 ml) was stirred under argon for 10 minutes. Afterwards the mixture was cooled down to –30 °C and **2.26** (658 mg, 1.65 mmol) dissolved in dry THF (5 ml) was added. Stirring was continued for 4 hours allowing the reaction mixture to warm up to room temperature. After HCl (8 ml, 1M) and hexane (8 ml) had been added, the organic phase was washed with brine (20 ml), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography [hexane/CH_2Cl_2 (1:1), R_f = 0.48] to yield *N*-stannylmethylcarbamate **2.58** (446 mg, 53%) as a colorless oil.

^{1}H NMR (400.27 MHz, $CDCl_3$): δ = 7.34-7.16 (m, 5H, H_{arom}), 4.37 (s, 2H, CH_2N), 2.95 (s, $J(^{117/119}Sn)$ = 18.8 Hz, 0.6H, $\underline{CH_2}Sn$, conformer A), 2.77 (s, $J(^{117/119}Sn)$ = 26.0 Hz, 1.4H, $\underline{CH_2}Sn$, conformer B), 1.53-1.37 (m, 15H, 3 x $\underline{CH_2}CH_2Sn$ + 3 x $C\underline{CH_3}$), 1.25 (sext, J = 7.3 Hz, 6H, 3 x $\underline{CH_2}(CH_2)_2Sn$), 0.90-0.73 (m, $J(^{117/119}Sn)$ = 53.2 Hz, 6H, 3 x $\underline{CH_2}Sn$), 0.85 (t, J = 7.3 Hz, 9H, 3x $\underline{CH_3}(CH_2)_3Sn$).

_t_-Butyl _N_-(naphthylmethyl)carbamate (2.57)[39]



2.55 **2.57**

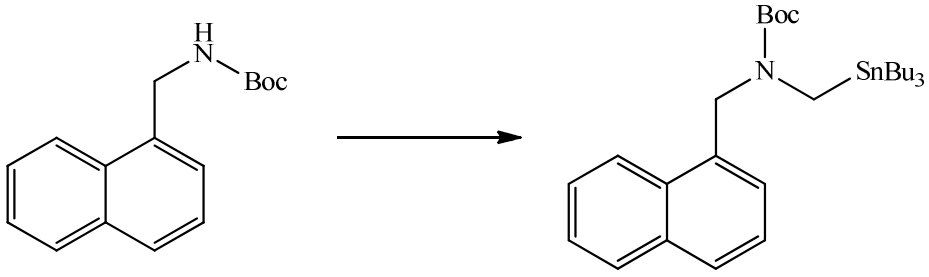
Di-*tert*-butyl dicarbonate (2.39 g, 11 mmol) was dissolved in dry CH_2Cl_2 (30 ml) and Et_3N (2.08 ml) and naphthylmethylamine (**2.55**, 1.47 ml, 1.572 g, 10 mmol) were added at 0 °C and the reaction mixture was stirred overnight. A solution of HCl (20 ml, 0.5 M) was added. The

mixture was extracted with EtOAc (3 x 30 ml) and the combined organic phases were washed with H_2O (50 ml), dried ($MgSO_4$), concentrated under reduced pressure and crystallized from hexane to yield carbamate **2.57** (1.969 g, 77%) as colorless crystals; m.p. = 99-100 °C (lit.[128]: 99-100 °C). TLC: hexane/EtOAc (5:1), R_f = 0.74.

^{1}H NMR (400.27 MHz, $CDCl_3$): δ = 8.10-8.00 (d, J = 8.1 Hz, 1H, H_{arom}), 7.90-7.80 (m, 1H, H_{arom}), 7.80-7.70 (m, 1H, H_{arom}), 7.60-7.45 (m, 2H, H_{arom}), 7.45-7.35 (m, 2H, H_{arom}), 4.77 (br. s, 3H, CH_2 and NH), 1.46 (s, 9H, 3xCH_3).

^{13}C NMR (100.61MHz, $CDCl_3$): δ = 155.7 (s, 1C, C=O), 134.1 (s, 1C, $C_{q\ arom}$), 133.9 (s, 1C, $C_{q\ arom}$), 131.4 (s, 1C, $C_{q\ arom}$), 128.7 (s, 1C, C_{arom}), 128.4 (s, 1C, C_{arom}), 126.4 (s, 1C, C_{arom}), 126.1 (s, 2C, C_{arom}), 125.9 (s, 1C, C_{arom}), 125.4 (s, 1C, C_{arom}), 123.5 (s, 1C, C_{arom}), 79.5 (s, 1C, C_q), 42.8 (s, 1C, $\underline{CH_2}$), 28.5 (s, 3C, 3x$\underline{CH_3}$).

Butyl *N*-(naphthylmethyl)-*N*-(tributylstannylmethyl)carbamate (2.59)



2.57 **2.59**

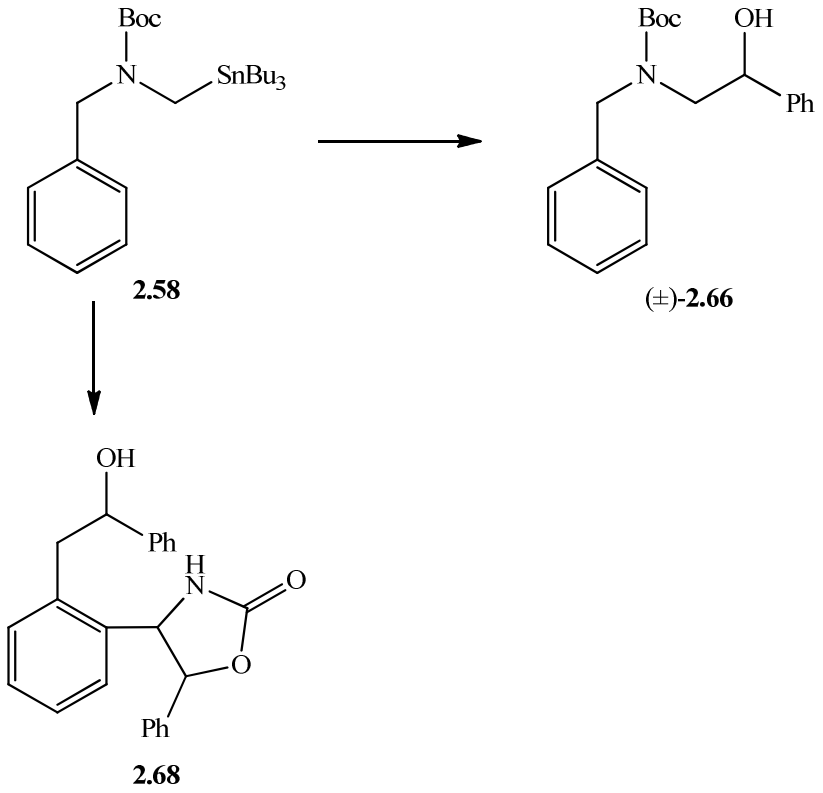
The mixture of *t*-BuONa (234 mg, 2.43 mmol) and **2.57** (625 mg, 2.43 mmol) in dry THF (8.0 ml) was stirred under argon for 10 minutes. Afterwards the reaction mixture was cooled to –30 °C and **2.26** (649 mg, 1.62 mmol) dissolved in dry THF (5 ml) was added. Stirring was continued overnight, allowing the reaction mixture to warm up to room temperature. After heating for 1 hour at 50 °C HCl (8 ml, 1M) and hexane (8 ml) were added. The organic phase was separated and washed with brine (20 ml), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography [hexane/CH_2Cl_2 (2:1), R_f = 0.53] to yield *N*-stannylmethylcarbamate **2.59** (623 mg, 68%) as a colorless oil.

IR (Si): ν = 2956, 2924, 1680, 1456, 1394, 1366, 1166, 913 cm^{-1}.

^{1}H NMR (400.27 MHz, $CDCl_3$): δ = 8.17 (d, J = 8.2 Hz, 0.5H, H_{arom}, conformer A), 8.10-8.03 (m, 0.5H, H_{arom}, conformer B), 7.90-7.81 (m, 1H, H_{arom}, conformer B), 7.77 (d, J = 8.0 Hz, 1H, H_{arom}, conformer A), 7.58-7.40 (m, 3H, H_{arom}), 7.40-7.25 (m, 1H, H_{arom}), 4.86 (s, 2H, $\underline{CH_2}NH$), 2.92 (s, $J(^{117/119}Sn)$ = 9.8 Hz, 0.86H, $\underline{CH_2}Sn$, conformer A), 2.78 (s, $J(^{117/119}Sn)$ = 13.3 Hz, 1.14H, $\underline{CH_2}Sn$, conformer B), 1.51 (br. s, 3.9H, 3xCH_3, conformer A), 1.47 (br. s, 5.1H, 3xCH_3, conformer B), 1.43-1.30 (m, 6H, 3 x $\underline{CH_2}CH_2Sn$), 1.23 (sext, J = 7.1 Hz, 6H, 3 x $\underline{CH_2}(CH_2)_2Sn$), 0.91-0.65 (m, 6H, 3 x $\underline{CH_2}Sn$), 0.83 (t, J = 7.1 Hz, 9H, 3x $\underline{CH_3}(CH_2)_3Sn$).

Anal. calculated for $C_{24}H_{47}NO_2S$ (560.40): C 62.15%, H 8.45%, N 2.50%; found: C 62.34%, H 8.27%, N 2.68%.

(±)-*t*-Butyl *N*-phenylmethyl-*N*-(2-hydroxy-2-phenylethyl)carbamate [(±)-2.66]



n-BuLi (0.96 ml, 1.54 mmol) was added to a solution of **2.58** (227 mg, 0.44 mmol) in dry THF (3.1 ml) at –50 °C under argon. After 10 minutes benzaldehyde (0.77 ml, 1.54 mmol, 2M in dry THF) and the reaction mixture was stirred for 15 minutes. Then a saturated aqueous solution of $NaHCO_3$ (4 ml) was added and the mixture was extracted with EtOAc (3 x 15 ml). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure.

The residue was purified by flash chromatography [hexane/EtOAc (3:1), R_f = 0.39] to yield carbamate (±)-**2.66** (78 mg, 55%) as a colorless oil.

IR (Si): ν = 3423, 2926, 2852, 1688, 1495, 1455, 1415, 1265, 1165 cm^{-1}.

^{1}H NMR (400.13 MHz, toluene-d_8): δ = 7.26-7.19 (m, 2H, H_{arom}), 7.15-6.94 (m, 8H, H_{arom}), 4.79 (X-part of ABX-sys., J = 7.0, 4.4 Hz, 1H, CHOH), 4.27 (AB-sys., J = 15.4 Hz, 2H, CH_2N), 3.36 (AB-part of ABX-sys., J_{AB} = 14.7 Hz, 7.0, 4.4 Hz, 2H, CH_2CH), 1.38 (s, 9H, 3xCH_3).

^{13}C NMR (100.61MHz, toluene-d_8): δ = 157.9 (s, 1C, C=O), 143.8 (s, 1C, $C_{q\ arom}$), 139.3 (s, 1C, $C_{q\ arom}$), 128.8 (s, 2C, C_{arom}), 128.6 (s, 2C, C_{arom}), 128.4 (s, 1C, C_{arom}), 128.0 (s, 1C, C_{arom}), 127.6 (s, 1C, C_{arom}), 127.5 (s, 1C, C_{arom}), 126.3 (s, 2C, C_{arom}), 80.2 (s, 1C, C$(CH_3)_3$), 74.3 (s, 1C, CHOH), 56.1 (s, 1C, CH_2CH), 52.7 (s, 1C, CH_2N), 28.6 (s, 3C, 3x CH_3).

HRMS (ESI): Anal. calculated for $C_{20}H_{25}NO_3$: 328.1913; found: 328.1908.

Anal. calculated for $C_{20}H_{25}NO_3$ (327.42): C 73.37%, H 7.70%, N 4.28%; found: C 73.56%, H 7.57%, N 4.09%

2.68

IR (Si): ν = 3418, 2920, 2850, 1730, 1494, 1454, 1410, 1332, 1276, 1261 cm^{-1}.

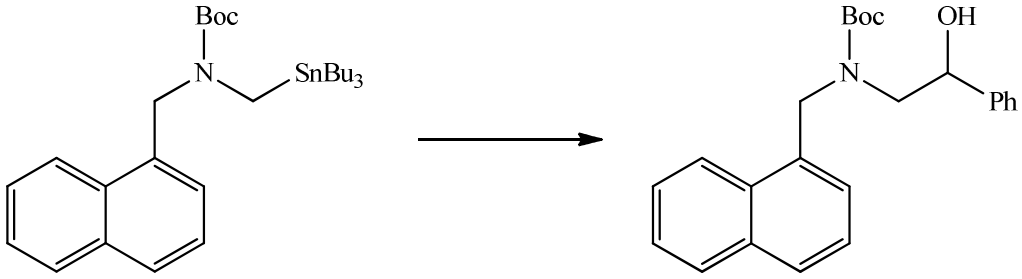
^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 7.43-7.37 (m, 3H, H_{arom}), 7.37-7.31 (m, 3H, H_{arom}), 7.30-7.22 (m, 4H, H_{arom}), 7.20-7.13 (m, 4H, H_{arom}), 5.22 (d, J = 7.1 Hz, 1H, CHO), 4.98 (X-part of ABX-sys., J = 7.6, 2.8 Hz, 1H, CHOH), 4.46 (d, J = 7.1 Hz, 1H, CHNH), 3.63 (A- part of ABX-sys., J_{AB} = 14.9 Hz, J = 2.8 Hz, 1H, CH_2CH), 3.20 (br. d, J = 3.6 Hz, 1H, OH), 3.07 (B-part of ABX-sys., J_{AB} = 14.9 Hz, J = 7.6 Hz, 1H, CH_2CH).

^{13}C NMR (100.61MHz, toluene-d_8): δ = C_q not detected, 129.1 (s, 2C, C_{arom}), 128.7 (s, 1C, C_{arom}), 128.3 (s, 2C, C_{arom}), 128.2 (s, 1C, C_{arom}), 128.1 (s, 1C, C_{arom}), 128.0 (s, 1C, C_{arom}), 127.6 (s, 2C, C_{arom}), 127.4 (s, 2C, C_{arom}), 125.83 (s, 1C, C_{arom}), 125.80 (s, 1C, C_{arom}), 83.4 (s, 1C, CHO), 73.8 (s, 1C, CHOH), 70.2 (s, 1C, CHNH), 50.7 (s, 1C, CH_2CH).

2D NMR spectra (COSY, NOSY, HSQC, HMBC) were in accordance with the assignment.

HRMS (ESI): Anal. calculated for $C_{23}H_{21}NO_3Na$: 382.1419; found: 382.1423.

(±)-*t*-Butyl *N*-(naphth-1-yl)methyl-*N*-(2-hydroxy-2-phenylethyl)carbamate [(±)-2.62]



2.59 (±)-**2.62**

n-BuLi (0.96 ml, 1.54 mmol) was added to a solution of **2.59** (245 mg, 0.44 mmol) in dry THF (3.1 ml) at –50 °C under argon. After 3 minutes benzaldehyde (0.66 ml, 1.32 mmol, 2M in dry THF) and the reaction mixture was stirred for another 15 minutes. Then a saturated aqueous solution of $NaHCO_3$ (4 ml) was added and the mixture was extracted with EtOAc (3 x 15 ml). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography [hexane/EtOAc (3:1), R_f = 0.39] to yield *N*-Boc-protected aminoalcohol (±)-**2.62** (86 mg, 52%) as a colorless oil.

IR (Si): ν = 3432, 3052, 2978, 2928, 1681, 1455, 1415, 1367, 1265, 1165 cm^{-1}.

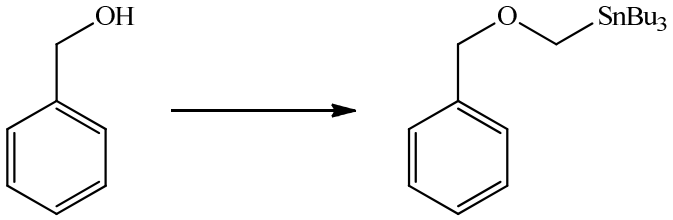
^{1}H NMR (400.13 MHz, toluene-d_8, 353 K): δ = 7.99 (d, J = 8.0 Hz, 1H, H_{arom}), 7.60 (d, J = 8.0 Hz, 1H, H_{arom}), 7.56-7.49 (m, 1H, H_{arom}), 7.32-6.90 (m, 9H, H_{arom}), 4.83 (AB-sys., J = 13.7 Hz, 2H, $\underline{CH_2}N$), 4.74 (X-part of ABX-sys., J = 7.7, 3.8 Hz, 1H, $\underline{CH}OH$), 3.33 (AB-part of ABX-sys., J_{AB} = 14.6 Hz, J = 7.7, 3.8 Hz, 2H, $\underline{CH_2}CH$), 1.41 (s, 9H, $3xCH_3$).

^{13}C NMR (100.61MHz, toluene-d_8, 353 K): δ = 157.7 (s, 1C, C=O), 143.8 (s, 1C, $C_{q\ arom}$), 134.8 (s, 1C, $C_{q\ arom}$), 134.3 (s, 1C, $C_{q\ arom}$), 132.6 (s, 1C, $C_{q\ arom}$), 129.0 (s, 1C, C_{arom}), 128.6 (s, 2C, C_{arom}), 128.5 (s, 1C, C_{arom}), 127.6 (s, 1C, C_{arom}), 126.5 (s, 1C, C_{arom}), 126.33 (s, 2C, C_{arom}), 126.27 (br. s), 126.0 (s, 1C, C_{arom}), 125.5 (s, 1C, C_{arom}), 123.9 (br. s, 1C, C_{arom}), 80.3 (s, 1C, $\underline{C}(CH_3)_3$), 74.3 (s, 1C, $\underline{CH}OH$), 55.2 (s, 1C, $\underline{CH_2}CH$), 50.1 (s, 1C, $\underline{CH_2}N$), 28.6 (s, 3C, $3xCH_3$).

HRMS (ESI): Anal. Calculated for $C_{24}H_{27}NO_3$: 378.2069; found: 378.2079.

Anal. calculated for $C_{24}H_{27}NO_3$ (377.48): C 76.36%, H 7.21%, N 3.71%; found: C 76.04%, H 7.29%, N 3.46%

(Benzyloxymethyl)tributylstannane (2.71)



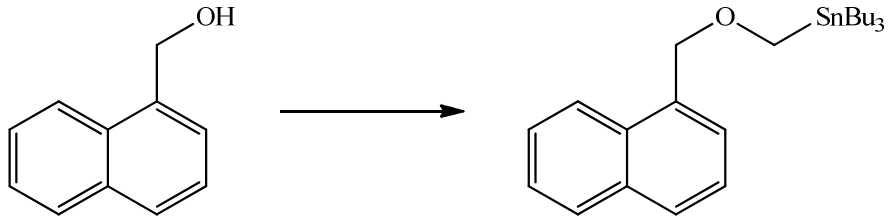
2.69 **2.71**

A solution of *t*-BuONa (268 mg, 2.48 mmol) and benzylalcohol (**2.69**, 268 mg, 0.26 ml, 2.48 mmol) in dry THF (8.0 ml) was stirred under argon for 10 minutes. Afterwards the reaction mixture was cooled down to –30 °C and **2.26** (658 mg, 1.65 mmol) in dry THF (5 ml) was added. Stirring was continued for 4 hours allowing the reaction mixture to warm up to room temperature. Afterwards HCl (8 ml, 1M) and hexane (8 ml) were added, the organic phase was washed with brine (20 ml), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography [hexane/CH_2Cl_2 (2:1), R_f = 0.72] to yield stannane **2.71** (538 mg, 79%) as a colorless oil.

^{1}H NMR (400.27 MHz, $CDCl_3$): δ = 7.36-7.20 (m, 5H, H_{arom}), 4.40 (s, 2H, CH_2O), 3.73 (s, $J(^{117/119}Sn)$ = 15.0 Hz, 2H, $\underline{CH_2}Sn$), 1.58-1.40 (m, $J(^{117/119}Sn)$ = 18.4 Hz, 6H, 3 x $\underline{CH_2}CH_2Sn$), 1.28 (sext, J = 7.3 Hz, 6H, 3 x $\underline{CH_2}(CH_2)_2Sn$), 0.95-0.80 (m, $J(^{117/119}Sn)$ = 50.0 Hz, 6H, 3 x $\underline{CH_2}Sn$), 0.87 (t, J = 7.3 Hz, 9H, 3x $\underline{CH_3}(CH_2)_3Sn$).

^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 139.0 (s, 1C, $C_{q\ arom}$), 128.2 (s, 2C, C_{arom}), 127.5 (s, 2C, C_{arom}), 127.3 (s, 1C, C_{arom}), 77.2 (s, 1C, CH_2O), 61.5 (s, $J(^{117/119}Sn)$ = 356.8 Hz, CH_2Sn), 29.1 (s, $J(^{117/119}Sn)$ = 21.5 Hz, 3C, 3 x $\underline{CH_2}(CH_2)_2Sn$), 27.3 (s, $J(^{117/119}Sn)$ = 51.9 Hz, 3C, 3 x $\underline{CH_2}CH_2Sn$), 13.7 (s, 3C, 3 x $\underline{CH_3}(CH_2)_3$), 9.0 (s, $J(^{117/119}Sn)$ = 321.7, 307.4 Hz, 3C, 3 x $Sn\underline{CH_2}(CH_2)_2$).

Tributylstannylmethyl naphth-1-ylmethyl ether (2.72)



2.70 **2.72**

The solution of *t*-BuONa (234 mg, 2.43 mmol) and naphthalene-1-methanol (**2.70**, 384 mg, 2.43 mmol) in dry THF (8.0 ml) was stirred under argon for 10 minutes. Afterwards the reaction mixture was cooled down to –30 °C and **2.26** (649 mg, 1.62 mmol) in dry THF (5 ml) was added, stirring was continued for another 4 hours, allowing the reaction mixture to warm up to room temperature. Afterwards HCl (8 ml, 1M) and hexane (8 ml) were added. The organic phase was separated and washed with brine (20 ml), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography [hexane/CH_2Cl_2 (5:1), R_f = 0.38] to yield stannylmethyl ether **2.72** (543 mg, 73%) as a colorless oil.

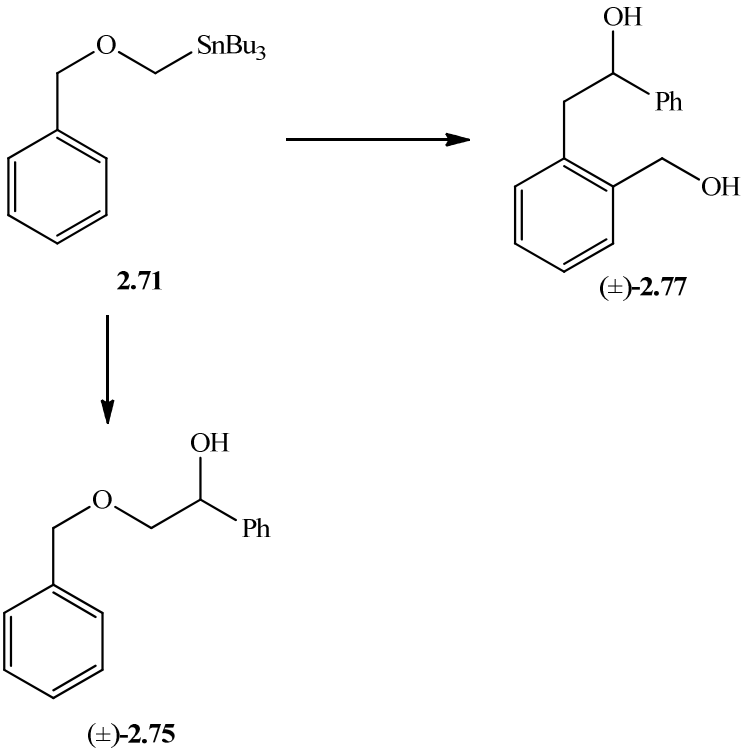
IR (Si): ν = 3047, 2956, 2925, 2852, 1463, 1062, 913 cm^{-1}.

^{1}H NMR (400.27 MHz, $CDCl_3$): δ = 8.13-8.06 (m, 1H, H_{arom}), 7.87-7.80 (m, 1H, H_{arom}), 7.77 (d, J = 8.0 Hz, 1H, H_{arom}), 7.52-7.38 (m, 4H, H_{arom}), 4.85 (s, 2H, CH_2N), 3.79 (s, $J(^{117/119}Sn)$ = 15.4 Hz, 2H, $\underline{CH_2}Sn$), 1.55-1.38 (m, 6H, 3 x $\underline{CH_2}CH_2Sn$), 1.26 (sext, J = 7.3 Hz, 6H, 3 x $\underline{CH_2}(CH_2)_2Sn$), 0.96-0.86 (m, $J(^{117/119}Sn)$ = 49.8 Hz, 6H, 3 x $Sn\underline{CH_2}$), 0.84 (t, J = 7.3 Hz, 9H, 3x $\underline{CH_3}(CH_2)_3Sn$).

^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 134.4 (s, 1C, $C_{q\ arom}$), 133.7 (s, 1C, $C_{q\ arom}$), 131.8 (s, 1C, $C_{q\ arom}$), 128.4 (s, 1C, C_{arom}), 128.2 (s, 1C, C_{arom}), 126.2 (s, 1C, C_{arom}), 125.9 (s, 1C, C_{arom}), 125.6 (s, 1C, C_{arom}), 125.1 (s, 1C, C_{arom}), 124.2 (s, 1C, C_{arom}), 70.0 (s, $J(^{117/119}Sn)$ = 45.7 Hz, 1C, $\underline{CH_2}O$), 61.4 (s, $J(^{117/119}Sn)$ = 358.3 Hz, 1C, $\underline{CH_2}Sn$), 29.1 (s, $J(^{117/119}Sn)$ = 20.5 Hz, 3C, 3 x $\underline{CH_2}(CH_2)_2Sn$), 27.3 (s, $J(^{117/119}Sn)$ = 52.7 Hz, 3C, 3 x $\underline{CH_2}CH_2Sn$), 13.7 (s, 3C, 3 x $\underline{CH_3}(CH_2)_3$), 9.0 (s, $J(^{117/119}Sn)$ = 322.2, 307.9 Hz, 3C, 3 x $Sn\underline{CH_2}(CH_2)_2$).

Anal. calculated for $C_{24}H_{38}OSn$ (461.27): C 62.49%, H 8.30%; found: C 62.40%, H 8.21.

(±)-2-(2-Hydroxymethylphenyl)-1-phenylethanol [(±)-2.77]



n-BuLi (1.47 ml, 2.34 mmol) was added to a solution of **2.71** (277 mg, 0.67 mmol) in dry THF (4.7 ml) at –50 °C under argon. After 3 minutes benzaldehyde (1.17 ml, 2.34 mmol, 2M in dry THF) and the reaction mixture was stirred for another 15 minutes. Then a saturated aqueous solution of $NaHCO_3$ (4 ml) was added and the mixture was extracted with EtOAc (3 x 15 ml). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography [hexane/EtOAc (3:1), R_f = 0.20 for diol, 0.59 for alcohol] to yield diol (±)-**2.77** (44 mg, 28%) as colorless crystals and alcohol (±)-**2.75** (86 mg, 55%) as a colourless oil.

When the benzaldehyde was added 10 minutes after the addition of *n*-BuLi, the ratio of diol (±)-**2.77** (40 mg, 27%) and alcohol (±)-**2.75** (47 mg, 32%) changed.

Diol (±)-2.77:

^{1}H NMR (400.27 MHz, $CDCl_3$): δ = 7.42-7.18 (m, 9H, H_{arom}), 4.88 (X-part of ABX-sys., J = 9.4, 3.6 Hz, 1H, CHOH), 4.63 (AB-sys., J = 11.9 Hz, 2H, CH_2OH), 3.07 (AB-part of ABX-sys., J_{AB} = 14.1 Hz, J = 9.4, 3.6 Hz, 2H, CH_2CH).

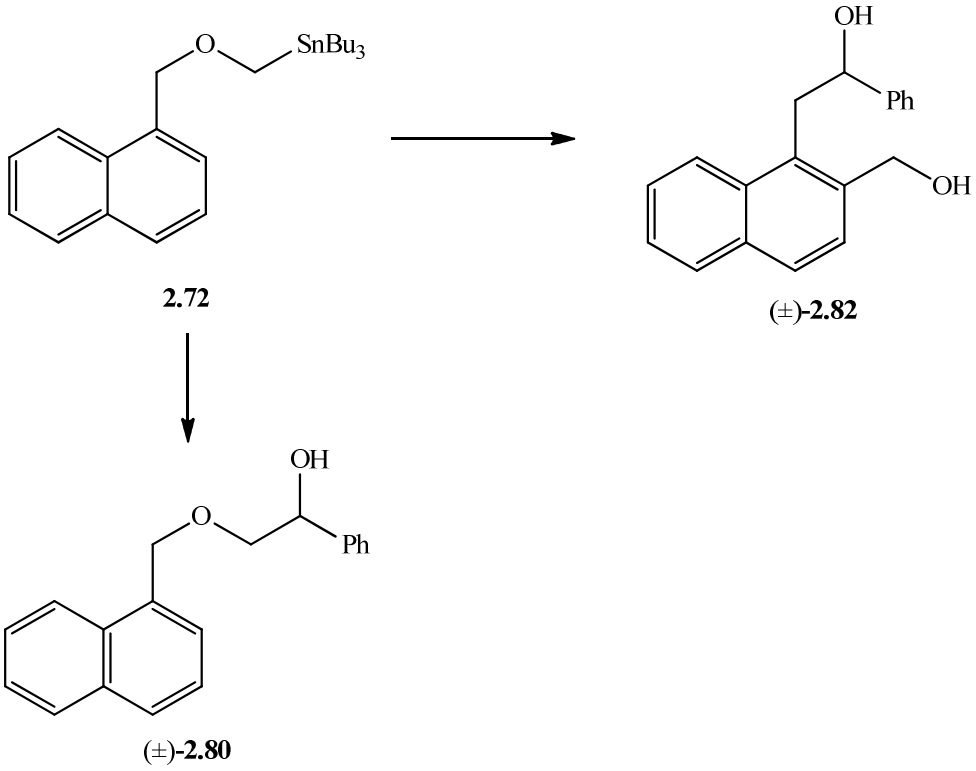
^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 144.2 (s, 1C, $C_{q\ arom}$), 139.6 (s, 1C, $C_{q\ arom}$), 137.3 (s, 1C, $C_{q\ arom}$), 130.5 (s, 1C, C_{arom}), 130.1 (s, 1C, C_{arom}), 128.6 (s, 2C, C_{arom}), 128.5 (s, 1C,

C_{arom}), 127.8 (s, 1C, C_{arom}), 127.0 (s, 1C, C_{arom}), 125.7 (s, 2C, C_{arom}), 75.7 (s, 1C, CHO), 63.4 (s, 1C, $\underline{CH_2}$OH), 42.2 (s, 1C, $\underline{CH_2}$CH).

Alcohol (±)-2.75:

^{1}H NMR (400.27 MHz, $CDCl_3$): δ = 7.39-7.24 (m, 10H, H_{arom}), 4.92 (X-part of ABX-sys., J = 9.0, 3.2 Hz, 1H, $\underline{CH}$OH), 4.59 (AB-sys., J = 11.9 Hz, 2H, $\underline{CH_2}$O), 3.56 (AB-part of ABX-sys., J_{AB} = 9.8 Hz, J = 9.0, 3.2 Hz, 2H, $\underline{CH_2}$CH).

(±)-2-[2-(Hydroxymethyl)naphth-1-yl]-1-phenyl-ethanol [(±)-2.82]



n-BuLi (0.88 ml, 1.40 mmol) was added to a solution of **2.72** (259 mg, 0.56 mmol) in dry THF (4.0 ml) at –50 °C under argon. After 3 minutes benzaldehyde (0.84 ml, 1.68 mmol, 2M in dry THF) and the reaction mixture was stirred for another 15 minutes. Then a saturated aqueous solution of $NaHCO_3$ (4 ml) was added and the mixture was extracted with EtOAc (3 x 15 ml). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography [hexane/EtOAc (2:1), R_f = 0.39] to yield diol (±)-**2.82** (43 mg, 27%) as colorless crystals.

When the same reaction with tributylstannylmethyl naphth-1-ylmethyl ether (264 mg, 0.57 mmol) was performed at –78 °C, alcohol (±)-**2.80** (116 mg, 74%) was isolated as a colourless oil.

Diol (±)-2.82:

^{1}H NMR (400.27 MHz, $CDCl_3$): δ = 8.11 (d, J = 8.5 Hz, 1H, H_{arom}), 7.88 (d, J = 8.6 Hz, 2H, H_{arom}), 7.78 (d, J = 8.4 Hz, 1H, H_{arom}), 7.61-7.47 (m, 5H, H_{arom}), 7.46-7.39 (m, 2H, H_{arom}), 7.38-7.31 (m, 1H, H_{arom}), 5.07 (X-part of ABX-sys., J = 9.9, 3.0 Hz, 1H, CHOH), 4.81 (AB-sys., J = 11.8 Hz, 2H, CH_2OH), 3.58 (AB-part of ABX-sys., J_{AB} = 14.7 Hz, J = 9.9, 3.0 Hz, 2H, CH_2CH).

^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 144.5 (s, 1C, $C_{q\ arom}$), 137.7 (s, 1C, $C_{q\ arom}$), 133.9 (s, 1C, $C_{q\ arom}$), 132.8 (s, 1C, $C_{q\ arom}$), 132.1 (s, 1C, $C_{q\ arom}$), 129.1 (s, 1C, C_{arom}), 128.8 (s, 2C, C_{arom}), 128.5 (s, 1C, C_{arom}), 128.1 (s, 1C, C_{arom}), 127.7 (s, 1C, C_{arom}), 126.4 (s, 1C, C_{arom}), 125.7 (s, 1C, C_{arom}), 125.6 (s, 2C, C_{arom}), 123.8 (s, 1C, C_{arom}), 74.0 (s, 1C, CHOH), 63.8 (s, 1C, CH_2OH), 38.2 (s, 1C, CH_2CH).

Alcohol (±)-2.80:

IR (ATR): ν = 3297, 2906, 2856, 1451, 1335, 1199, 1126, 1068, 1027, 974 cm^{-1}.

^{1}H NMR (400.27 MHz, $CDCl_3$): δ = 8.10 (d, J = 8.0 Hz, 1H, H_{arom}), 7.86 (d, J = 8.2 Hz, 2H, H_{arom}), 7.81 (d, J = 8.0 Hz, 1H, H_{arom}), 7.57-7.38 (m, 4H, H_{arom}), 7.37-7.22 (m, 5H, H_{arom}), 5.03 (AB-sys., J = 11.9 Hz, 2H, CH_2O), 4.90 (X-part of ABX-sys., J = 9.1, 3.1 Hz, 1H, CHOH), 3.70 (A-part of ABX-sys., J_{AB} = 9.5 Hz, J = 3.1 Hz, 1H, CH_2CH), 3.57 (B-part of ABX-sys., J_{AB} = 9.5 Hz, J = 9.1 Hz, 1H, CH_2CH).

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5. Summary

Heteroatom-substituted methyllithiums, chiral by virtue of four different substituents H, D, a heteroatom like bromine or sulfur and lithium were prepared. Their enantiomers were generated from appropriate tributylstanne precursors via tin-lithium exchange and their configurational stability was investigated. The experiments were performed at low temperatures, where the chemical stability and the lifetime of chiral methyllithiums were significantly higher than at room temperature.

I managed to prepare chiral bromo-[D_1]methyllithiums (ee up to 99%), which were intercepted with benzaldehyde or acetophenone to give labeled bromohydrines of the same ee at the deuterium bearing carbon atom. Therefore, chiral bromomethyllithiums are microscopically configurationally stable at –78 °C on the timescale of their addition to benzaldehyde or acetophenone. Unfortunately they are chemically too labile to address the macroscopic configurational stability.

Configurational stability of chiral thio-[D_1]methyllithiums was studied relative to rearrangements. Chiral diisopropoxyphosphinylthio-[D_1]methyllithiums underwent a thiophosphate-mercaptophosphonate rearrangement giving mercapto-[D_1]methylphosphonate after work-up. The best obtained ee was 77% for the experiment performed at –95 °C in Et_2O. Consequently, they were configurationally labile relative to the rearrangement. Allyl-, phenylmethyl- and (naphthylmethylthio)methyllithiums underwent [2,3]-thia-Wittig rearrangements. Chiral allylthiomethyllithiums were found to be virtually microscopically configurationally stable below –95 °C in THF (–95 °C, ee ≥ 95%) relative to the [2,3]-rearrangement. Benzylthio-[D_1]methyllithium rearranged only down to –50 °C and gave racemic thiols. As the [2,3]-rearrangement did not occur at –78 °C after transmetalation, I investigated the stability of the intermediate thiomethyllithiums relative to the addition to benzaldehyde as electrophile. They proved to be microscopically configurationally very labile even at –95 °C (ee 26%) and macroscopically configurationally unstable on the timescale of the addition to benzaldehyde. The activation energy for the [2,3]-rearrangement of the (naphthylmethylthio)methyllithium is lower than that for the phenyl analogue so that it still rearranged at –95 °C, whereas the latter did not rearrange even at –78 °C. It turned out to be configurationally labile relative to the [2,3]-rearrangement, however its ee was higher (72%) than that obtained for the benzylthiomethyllithiums.

It was found that [2,3]-rearrangement of phenyl- and naphthylmethylthiomethyllithiums generated intermediate 6-methylene-2,4-cyclohexadienyl systems, which either rearomatized or were deprotonated by excess *n*-BuLi to yield arylmethyllithiums. These reacted with H^+, D^+, benzaldehyde and chlorotrimethylsilane as electrophiles. Experiments with nitrogen and oxygen instead of sulfur as heteroatoms were performed as well. The oxygen analogues rearranged at –50 °C and the arylmethyllithiums could be quenched with benzaldehyde. Although, the nitrogen analogues were transmetalated smoothly, they did not rearrange at –50 °C, but probably at 0 °C. It follows that the feasibility of the [2,3]-rearrangement for the three heteroatom-substituted methyllithiums is given by the following sequence: S > O >>> N.

6. Zusammenfassung

Heteroatom-substituierte Methyllithium-Verbindungen, chiral auf Grund der vier unterschiedlichen Substituenten H, D, einem Heteroatom wie Brom oder Schwefel und Lithium, wurden hergestellt. Ihre Enantiomere wurden aus entsprechenden Tributylstannylvorstufen durch Zinn-Lithium-Austausch erzeugt und auf ihre konfigurative Stabilität untersucht. Die Experimente wurden bei tiefer Temperatur durchgeführt, wo die chemische Stabilität und die Lebensdauer der chiralen Methyllithium-Verbindungen gegenüber Raumtemperatur beträchtlich erhöht ist. Ich konnte chirale Brom-[D_1]methyllithium-Verbindungen (ee bis 99%) herstellen, die mit Benzaldehyd oder Acetophenon abgefangen wurden und markierte Bromhydrine lieferten, die den gleichen Enantiomerenüberschuss wie die Edukte aufwiesen. Deshalb ist das chirale Brom-[D_1]methyllithium mikroskopisch konfigurativ stabil bei –78 °C, relativ zur Zeitskala seiner Addition an Benzaldehyd oder Acetophenon. Leider ist es chemisch zu labil, um die makroskopische konfigurative Stabilität zu untersuchen.

Die konfigurative Stabilität der chiralen Thio-[D_1]methyllithium-Verbindungen wurde relativ zu Umlagerungen untersucht. Die chiralen (Diisopropoxyphosphinylthio)-[D_1]methyllithium-Verbindungen gingen die Thiophosphat-Mercaptophosphonat-Umlagerung ein und lieferten nach der Aufarbeitung Mercapto-[D_1]methylphosphonate. Der beste Enantiomerenüberschuss (77%) wurde für das bei –95 °C in Et_2O durchgeführte Experiment erhalten. Damit waren die intermediären Thiomethyllithium-Verbindungen relativ zur Umlagerung konfigurativ labil.
Allyl-, Phenylmethyl- und (Naphthylmethylthio)methyllithium-Verbindungen gingen [2,3]-thia-Wittig-Umlagerungen ein. Chirale Allylthiomethyllithium-Verbindungen erwiesen sich in THF unterhalb von –95 °C als praktisch mikroskopisch konfigurativ stabil (–95 °C, ee ≥ 95%) relativ zur [2,3]-Umlagerung. Benzylthio-[D_1]methyllithium-Verbindungen lagerten nur bis –50 °C um und lieferten racemische Thiole. Da die [2,3]-Umlagerung bei –78 °C nach der Transmetallierung nicht mehr stattfand, studierte ich die konfigurative Stabilität der intermediären Thiomethyllithium-Verbindungen relativ zur Addition an Benzaldehyd als Elektrophil. Es stellte sich heraus, dass sie selbst bei –95 °C (ee 26%) mikroskopisch konfigurativ auf der Zeitskala der Addition an Benzaldehyd sehr labil sind. Die Aktivierungsenergie für die [2,3]-Umlagerung der (Naphthylmethylthio)methyllithium-Verbindung ist niedriger als für das Phenylanalogon, sodass sie noch bei –95 °C umlagerte,

während letztere Verbindung es bei –78 °C nicht mehr tat. Sie war bezüglich [2,3]-Umlagerung konfigurationslabil, jedoch war der ee höher (72%) als jener, der für Benzylthiomethyllithium erhalten wurde. Die [2,3]-Umlagerung der Phenyl- und Naphthylmethyltiomethyllithium-Verbindungen generierte intermediäre 6-Methylen-2,4-cyclohexadienyl-Systeme, die entweder rearomatisierten oder durch überschüssiges BuLi deprotoniert wurden, um Arylmethyllithium-Verbindungen zu bilden. Diese reagierten mit H^+, D^+, Benzaldehyd und Chlortrimethylsilan als Elektrophile. Experimente mit Stickstoff und Sauerstoff anstelle von Schwefel als Heteroatom wurden ebenfalls durchgeführt. Die Sauerstoffanaloga lagerten bei –50 °C um und die gebildeten Arylmethyllithium-Verbindungen konnten mit Benzaldehyd gequencht werden. Die Stickstoffanaloga jedoch wurden glatt transmetalliert, aber lagerten nicht bei –50 °C, vermutlich aber bei 0 °C um. Damit ist die Realisierbarkeit der [2,3]-Umlagerung für die drei Heteroatom-substituierten Methyllithium-Verbindungen durch nachstehende Reihenfolge gegeben: S > O >>> N.

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Education

03. 2008 - present

University of Vienna, Department of Organic Chemistry, Austria
PhD Studies, thesis title: "Preparation and Determination of Configurational Stability of *Chiral Bromo- and Thio-[D$_1$]methyllithiums".*
Supervisor: Prof. Dr. Friedrich Hammerschmidt.

10.2002 – 07.2007

Wroclaw University of Technology, Department of Chemistry, Poland Biotechnology, Medicinal Chemistry. Graduated with the best grade receiving **Master of Science Degree**.
Master thesis title: *"New Method for Synthesis of P-methylphosphinic Acids and Its Application to The Preparation of Phosphinothricin".*
Supervisor: Dr. Łukasz Berlicki, Department of Bioorganic Chemistry in charge of Prof. Dr. Paweł Kafarski.

02.2007 – 07.2007

Socrates-Erasmus Programme at **The University of Ferrara**, Italy.
Project titl: *"Evaluation of Analogues of 3,5-dichloropyridyl-aminomethylenebisphosphonic Acid as Inhibitors of Plant P5C Reductase"*
Supervisor: Prof. Giuseppe Forlani.

09.1997 – 05.2002

III High School in Opole, Poland
Language class focused on English and German. Graduated with honours.
Several subjects lectured in English (chemistry, mathematics, biology).

Experience

01.02.2010 - present

University of Vienna – University Assistant, scientific research in frame of the PhD thesis.

01.03.2008 – 31.01.2010

University of Vienna – Research Assistant, scientific research in frame of the PhD thesis – FWF project nr L420-N19.

01.10.2008 - present

University of Vienna – Teaching Assistant, biological-chemical laboratory.

01.12.2007 - 28.02.2008

NUTRICIA *Zakłady Produkcyjne Sp. z o. o.* - Quality Control Inspector in the *Quality Assurance* Department.

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WHIRLPOOL *Poland* - Assistant in *Global Product Development* Department.

Conferences and Meetings

07.06.2011, Vienna, Austria

Participation in 'ENVIRONMENT DAY Talks '11 – Chemistry takes Responsibility' organized by Eco Counseling Austria and UNO.

20. - 24.07.2010, Firenze, Italy

Oral presentation at 9th International Symposium on Carbanion Chemistry: *'Configurational Stability of Chiral Bromo- and Thio-[D_1]methyllithiums'*.

24. - 27.08.2009, Vienna, Austria

Oral presentation at XIII. Austrian Chemistry Days - a joint meeting of the Slovak, the Czech and the Austrian Chemical Society: *'Configurational Stability of Chiral Bromo- and (Diisopropoxyphosphinylthio)-[D_1]methyllithium'*.

13. - 21.09.2008, Niederoeblarn, Austria

Participation in international NMR Summerschool: 1D- and 2D-NMR Spectroscopy in Liquids organized by Austrian Chemical Society.

18. - 22.09.2006, Gdansk, Poland

Poster at XLIX. Congress of Polish Chemical Society: *'Application of the Barton reaction in the synthesis of P-methylphosphinic acids'*.

Language skills

English – fluent (Certificate in Advanced English, University of Cambridge, 2002).

German – fluent (Zertifikat Deutsch, Goethe-Institute, TELC, 2005).

Italian – good

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Trainings

08. - 09.09.2010

'Teaching – qualifications for beginners', University of Vienna.

28.01 - 03.02.2002

'Solving social problems – The role of a mediator in conflicts, elaboration of common opinions and compromises in a team', University of Opole.

Publications

- Forlani, G.; Occhipinti, A.; Berlicki, L.; Dziędzioła, G.; Wieczorek, A.; Kafarski, P., Tailoring the Structure of Aminobisphosphonates to Target Plant P5C Reductase, *J. Agric. Food Chem.* **2008**, *56*, 3193–3199.

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