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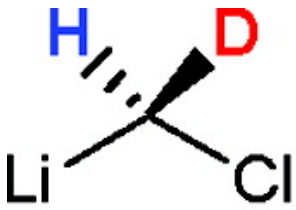
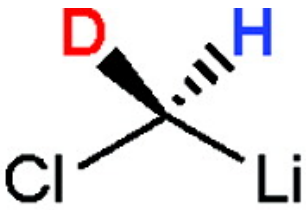


(*R*)-[D_1]**1**



(*S*)-[D_1]**1**

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Preparation and Configurational Stability of Chiral Chloro-[D_1]methyllithiums of 98% Enantiomeric Excess

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Abstract: Enantiopure stannyl-[D_1]methanol was converted to chloro-[D_1]methylstannane under complete inversion of configuration using Ph_3P/*N*-chlorosuccinimide in THF. It was transmetalated to stereospecifically give chloro-[D_1]methyllithium (ee up to 98%). Its microscopic configurational stability was tested by performing tin-lithium exchange in the presence of benzaldehyde as the electrophile under various conditions. The macroscopic configurational stability was addressed by using the same electrophile but by adding it 30 s after the addition of MeLi used for transmetalation. Chloro-[D_1]methyllithium is chemically very labile, however completely configurationally stable on both time scales up to the temperature of rapid decomposition (−78 °C).

Introduction

Organometallic compounds containing lithium and at least one heteroatom, preferably a halogen, at the same carbon atom [$XC(R^1)(R^2)Li$] are referred to as carbenoids.[1] Depending on the experimental conditions, they exhibit a diverse reactivity spectrum. At low temperatures, these thermolabile species behave as nucleophiles and can be trapped with a variety of electrophiles. At higher temperatures, their electrophilic character comes into play. They either insert into C−H bonds, react with RLi to give $RC(R^1)(R^2)Li$ and LiX, form alkenes by eliminative dimerization, or add to olefinic double bonds to produce cyclopropanes.[2] The versatility of carbenoids forms the basis for their manifold synthetic applications.

The first to mention the term carbenoid was Closs and Closs in 1962.[3] They treated a mixture of dibromodiphenylmethane and an alkene with methyllithium at −10 °C and isolated tetraphenylethene and stereospecifically formed cyclopropanes. Later, Closs and Moss proposed "the use of the term 'carbenoid' as a noun for the description of the intermediates which exhibit reactions qualitatively similar to those of carbenes without necessarily being free divalent carbon species".[4] Köbrich argued that carbenoids are lithium halide complexed carbenes.[5] Their notorious instability complicated structural investigations. Only in recent years have high level quantum-chemical calculations,[1c,6] modern NMR techniques,[7] and X-ray structure analyses[8] at low temperatures in combination with structural data in solution and in the solid state allowed us to deduce their chemical behavior.

The strongest argument to delineate the carbenoid nature of α-haloalkyllithiums is the enhanced s-character of the C−Li bond and the increased p-character of the other bonds as demonstrated by NMR studies. The carbenoid ^{13}C resonates at a lower field than that of the non-lithiated species (e.g., $\Delta\delta$ = 32.3 ppm for chloromethyllithium).[6b,7b,c] An X-ray structure analysis of $LiCHCl_2 \cdot 3pyr$ supports these findings.[8] Finally, quantum-chemical calculations revealed that the methyllithiums $LiCH_2X$ (X = F, Cl, Br, I) have elongated C−X bonds as compared to the non-metalated species, whereby the elongation decreases (F > Cl > Br > I) with increasing atomic weight of the halogen.[1c] In the calculated most stable monomeric structures, the lithium atom bridges the carbon and heteroatom.

Köbrich was one of the pioneers of carbenoid chemistry, whose seminal work is still unparalleled.[5] He prepared a number of various α-bromo- and α-chloroalk(en)yllithiums, among them the quite labile mono-,[9] di-,[10] and trichloromethyllithi-

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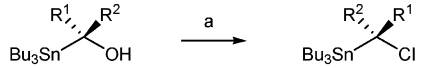
ums,[11] by either metalation with alkyllithiums or amides or halogen/lithium exchange. He examined their stability and reactivity, proving the latter to be different from classical carbenes generated photochemically from diazo compounds. The least stable species of the three chloromethyllithiums was found to be monochloromethyllithium, which was prepared from $BrCH_2Cl$ by halogen-lithium exchange with *n*-BuLi at −110 °C and could be carboxylated in very low yield at that temperature.[9] Later, monochloromethyllithium proved to be a useful reagent for homologations, similar to the more stable bromomethyllithium.[12] Because of their thermal instability, however, these carbenoids had to be and were prepared in situ and trapped with electrophiles such as carbonyl compounds, boranes, borates, trialkylsilyl halides, and trialkyltin halides.

Köbrich was among the first to report the configurational stability of carbenoids, of which there is still very little known. He found that the epimers of 7-chloro-7-lithionorcarane rearranged only slowly at −80 °C at a rate comparable to their decomposition, attributed to the strained cyclopropane ring resisting inversion of configuration at the carbanionic center.[13] This result was supported by the finding that a variety of α-bromo- and α-chlorocyclopropyllithiums were configurationally stable below −78 °C but started to epimerize above that temperature.[14] Pioneering work by Hoffmann et al. demonstrated that α-bromoalkyllithiums prepared by halogen-lithium exchange from geminal dihalides could form products of high diastereoselectivity.[15] Furthermore, they proved that acyclic α-bromoalkyllithiums were configurationally stable at −110 °C in the absence of their dibromo precursors.[16]

Results and Discussion

Recently, we launched a project to study the configurational stability of chiral methyllithiums with a variety of heteroatom substituents. So far, we have unraveled the microscopic and macroscopic configurational stability of oxygen-substituted chiral methyllithiums.[17,18] Now, as the first halomethyllithium, we address the chlorine-substituted one, despite its chemical instability observed by Köbrich and Fischer[9a] and the known fact that 1-chloroalkylstannanes produce alkenes upon treatment with *n*-BuLi.[19] We were primarily interested in its preparation and the determination of its microscopic and macroscopic configurational stability. Admittedly, the search for the smallest configurationally stable methyllithium contributed to that interest. Fluoromethyllithium, although even smaller, had been reported to be chemically too unstable,[1c] and bromo- and iodomethyllithium were anticipated to be configurationally too labile.

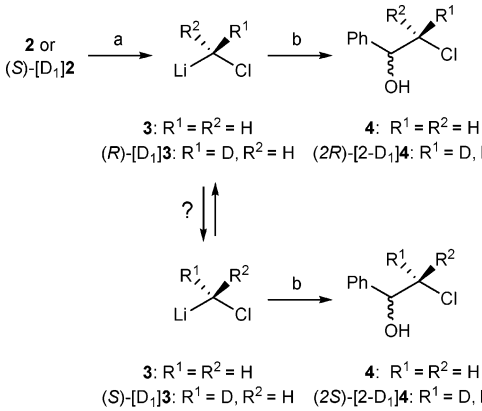
Scheme 1. Preparation of Tributyl(chloromethyl)stannane and Tributyl(chloro-[D_1]methyl)stannane via Appel Conditions[a]



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

[a] (a) Ph_3P, CCl_4, CH_3CN, 1 h, room temperature {93% for **2** and [D_1]**2**}.

Scheme 2. Generation and Trapping of Chloromethyllithiums **3** and [D_1]**3**: in Situ Method[a]



3: $R^1 = R^2 = H$ **4**: $R^1 = R^2 = H$
(*R*)-[D_1]**3**: $R^1 = D, R^2 = H$ (2*R*)-[2-D_1]**4**: $R^1 = D, R^2 = H$

3: $R^1 = R^2 = H$ **4**: $R^1 = R^2 = H$
(*S*)-[D_1]**3**: $R^1 = D, R^2 = H$ (2*S*)-[2-D_1]**4**: $R^1 = D, R^2 = H$

[a] (a) PhCHO (5 equiv) followed by alkyllithium (5 equiv) (for yields of **4**, see Table 1).

As such, we envisioned preparing chiral chloro-[D_1]-methyllithium by tin-lithium exchange. We considered it the method of choice as it allows for complete stereocontrol, contrary to halogen-lithium exchange or deprotonation, the most widely used methods for generating halomethyllithiums. Therefore, enantiopure chloromethylstannane [D_1]**2** had to be synthesized as a precursor from homochiral tributylstannyl-[D_1]-methanol {(*R*)-[D_1]**1**} (Scheme 1). This was first performed with the unlabeled compound, as all of the following reactions, to evaluate the feasibility of the approach and to optimize the conditions and yields. Transformation of tributylstannylmethanol into the corresponding chloride worked cleanly with Ph_3P/CCl_4 in dry acetonitrile (Appel protocol), giving **2** and later on [D_1]-**2** in 93% yield.[20]

To test the microscopic stability of chloromethyllithium, we used an in situ quench method, which means that the stannane was transmetalated with the electrophile already in the reaction mixture (Scheme 2). We used benzaldehyde as the standard electrophile, which facilitates comparison of results with the oxymethyllithiums tested previously. This protocol ensures a very short half-life for the chemically labile chloromethyllithium because it is trapped as soon as it is formed. To optimize the yield, several conditions for transmetalation of the easily available unlabeled compound were tested first (Table 1).

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Table 1. Reaction Conditions and Yields of Chlorohydrine **4**

entry	base	solvent	temp (°C)	yield[a] (%)
1	*n*-BuLi	THF	−78	16[b]
2	*n*-BuLi	THF	−100	*c*
3[d]	*n*-BuLi	THF	−100	0
4	*n*-BuLi	Et$_2$O/TMEDA	−78	1
5	*s*-BuLi	THF	−78	0
6	MeLi	THF	−78	77
7	MeLi	THF	−95	21
8	MeLi	THF	0	0

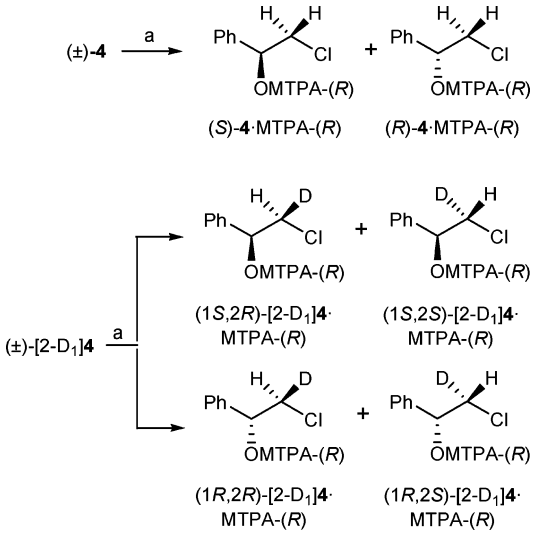
[a] Determined from ^{1}H NMR spectrum of the crude product (losses upon chromatography). [b] Recovered starting material: 23%. [c] Recovered starting material: 53%. [d] Benzaldehyde was added 30 s after the addition of *n*-BuLi.

Using similar conditions as in previous experiments with carbamoyloxy-substituted methyllithiums,[17] we transmetalated chloromethylstannane **2** with *n*-BuLi at −78 °C (entry 1 in Table 1). The yield of chlorohydrine **4** was only 16%. It seemed that the addition of *n*-BuLi to benzaldehyde was faster than transmetalation, as there was still starting material left after the workup. This effect was even more pronounced when the temperature was lowered to −100 °C (entry 2 in Table 1). The yield decreased to zero, while the percentage of starting material increased to over 50%. When benzaldehyde was not present upon the addition of *n*-BuLi to stannane, but added 30 s later, no product could be isolated (entry 3 in Table 1). This experimental setup would address the macroscopic configurational stability in the case of labeled methyllithium. The solvent used in all cases was THF, which was reported to accelerate metalation, especially at low temperatures.[21] We can confirm these findings by repeating the experiment in Et$_2$O/TMEDA (entry 4 in Table 1). Only traces of the product were found under these conditions. As we did not obtain any chlorohydrine **4**, we discontinued the approach with *n*-BuLi as the alkyllithium. Replacing it with *s*-BuLi did not improve the yield either (entry 5 in Table 1).

Before investing more time into optimizing the conditions for transmetalation, we wanted to obtain a first result regarding the microscopic configurational stability of [D$_1$]**3**. If (*R*)-[D$_1$]**3** retained its configuration for the short lifetime between its generation and its addition to benzaldehyde being present upon transmetalation, two labeled stereoisomers, (1*RS*,2*R*)-[2-D$_1$]**4**, would result, as the enantioselectivity concerning the configuration at C-1 is zero. If (*R*)-[D$_1$]**3** enantiomerizes, all four possible chlorohydrines would be formed, their ratio depending on the difference in the reaction rate between racemization and trapping. The experiment described in Table 1, entry 1 (THF, −78 °C) was repeated with chloromethylstannane (*R*)-[D$_1$]**2**. The crude product contained indeed chlorohydrine [2-D$_1$]**4** in about 25% yield (by ^{1}H NMR). But, it was in an admixture with several byproducts, among them tetrabutyltin and a large excess of 1-phenylpentanol, the latter derived from the addition of *n*-BuLi to benzaldehyde, preventing isolation of the desired product by flash chromatography. Isolation was therefore postponed until a suitable reagent to derivatize the chlorohydrines to determine their configuration at C-1 by ^{1}H NMR spectroscopy was found.

Thus, a sample of unlabeled (±)-2-chloro-1-phenylethanol was converted to the (*R*)-Mosher esters (Scheme 3). The two

Scheme 3. Preparation of (*R*)-Mosher Esters from (±)-**4** and (±)-[2-D$_1$]**4**[a]



[a] (a) (*S*)-MTPACl/pyridine (quantitative).

diastereomers could be separated by flash chromatography. Anticipating later results, the less polar ester (R_f = 0.38 in hexanes/EtOAc = 15:1) was derived from chlorohydrine (*R*)-**4**, while the more polar one (R_f = 0.34) was from (*S*)-**4**. But actually, this was not necessary for ee determination at C-2 and thus only was performed in rare cases. As expected, two sets of ABX-systems with well-separated X-parts for the benzylic hydrogens were found in the ^{1}H NMR spectrum (Figure 1).

The two sets of the diastereotopic hydrogen atoms at C-2 resonated as AB-systems, which were sufficiently resolved to allow for integration of the signals, when the spectrum was recorded in toluene-d_8. Figure 1A shows the section of the two right parts of the AB-systems of **4**·MTPA-(*R*) that were used for integration in the labeled series. The four resonances at the lower field were assigned to the pro-S hydrogen atom of unlabeled (*S*)-chlorohydrine and those at higher field to the pro-R hydrogen of the (*R*)-enantiomer.

Now, the separation of the components of the crude product containing the deuterated chlorohydrine was resumed. Lengthy purification by HPLC was necessary to finally give [D$_1$]**4** in 10% yield, still containing 35% of another alcohol that was identified as 1-phenyl-[2-D$_1$]hexanol. This side product originated from *n*-BuLi attacking chloromethyllithium, a reaction that had first been observed by Köbrich and Merkle and later on by Huisgen and Burger (Scheme 4).[10,22] The ee of the resulting alcohols was then determined by transformation into diastereomeric Mosher esters. [D$_1$]**6** was racemic; however, (*S*)-[D$_1$]**4** was found to have an ee of 70% (^{1}H NMR of Mosher esters). For the sake of clarity, it is more convenient here to give the enantiomeric excess for each chiral center individually (ee). As the enantioselectivity of the chiral chloromethyllithium is zero, (*R*)- and (*S*) configurations at C-1 were always formed in equal amounts, resulting in a product with zero ee (i.e., racemic at C-1). However, the Mosher esters were not racemic at C-2 (ee 70%). This result was quite encouraging, as it indicated that the chiral chloromethyllithium was at least partly microscopically configurationally stable.

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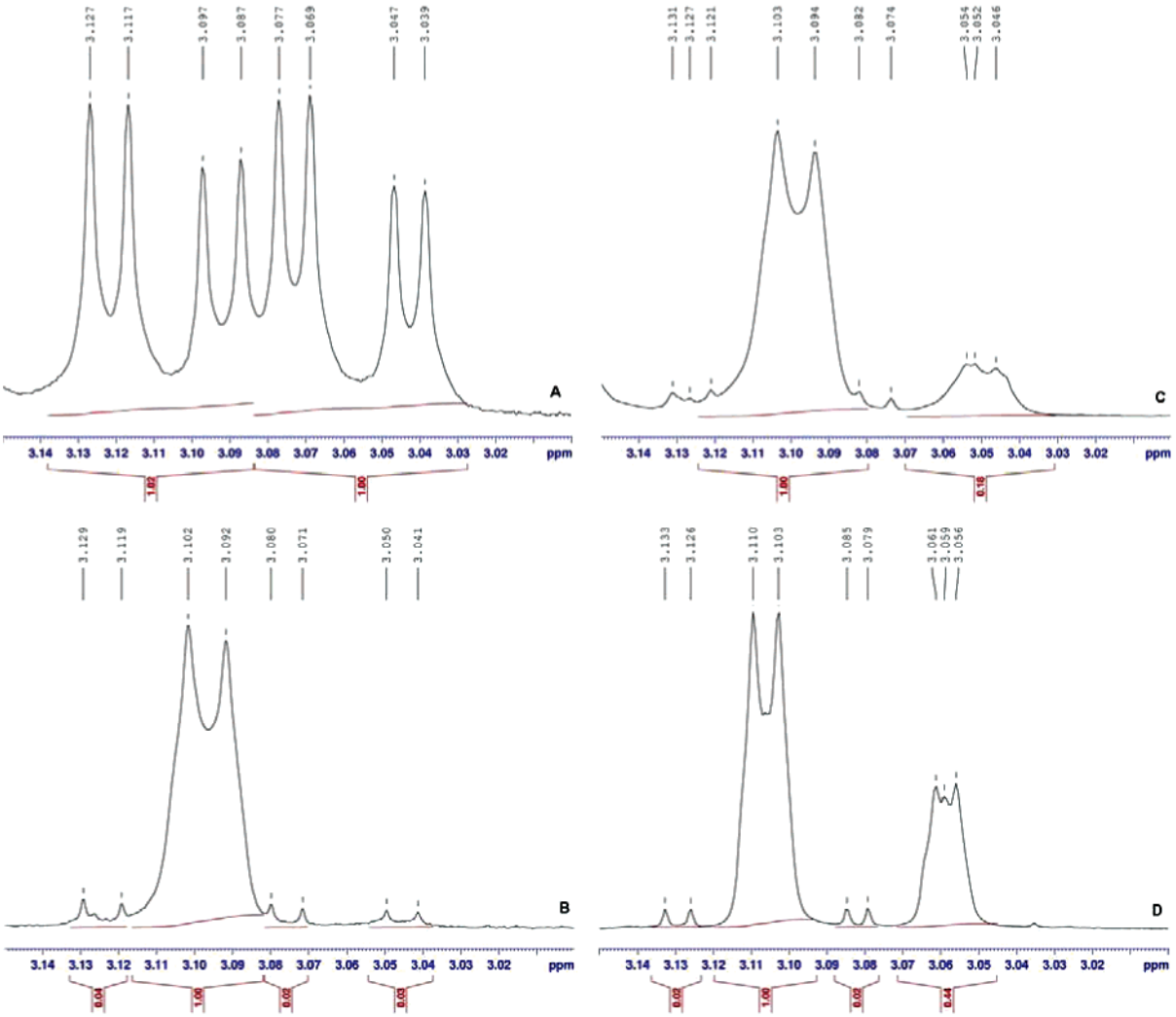
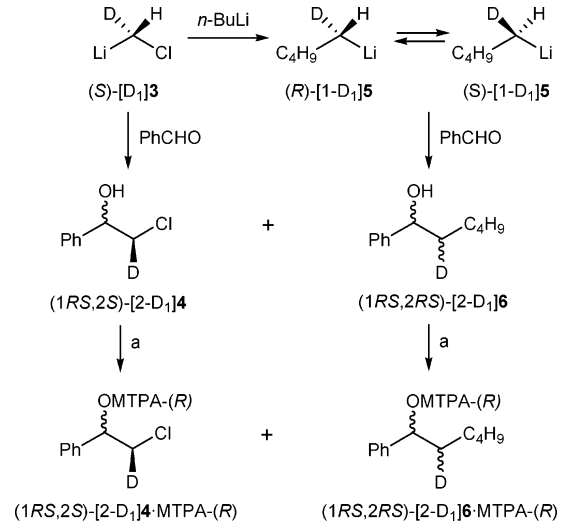


Figure 1. Relevant sections of selected ^{1}H NMR spectra of Mosher esters of unlabeled (A: 400 MHz, toluene-d_8, right parts of AB-systems) and labeled **4** (B and C: 400 MHz and D: 600 MHz toluene-d_8). (A) (±)-**4**·MTPA-(*R*) derived from (±)-**4**; (B) (1*S*,2*R*)-[2-D$_1$]**4**·MTPA-(*R*) of 98% ee plus 3% (±)-**4**·MTPA-(*R*); (C) (1*S*,2*R*)-[2-[D$_1$]**4**·MTPA-(*R*) of 70% ee {signal at 3.05 ppm of (1*R*,2*S*)-[2-[D$_1$]**4**·MTPA-(*R*)} plus 3% (±)-**4**·MTPA-(*R*); and (D) (1*S*,2*R*)-[2-D$_1$]**4**·MTPA-(*R*) of 40% ee {signal at 3.06 ppm of (1*R*,2*S*)-[2-[D$_1$]**4**·MTPA-(*R*)} plus 3% (±)-**4**·MTPA-(*R*).

Scheme 4. Formation and Esterification of (2*S*)-[D$_1$]**4** and [D$_1$]**6** with (*S*)-Mosher Chloride[a]



[a] (a) (*S*)-MTPACl, pyridine, CH_2Cl_2 (both 98%).

To prove the stereochemistry, overall retention, or inversion of configuration, we independently synthesized two diastereomeric chlorohydrines [2-D$_1$]**4** as reference compounds and converted them to (*R*)-Mosher esters (Scheme 5). Starting from diol (1*R*,2*R*)-[2-D$_1$]**7**,[17] the primary hydroxyl group was selectively protected with TBDMSCl/Et$_3$N.[23] Then, the secondary group was benzoylated using either benzoyl chloride/Et$_3$N or the Mitsunobu reaction [Ph$_3$P/diisopropyl azodicarboxylate (DIAD)/PhCO$_2$H] to give benzoates (1*R*,2*R*)- and (1*S*,2*R*)-[2-D$_1$]**9**, respectively.[24] The silyl groups were removed from the protected diols **9**,[25] and the alcohols **10** were transformed into the diastereomeric benzoates **10** under Appel conditions.[20] Reductive removal of the benzoyl groups finally furnished the diastereomeric deuterated chlorohydrines (1*R*,2*S*)- and (1*S*,2*S*)-[2-D$_1$]**4**, respectively, which were further transformed into the Mosher esters. The yields for the individual steps of the sequence ranged from 71 to 99%. The diagnostic CHD groups of these (*R*)-Mosher esters resonated as deuterium induced broadened doublets at different chemical shifts in the ^{1}H NMR spectra (600

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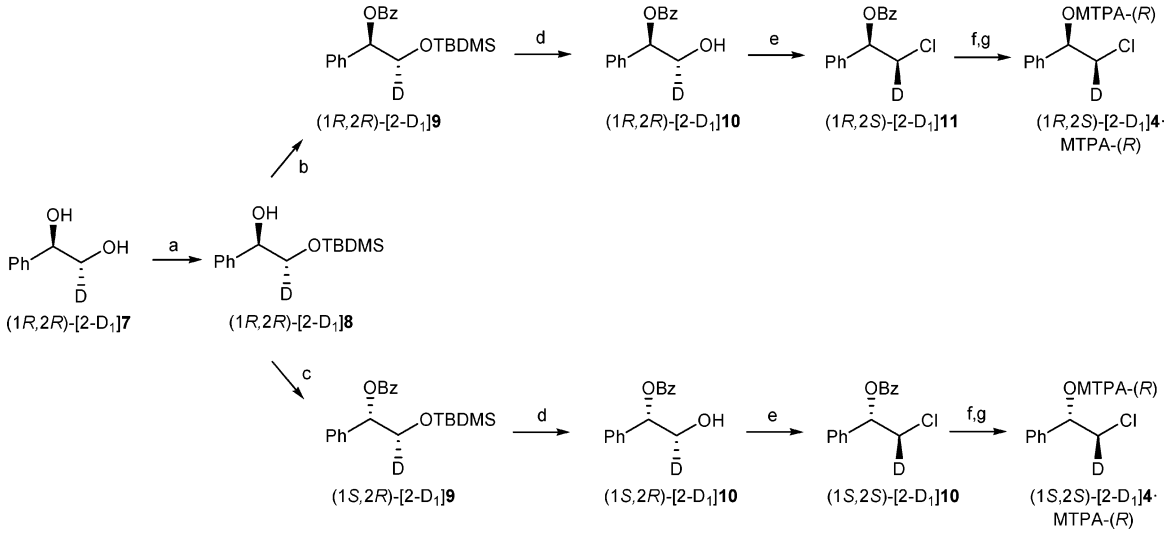
Scheme 5. Synthesis of Reference Compounds of Deuterated Chlorohydrines [2-D$_1$]**4** and Their (*R*)-Mosher Esters[a]



[a] (a) TBDMSCl, Et_3N, DMAP, CH_2Cl_2 (87%); (b) PhC(O)Cl, Et_3N, CH_2Cl_2 (99%); (c) $PhCO_2H$, Ph_3P, DIAD, THF (97%); (d) KF, $PhCO_2H$, CH_3CN, 75 °C (78 and 87%); (e) Ph_3P, CCl_4, CH_3CN (95% and 99%); (f) DIBAH, THF, −50 °C (71 and 76%); and (g) (*S*)-MTPACl, pyridine, CH_2Cl_2 (quantitative).

MHz, toluene-d_8) [(1*R*,2*S*)-[2-D$_1$]**4**·MTPA-(*R*): $\delta = 3.06$ ppm, $J = 3.3$ Hz and (1*S*,2*S*)-[2-D$_1$]**4**·MTPA-(*R*): $\delta = 3.31$ ppm, $J = 8.8$ Hz]. Comparison with the spectrum of the (*R*)-Mosher ester of the chlorohydrine derived from chiral chloromethylstannane (*R*)-[D$_1$]**2** revealed that 85% of the molecules had an (*S*) configuration at C-2, and 15% had an (*R*) configuration [i.e., ee 70%; spectral data deduced from transmetalation experiments and the unlabeled compound: (1*S*,2*R*)-[2-D$_1$]**4**·MTPA-(*R*): $\delta = 3.10$ ppm, $J = 4.0$ Hz]. Consequently, transmetalation and trapping with benzaldehyde followed an overall retentive course, implying for both steps a retention of configuration, as tin-lithium exchange proceeded with retention.

Now, we returned to optimizing the transmetalation process with the unlabeled chloromethylstannane (Scheme 2). Using MeLi instead of *n*-BuLi finally led to success. Performing the reaction at −78 °C furnished chlorohydrine **4** in 77% yield (Table 1, entry 6), which again decreased when the temperature was lowered to −95 °C (entry 7 in Table 1). The yields given in Table 1 for entries 6−8 were calculated from the ^{1}H NMR spectra of the crude products, using the CH_3Sn group as a convenient internal standard. Another positive effect of this switch in alkyllithium reagent was the easier isolation of chlorohydrine **4**, as 1-phenylethanol, formed by the addition of excess MeLi to excess benzaldehyde, could be removed by flash chromatography as compared to 1-phenylpentanol and 1-phenylhexanol. Furthermore, in neither case were we able to detect 1-phenylpropanol, formed by homologation of MeLi analogously to *n*-BuLi (see Scheme 4). Perhaps the lower basicity of MeLi as compared to *n*-BuLi inhibited its attack on the intermediate chloromethyllithium.[5a]

With this optimized procedure, we repeated the transmetalation and quenching of the intermediate chloromethyllithium (*R*)-[D$_1$]**3**, generated from the (*S*)-chloro-[D$_1$]methylstannane (Table 2). The yield was excellent (90%) when the reaction was performed at −78 °C, but the ee at C-2 of the isolated chlorohydrine was surprisingly low (entry 1 in Table 2). Changing THF for Et_2O/TMEDA as the solvent only led to the expected decrease in yield and no change in ee (entry 2 in Table 2). The same was true for lowering the temperature to −95 °C (entry 3 in Table 2). Despite these changes in the reaction conditions, the ee stayed virtually the same, reproducibly around 40%, which made us suspicious of the ee of the starting chloromethylstannane, which we had not assessed independently. We reasoned that perhaps the chiral chloromethyllithiums were configurationally stable but that the stannane precursor partially racemized during preparation. Chloride ions could react with part of the chiral chloromethylstannane, prone to S_N2 reactions in acetonitrile, leading to inversion of configuration.

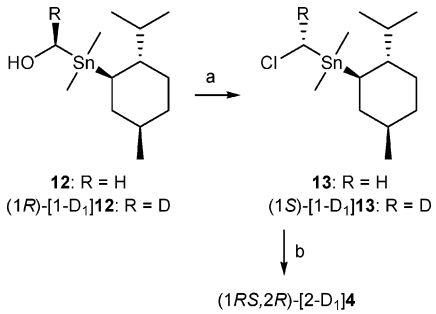
Table 2. Conditions and Results for Transmetalation/Addition Sequence of (*S*)-[D$_1$]**2** (Preparation via Appel Protocol) with MeLi

entry	solvent	temp (°C)	yield[a] (%)	ee (%)
1	THF	−78	90	39
2	Et_2O/TMEDA	−78	36	41
3	THF	−95	45	40

[a] Determined from ^{1}H NMR spectra of the crude product (losses upon chromatography).

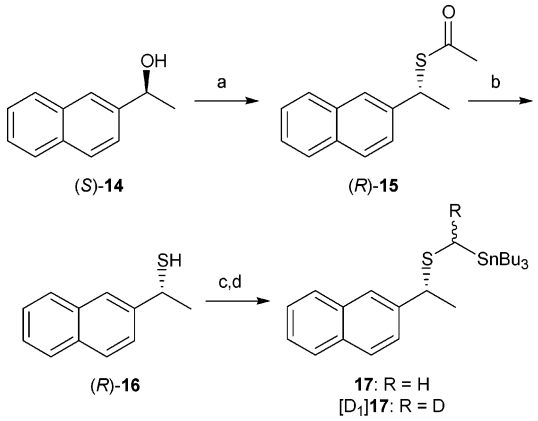
To prove this, we needed to find a way to determine the ee of chloromethylstannane [D$_1$]**2**. Therefore, we attempted to replace the butyl group at tin by a substituent with stereogenic centers. We hoped that the diastereotopicity induced at the $SnCH_2Cl$ group would be enough to differentiate between the two hydrogen atoms by ^{1}H NMR spectroscopy. Building on chemistry previously performed in our laboratory, we exchanged the tributylstannyl group for the menthyldimethylstannyl group derived from (−)-menthol (Scheme 6).[17] (−)-Menthyldimethylstannylmethanol (**12**) and its deuterated analogue (1*R*)-[1-D$_1$]-**12** were transformed under the same conditions as used for the tributylstannyl series into the chlorides **13** and (1*S*)-[1-D$_1$]**13**, respectively. But despite screening several solvents ($CDCl_3$, toluene-d_8, and DMSO-d_6), the two diastereotopic hydrogen atoms of the $SnCH_2Cl$ group of chloride **13** always resonated as a singlet in the ^{1}H NMR spectrum, making determination of the diastereomeric ratio futile in the labeled series. Despite that failure, we finally decided to transmetalate (1*S*)-[1-D$_1$]**13** and to react the formed chiral chloromethyllithium with benzaldehyde as usual. As expected, chlorohydrine (1*RS*,2*R*)-[2-D$_1$]**4** was obtained in 57% yield with an ee of 70% at C-2. This result

Scheme 6. Preparation of (−)-(Chloromethyl)menthyldimethylstannanes [**13** and (*S*)-[D$_1$]**13**] and Conversion of (*S*)-[D$_1$]**13** to Chlorohydrine [2-D$_1$]**4**[a]



[a] (a) Ph_3P, CCl_4, CH_3CN {yield for **13**: 80%; yield for (1*S*)-[1-D$_1$]**13**: 88%} and (b) PhCHO, MeLi {yield for (1*RS*,2*S*)-[2-D$_1$]**4**: 54%}.

Scheme 7. Synthesis of Homochiral Thiol (*R*)-**16** and Its Alkylation with (*R*)-[D$_1$]**2**[a]



[a] (a) Ph_3P, DIAD, MeC(O)SH, THF, room temperature (46%); (b) $LiAlH_4$, Et_2O, reflux (90%); (c) *n*-BuLi, THF, 0 °C to room temperature; and (d) **2** or (*S*)-[D$_1$]**2** (99% in both cases).

substantiated our suspicions but left us without proof and made the determination of the ee of the starting chloromethylstannane mandatory.

Our next approach was based on an excellent homochiral nucleophile, which would react with the chloride to form diastereomers. Assuming that the chloride ions replaced by the nucleophile did not compete with it, the diastereomeric ratio would accurately reflect the ee of the chiral chloromethylstannanes. The salt of an enantiomerically pure thiol, such as (*R*)-**16**, should be the nucleophile of choice and should be alkylated very rapidly with the chloromethylstannane at low temperature, thus preventing an interfering S_N2 reaction by the chloride ions (Scheme 7). Thiol (*R*)-**16**, a known but inadequately characterized compound,[26] was accessed from enantiopure naphthylethanol (*S*)-**14**,[27] which was transformed into thioacetate (*R*)-**15** by a Mitsunobu reaction in low yield (46%) and then reduced to thiol (*R*)-**16** with $LiAlH_4$.[28] Thiol (*R*)-**16** was converted to the thiolate with *n*-BuLi and alkylated with chlorostannane **2** to yield sulfide **17**. Its ^{1}H NMR spectrum gave an AB-system (J_{AB} = 9.4 Hz with calculated shifts for the diastereotopic protons at δ = 1.74 and 1.57 ppm) for the $SnCH_2S$ group, allowing ee determination in the labeled series. Similarly, (*R*)-[D$_1$]**2** prepared by the Appel method was transformed into chiral sulfides [D$_1$]-**17**, displaying a strong singlet at δ 1.72 ppm [diastereomer with an (*S*) configuration at CHD] and a weak one at δ 1.56 ppm [diastereomer with an (*R*) configuration at CHD] with a small deuterium induced shift to higher field as compared to the unlabeled species. Integration revealed an ee of 69% for the chloromethylstannane (*R*)-[D$_1$]**2**. With this irrevocable proof for partial racemization under Appel conditions, we had to search for a method to obtain enantiopure [D$_1$]**2**.

Table 3. Transmetalation/Quench Sequence of (*S*)-[D$_1$]**2** on the Macroscopic Time Scale

entry	temp (°C)	time (s)	yield (%)	ee (%)
1	−95	30	54[a]	98
2	−78	30	traces	97

[a] ^{1}H NMR spectroscopy of the crude product showed 29% starting material.

Compelled by this finding, we switched to the system of *N*-chlorosuccinimide/Ph_3P in dry THF.[29] Thus, stannylmethanol (*R*)-[D$_1$]**1** furnished (*S*)-[D$_1$]**2** in 80% yield with an ee of >98% as determined by ^{1}H NMR spectroscopy after conversion to the sulfide (*R*,*R*)-[D$_1$]**17**. Repeating the experiment (Table 2, entry 1, −78 °C, THF) with this homochiral chloromethylstannane yielded chlorohydrine (2*R*)-[2-D$_1$]**4** of 98% ee at C-2, confirming that the intermediate chiral chloromethyllithium **3** was completely configurationally stable on the microscopic time scale.

Macroscopic Configurational Stability

After our success on the microscopic time scale, we focused on the macroscopic configurational stability of chloromethyllithium as well. This could be achieved in a similar experimental setup as before, except that benzaldehyde was now added after a certain period of time (aging of chloromethyllithium) following transmetalation with MeLi. A lengthy trial and error period with the unlabeled compound was required to find the thin line between transmetalation and decomposition. The reproducibility of yields was quite low, which was attributed to the chemical instability of chloromethyllithium [D$_1$]**3**. The best results (50%) were achieved at −95 °C in THF, adding benzaldehyde 30 s after the addition of MeLi. This, when repeated with the labeled compound, gave chlorohydrine (2*R*)-[D$_1$]**4** in 54% yield with an ee of 98% at C-2 (Table 3, entry 1). We also performed the transmetalation at −78 °C, a temperature where decomposition prevailed. We did not try to isolate the traces of the resulting chlorohydrine, whose resonances were hardly visible in the ^{1}H NMR spectrum of the crude product. Instead, we converted it directly into the (*R*)-Mosher ester, at which stage purification by flash chromatography was possible. Satisfyingly, the ee at C-2 was 97%. This means that chloromethyllithium [D$_1$]**3** is macroscopically configurationally stable, although its half-life at −78 °C must be in the rage of seconds. It rather decomposes than racemizes. Our findings demonstrate that (chiral) chloromethyllithium is a thermally very labile but configurationally stable heteroatom-substituted organolithium of unknown aggregation state.[30]

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Conclusion

In summary, we found that homochiral chloromethyllithium prepared by tin-lithium exchange from the corresponding tributyl(chloro-[D_1]methyl)stannane was completely microscopically and macroscopically configurationally stable up to the border of its chemical stability. Chloromethyllithium adds to benzaldehyde under retention of configuration. Microscopically, yields of up to 90% (at −78 °C) were achieved, while macroscopically, the best yield was 56% (−95 °C, 30 s). Generally, the transmetalation reactions were highly reproducible concerning the ee values, but the yields for the addition of the intermediate chloromethyllithium varied, which was due to the chemical instability of this particular organolithium.

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Supporting Information Available: All experimental procedures and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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