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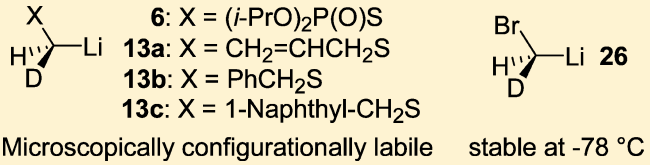
On the Preparation and Determination of Configurational Stability of Chiral Thio- and Bromo[D_1]methyllithiums

Anna Wieczorek and Friedrich Hammerschmidt*

Institute of Organic Chemistry, University of Vienna, Währingerstrasse 38, A-1090 Vienna, Austria

Supporting Information

ABSTRACT: Thio- and bromo[D_1]methyllithiums (ee 99%) were generated from the respective stannanes by tin−lithium exchange at temperatures ranging from 0 to −95 °C. Thio[D_1]methyllithiums **6** were found to be microscopically configurationally labile on the time scale of the thiophosphate-α-mercaptophosphonate rearrangement even at −95 °C. Thio[D_1]methyllithiums **13a** and **13b** underwent a thia-[2,3]-Wittig rearrangement down to −95 °C and **13b** only down to −50 °C. The former were microscopically configurationally stable below −95 °C, and the latter racemized completely at −50 °C. Chiral bromo[D_1]methyllithiums are chemically unstable at −78 °C but microscopically configurationally stable at the time scale of their addition to benzaldehyde and acetophenone.



INTRODUCTION

In previous papers, we have shown that heteroatom-substituted chiral [D_1]methyllithiums, the smallest organometallic compounds, can be prepared in homochiral form by tin−lithium exchange from the respective tributylstannyl derivatives at low temperatures. They differ in their chemical as well as in their macro- and microscopic configurational stability, depending on the heteroatom, the solvent, and the temperature used. The oxygen-substituted chiral methyllithiums **1a**[1] and **1b**[1] are the macroscopically configurationally most stable ones, followed by **1c**[2] and **1d**[3] (Figure 1). The other oxygen-substituted ones are chemically unstable but microscopically configurationally stable on the time scale of a rearrangement. The silyloxy- and germyloxy-substituted ones **1e** and **1f** undergo retro-Brook rearrangements (1,2-Wittig rearrangements) with retention of configuration.[4] The (allyloxy)methyllithiums **1g** isomerize (2,3-Wittig rearrangement) with inversion of configuration, and the phosphate[2] **1h** rearranges (phosphate−phosphonate rearrangement) with retention of configuration. The chiral (dibenzylamino)methyllithiums[5] (**1i**) are the most stable of all nitrogen-substituted ones but not completely even at −95 °C. At the same temperature, compound **1j** is configurationally less stable than **1i**.[5] Homochiral isocyanomethyllithium (**1k**) racemizes completely at −95 °C when generated in the presence of benzaldehyde as electrophile.[5] The phosphoric acid amide **1l** undergoes a phosphoramidate−α-aminophosphonate rearrangement with retention of configuration.[5] Chloro[D_1]-methyllithium **1m** decomposes quickly but is macroscopically configurationally stable for its short lifetime.[6]

This paper addresses the configurational stability of chiral thio- and bromo[D_1]methyllithiums as compared to oxy- and chloromethyllithiums to study the influence of going from heteroatoms of the second (oxygen) and third (chlorine) row elements to ones of the third (sulfur) and fourth (bromine) one, respectively.

The Hoffmann test of α-(phenylthio)butyllithium and α-bromopentyllithium[7] and secondary α-thiobenzyllithium[8] established configurational stability of the former at −120 and −110 °C, respectively but instability of the latter at −78 °C on the time scale of their addition to (*S*)-*N*,*N*-dibenzylphenylalaninal. Secondary durylthioalkyllithiums are configurationally stable at −110 °C.[9] The configurationally most stable α-thioalkyllithiums are tertiary ones with a carbamoyl substituent at the sulfur atom.[10] Theoretical calculations for methyllithiums substituted with a heteroatom being an element of the third or a higher row show that they are configurationally less stable than those of the second row because of the increasing ease of planarization of the carbanionic center.[11] Thus, sulfur- and selenium-substituted alkyllithiums are configurationally less stable than the oxygen-substituted ones.[12] The same is true for phosphorus versus nitrogen and silicon versus carbon-substituted chiral methyllithiums.[13] Investigations of the structure of many α-heteroatom-substituted alkyllithiums[14] and mechanistic[15] studies on the enantiomerization of α-thioalkyllithiums have been performed. α-Alkyllithiums are highly important synthetic reagents.[16a−c] Reich has recently published an excellent Perspective of his structural work on organolithium reagents using low-temperature NMR spectroscopy.[16d] It addresses all questions of relevance to those studying or applying organolithiums.

RESULTS AND DISCUSSION

Generation of Chiral Thiomethyllithiums and Determination of Their Microscopic Configurational Stability. Anticipating that chiral thio[D_1]methyllithiums would not be macroscopically configurationally stable, but only microscopically at best, we decided to intercept them after generation at

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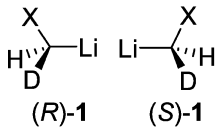


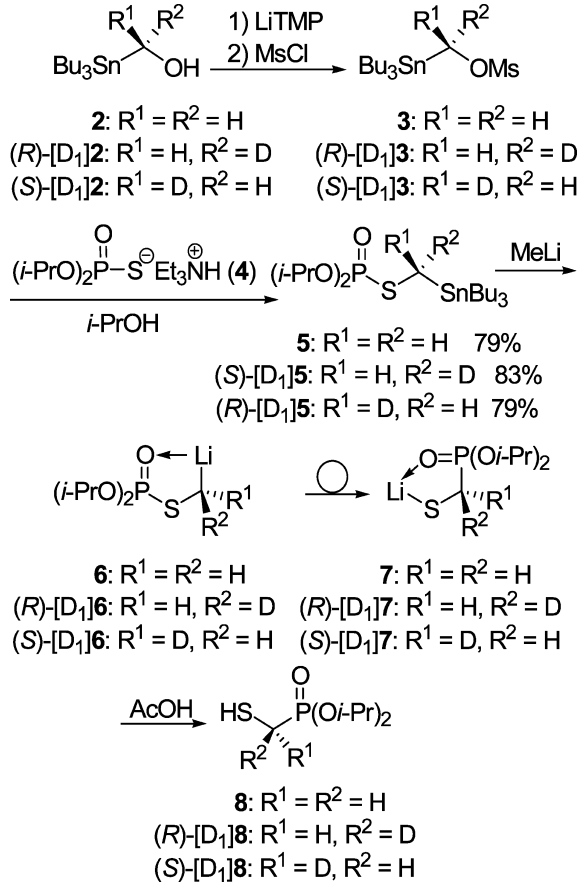
1a (X= THPO), **1b** (X = PMBO), **1c** (X= *i*-$Pr_2NC(O)O$), **1d** (X = *i*-$Pr_3H_2C_6C(O)O$), **1e** (X = $OSiR_3$), **1f** (X = $OGeEt_3$), **1g** (X = $OCHPhCH{=}CH_2$), **1h** (X = $(i\text{-PrO})_2P(O)O$), **1i** (X = NBn_2), **1j** (X = PMBNBoc), **1k** (X = NC), **1l** (X = $(i\text{-PrO})_2P(O)NBoc$), **1m** (X = Cl)

Figure 1. Known chiral [D_1]methyllithiums with a heteroatom as substituent.

low temperatures by intramolecular reactions. Two types were used, the thiophosphate α-mercaptophosphonate[17] and the thia-[2,3]-Wittig rearrangement[18] involving short-lived thioalkyllithiums. The former was found to follow a retentive course with microscopically configurationally stable (from −78 to 0 °C) (dialkoxyphosphinyl)thioalkyllithiums as intermediates and the latter an invertive one at the carbanionic center. α-Allylthioalkyllithiums as intermediates of the thia-[2,3]-Wittig rearrangement were found to be configurationally stable, but α-benzylthioalkyllithiums were found to be unstable and partially enantiomerized prior to the rearrangement.[19] Furthermore, Ikemoto et al. studied the effect of solvents and additives on the steric course of oxy-[2,3]-Wittig rearrangement of the chiral 1,3-diphenyl-1-propenyloxy-2-propen-1-yl carbanion. They found that the marked differences on the enantiomeric ratios obtained with different solvents can be ascribed to the extent of ion separation, which depends on the nature of solvent/additive. THF favors conversion of a contact ion pair to a separated ion pair. This finding induced us to study Et_2O beside THF as solvent.[20]

The substrates for testing the configurational stability of chiral (diisopropoxyphosphinyl)thiomethyllithiums, the diisopropyl *S*-tributylstannylmethyl thiophosphates, were prepared according to Scheme 1. Here and in all other cases, reactions were first optimized in the unlabeled series and then applied to the labeled ones. Tributylstannylmethanol (**2**) was converted via its lithium alkoxide at −78 °C to mesylate **3**,[4] which was used directly to alkylate the triethylammonium salt of diisopropyl thiophosphate[16] (**4**). The *S*-tributylstannylmethyl thiophosphate **5** was obtained in 79% overall yield. Similarly, the deuterated enantiomers (*S*)- and (*R*)-[D_1]**5** were prepared from (*R*)- and (*S*)-tributylstannyl[D_1]methanol[2] of 99% ee, respectively, obtained by an improved procedure (see the Experimental Section). To generate the short-lived dipole-stabilized[18] (diisopropoxyphosphinyl)thiomethyllithium (**6**), thiophosphate **5** was transmetalated in THF at −78 °C with MeLi added dropwise every 3 s. Normally, alkyllithiums were added with a syringe equipped with a needle to vigorously stirred reaction mixtures. In analogy to previous results, we assume tin−lithium exchange whenever used here in this paper to generate heteroatom-substituted methyllithiums to follow a retentive course.[16d,21] It was found by Reich and Phillips[22] and others[23] that tin−ate complexes form in quantities detectable by NMR spectroscopy under special conditions, e.g., the presence of HMPA as additive in THF, increasing the number of phenyl substituents at tin, and low temperature (−80 °C). Furthermore, tributyltin compounds are not favorable for the formation of ate complexes, which are substantially less reactive[21] than lithium reagents. These facts induce us to think that tin−ate complexes play only a minor role here, if at all, and that salt free species of heteroatom-substituted methyllithiums are produced. The migration of the phosphinyl group from the sulfur to the carbon atom, a thermodynamically driven reaction, gives phosphonate **7**. Addition of AcOH 2 min later, workup, and chromatographic purification furnished mercaptomethylphosphonate[17] **8** in 60% yield. As no starting material could be detected, transmetalation and the ensuing rearrangement must be rapid reactions. When the experiment was performed at 0 °C, it furnished merely 33% of the desired mercaptophosphonate, although no starting material was left. To determine the ee in the labeled series, mercaptophosphonate[24] **8** was derivatized with (*R*)-1-(1-naphthyl)ethyl isocyanate to give thiocarbamates **10** (Scheme 2). Its ^{1}H NMR spectrum displayed well-separated signals for the diastereotopic hydrogens of the SCH_2P group, allowing evaluation of the ee of the deuterated mercaptomethylphosphonates. With this information in hands, thiophosphates (*S*)- and (*R*)-[D_1]**5** were rearranged at temperatures ranging from −95 to 0 °C, plausibly assuming a retentive course as in the case of a secondary phosphinylthioalkyllithium.[17] The yields and the enantiomeric excesses of the mercaptomethylphosphonates [D_1]**8** are given in Table 1. The ee increased with decreasing temperature. The rearrangement in Et_2O at 0 °C gave racemic [D_1]**8**; however in THF a product with 23% ee (entries 3 and 1). The reason for the stronger influence of Et_2O compared to THF on the ee is

Scheme 1. Preparation of Diisopropyl Thiophosphates 5[a], Thiomethyllithiums 6, and Their Thiophosphate-α-mercaptophosphonate Rearrangement



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

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

5: $R^1 = R^2 = H$ 79%; (*S*)-[D_1]**5**: $R^1 = H$, $R^2 = D$ 83%; (*R*)-[D_1]**5**: $R^1 = D$, $R^2 = H$ 79%

6: $R^1 = R^2 = H$; (*R*)-[D_1]**6**: $R^1 = H$, $R^2 = D$; (*S*)-[D_1]**6**: $R^1 = D$, $R^2 = H$

7: $R^1 = R^2 = H$; (*R*)-[D_1]**7**: $R^1 = H$, $R^2 = D$; (*S*)-[D_1]**7**: $R^1 = D$, $R^2 = H$

8: $R^1 = R^2 = H$; (*R*)-[D_1]**8**: $R^1 = H$, $R^2 = D$; (*S*)-[D_1]**8**: $R^1 = D$, $R^2 = H$

[a]Ms = methanesulfonyl; LiTMP = 2,2,6,6-tetramethylpiperidinyllithium.

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Scheme 2. Derivatization of α-Mercaptomethylphosphonates 8 with Chiral Isocyanate

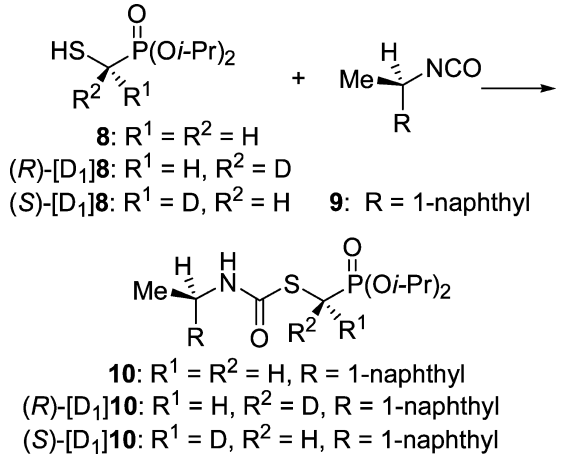


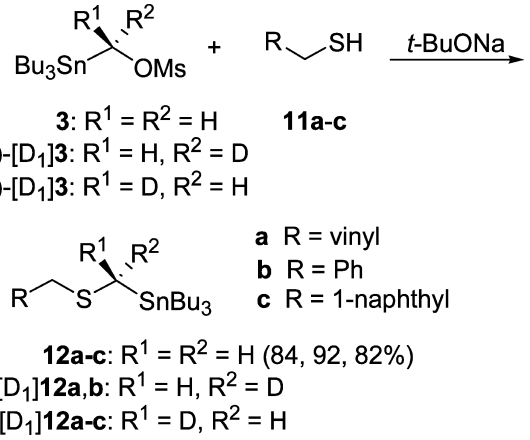
Table 1. Yields and ee of Mercapto[D_1]methylphosphonates [D_1]8 Obtained by Rearrangement of Thiophosphates [D_1]5

entry	solvent/RLi/conf of [D_1]5	temp (°C)	time (s)	yield (%)	ee (%)
1	THF/MeLi/(*S*)	0	15	41	23
2	Et_2O/MeLi/(*S*)	−95	60	22	77
3	Et_2O/MeLi/(*S*)	0	15	56	0
4	THF/MeLi/(*R*)	−95	180	25	61
5	THF/*n*-BuLi/(*R*)	−95	180	68	51

not clear, but possibly attributable to the differing degree of solvation of lithium.[20] The best result in terms of a combination of yield (68%) and ee (51%) was obtained in THF with *n*-BuLi at −95 °C (entry 5). In summary, these results show that chiral (phosphinylthio)methyllithiums [D_1]**6** are microscopically configurationally labile down to −95 °C on the time scale of the thiophosphate-α-mercaptophosphonate rearrangement.

Generation of Chiral Allylthio- and (Arylmethylthio)-methyllithiums and Determination of Their Microscopic Configurational Stability. Three systems with differing lifetimes for the intermediate thiomethyllithiums amenable to thia-[2,3]-Wittig rearrangement were investigated. The required stannanes **12a−c** were accessed from thiols **11a−c**, *t*-BuONa, and tributylstannylmethyl mesylates[4] **3** in yields of 82% to 92% (Scheme 3). The unlabeled allylthiomethylstannane **12a** was rearranged first. Tin−lithium exchange in THF at −95 °C with *n*-BuLi produced thiomethyllithium **13a** (Scheme 4). The ensuing thia-[2,3]-Wittig rearrangement furnished lithium thiolate **14a**, which would give on acidic workup and extraction 3-butenethiol. Its boiling point[25] of 70−80 °C is too low to allow direct isolation of small amounts (<1 mmol). Therefore, a substoichiometric amount of CF_3CO_2H (0.33 equiv relative to *n*-BuLi) was added 10 min after the addition of *n*-BuLi, followed by excess (*R*)-1-phenylethyl isocyanate, to convert thiol **15** for determination of yield and evaluation of ee in the labeled series to thiocarbamate **16** in 83% overall yield. The two diastereotopic hydrogens at C-1 formed an AB system in the ^1H NMR spectrum (DMSO-d_6, 600 MHz), which collapsed to two broadened singlets at 2.79 and 2.82 ppm on decoupling of protons at C-2. Similarly, deuterated stannanes (*R*)- and (*S*)-[D_1]**12a** were rearranged using either THF or Et_2O as solvent at temperatures ranging from −95 to 0 °C (Table 2).

Scheme 3. Preparation of Allyl-, Benzyl-, and (1-Naphthylmethyl)thiomethyltributylstannanes 12



Scheme 4. Thia-[2,3]-Wittig Rearrangement of Allylthiomethyllithiums 13a and Conversion of the 3-Butenethiols (15) Formed to Thiocarbamates 16

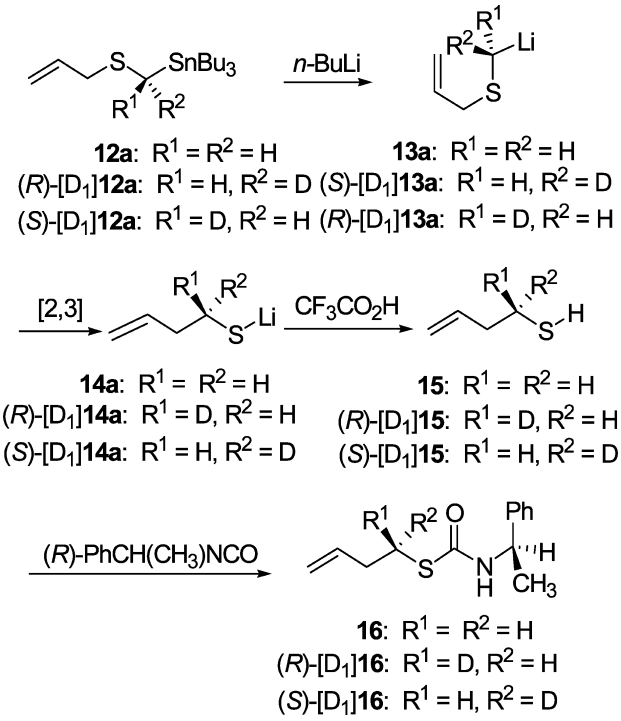


Table 2. Conditions, Yields, and ee of Thiocarbamates [D_1]16 Obtained by Rearrangement of [D_1]12a and Derivatization of 3-Butenethiols formed

entry	solvent/config of [D_1]12	temp (°C)	time (min)	yield (%)	ee (%)
1	THF/*S*	−95	10	83	≥95
2	THF/*S*	−78	10	95	91
3	THF/*S*	−40	10	99	83
4	THF/*S*	0	3	72	71
5	Et_2O/*R*	−78	10	62	50
6	Et_2O/*R*	0	3	45	20

The data show that the yields and the ee are significantly better for THF than Et_2O. In analogy to the results for secondary allythioalkyllithiums obtained by Brickmann and

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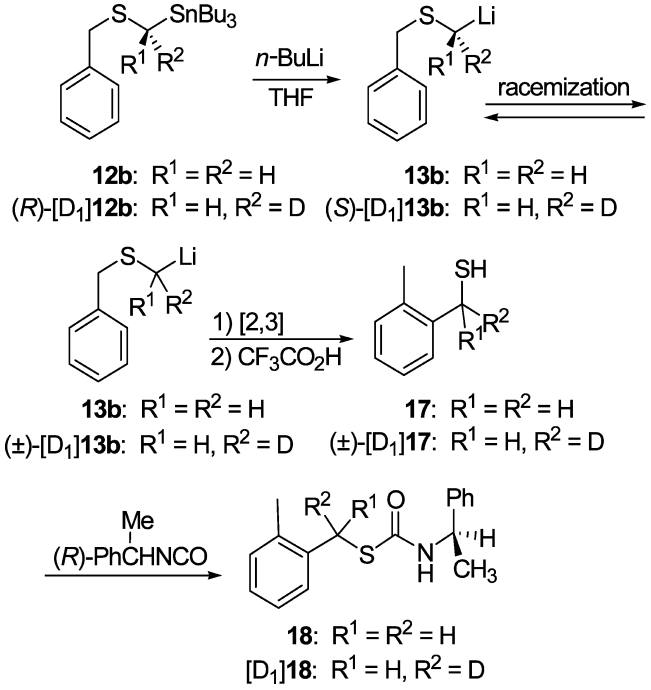
Brückner,[18] we assume that the rearrangement proceeds with inversion of configuration at the carbanionic center.[7] Surprisingly, chiral thiomethyllithiums [D_1]**13a** are configurationally stable on the time scale of thia-[2,3]-Wittig rearrangement below −95 °C in THF and ee of thiol obtained at 0 °C was still 71%. It decreased only from ≥95% to 71% by going from −95 to 0 °C in THF as solvent.

Next, the microscopic configurational stability of benzylthiomethyllithiums (**13b**) on time scale of [2,3]-rearrangement was addressed. Benzylthiomethylstannane **12b** was transmetalated with *n*-BuLi in THF already at −30 °C, as a higher activation energy was expected than for allyl analogue (Scheme 5). As before, the rearranged lithium thiolate was converted to

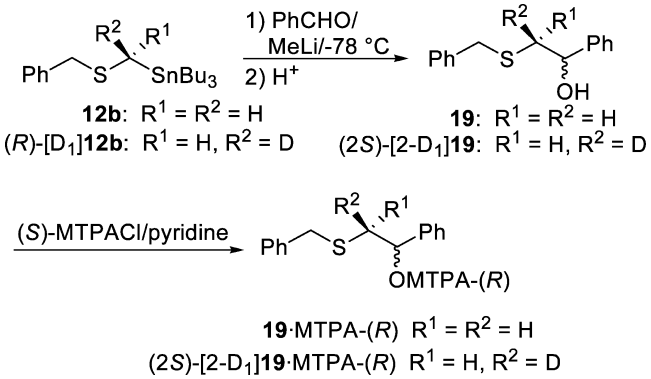
Scheme 5. Thia-[2,3]-Wittig Rearrangement of Benzylthiomethylstannanes 12b and Conversion of Phenylmethanethiols 17 to Thiocarbamates 18



thiocarbamate **18** via thiol **17**. When the same reaction was performed with stannane (*R*)-[D_1]**12b** at −50 °C (reaction time: 20 min), the yield of thiocarbamates [D_1]**18** was 59%. However, the underlying thiol was found to be racemic. When thiomethyllithium (*S*)-[D_1]**13b** was generated at −78 °C and quenched with CF_3CO_2H after 10 min, only benzyl methyl sulfide was detected besides tetrabutyltin by ^{1}H NMR spectroscopy (400 MHz) in the crude product. The following conclusions can be drawn from these three experiments. First, benzylthiomethyllithium (**13b**) undergoes thia-[2,3]-Wittig rearrangement down to −50 °C. At lower temperatures, the activation energy, at least that for dearomatization corresponding to resonance energy of benzene of 36 kcal·mol^{-1}, cannot be overcome. Second, this high activation energy increased the lifetime of intermediates **13b** and their chances to enantiomerize, compared to those for allylthiomethyllithium (**13a**). Racemization seems to be much faster than [2,3]-rearrangement. Third, chiral benzylthio[D_1]methyllithium is microscopically configurationally unstable on the time scale of thia-[2,3]-Wittig rearrangement.

The chemical stability of benzylthiomethyllithium toward thia-[2,3]-Wittig rearrangement at −78 °C enabled us to investigate its microscopic and macroscopic configurational stability. First, MeLi was added to a solution of unlabeled stannane **12b** in THF, followed by benzaldehyde as our standard electrophile for chiral [D_1]methyllithiums 10 min later. Workup after 5 min and flash chromatography furnished (±)-*β*-benzylthio alcohol **19** in 77% yield (Scheme 6). The

Scheme 6. Transmetalation of Thiomethylstannanes 12b and Interception of Benzylthiomethyllithiums Formed as Intermediates with Benzaldehyde



(*R*)-Mosher ester derived from (*S*)-*α*-methoxy-*α*-(trifluoromethyl)phenylacetyl chloride [(*S*)-MTPACl, (*S*)-Mosher chloride] was prepared and investigated by ^{1}H NMR spectroscopy. The SCH_2 group of each diastereomer displayed a well-separated AB part of an ABX system, enabling the determination of ee with an estimated accuracy of 3% at best at deuterium bearing carbon atom in the labeled series. To address macroscopic configurational stability of benzylthio-[D_1]methyllithium [(*S*)-**13b**], this experiment was repeated with (*R*)-[D_1]**12b** and yielded an alcohol being racemic at C-1 and C-2 as deduced from the ^{1}H NMR spectrum (400 MHz) of the mixture of (*R*)-Mosher esters. Despite the short time of 1 min between addition of MeLi for tin−lithium exchange and addition of benzaldehyde, the lifetime was long enough to allow complete racemization at deuterium bearing carbon atom.

To evaluate the microscopic configurational stability of (*S*)-**13b**, MeLi was added dropwise to a solution of stannane (*R*)-[D_1]**12b** and benzaldehyde in THF at −78 °C. The deuterated alcohol (*S*)-[2-D_1]**19** isolated in 24% yield, was derivatized with (*S*)-Mosher chloride and the mixture of esters was investigated by ^{1}H NMR spectroscopy. The ee at the deuterium bearing stereo center was only 16%, but significant. This time thio[D_1]methyllithium (*S*)-[D_1]**13b** was immediately intercepted by benzaldehyde as the electrophile. Despite the short time between generation and addition to carbonyl group, partial racemization of the (very) labile thio[D_1]methyllithium interfered. The yield dropped to 9%, but the ee increased to 26%, when the reaction was performed at −95 °C in the presence of 2 equiv of 12-crown-4. It was hoped that this Li^+ complexing agent might influence the C−Li bond length and thus enantiomerization.[14] When the reaction was performed at −50 °C, no thiol [D_1]**17** formed by rearrangement could be detected (^{1}H NMR) in the crude product besides deuterated alcohol **19** (25%, 8% ee). This experiment shows that addition of benzyl[D_1]thiomethyllithium to benzaldehyde is (much) faster than [2,3]-rearrangement. In the former case, the lifetime

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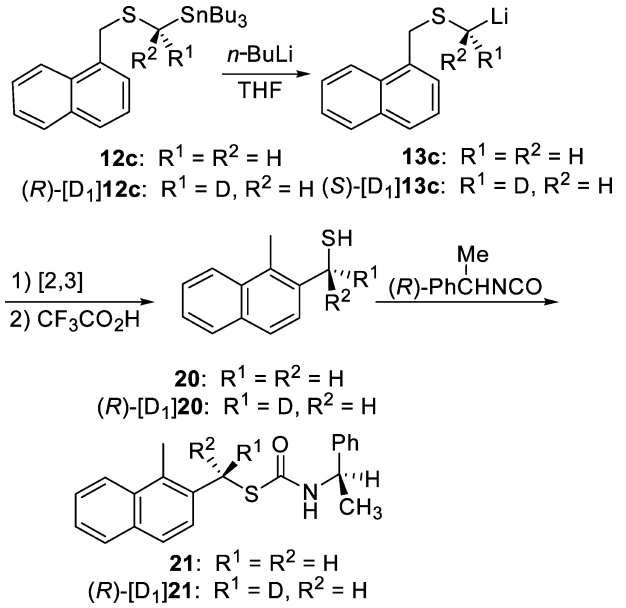
of the chiral carbanion is shorter and the chance to retain the configuration higher. Finally, the reaction was performed at 0 °C and furnished racemic [D$_1$]**19**. The low yields were attributed to addition of MeLi to benzaldehyde as competing reaction to transmetalation, a general phenomenon in experiments for the determination of the microscopic configurational stability of chiral heteroatom-substituted [D$_1$]methyllithiums.[5] Only part of the starting material was consumed. In summary, benzylthio[D$_1$]methyllithium is microscopically very labile on the time scale of the addition to benzaldehyde.

To lower the activation energy for the thia-[2,3]-Wittig rearrangement involving an aromatic compound, the phenyl ring was replaced by a naphthyl substituent. A preliminary experiment was performed with stannane **12c**, which was transmetalated with *n*-BuLi at −78 °C in THF and quenched after 10 min (Scheme 7). The rearranged product **20** could be

Scheme 7. Transmetalation of 12c and thia-[2,3]-Wittig rearrangement of thiomethyllithiums 13c



isolated in 45% yield. No methyl 1-naphthylmethyl sulfide and only a trace of starting material could be detected in the crude product by ^{1}H NMR spectroscopy. Thiol **20** was converted to thiocarbamate **21** to test its suitability for the determination of the ee in the labeled series. The SCH$_2$ group displayed an AB system in the ^{1}H NMR spectrum (400 MHz). Analogously, thiomethylstannane (*S*)-[D$_1$]**12c** was transmetalated at −50 and −95 °C, using either MeLi (entry 1) or *n*-BuLi (entries 2) for tin−lithium exchange (Table 3). Surprisingly, the ees were similar for the rearrangements at −50 and −95 °C. These findings demonstrate that the activation energy for isomerization of naphthyl derivative **13c** is significantly lower than that for phenyl derivative **13b**. Qualitatively, dearomatization of benzene could require up to 36 kcal·mol^{-1}, that of one benzene

Table 3. Yields and ee of Thiol (*R*)-[D$_1$]20 Formed by Thia-[2,3]-Wittig Rearrangement of (*R*)-[D$_1$]13c in THF

entry	RLi	temp (°C)	yield (%)	ee (%)
1	MeLi	−50	28	60
2	*n*-BuLi	−95	60	72

ring of naphthalene up to 13 kcal·mol^{-1} less, that is 23 kcal·mol^{-1} (resonance energy of naphthalene is 59 kcal·mol^{-1}, as one benzene ring is retained: 59−36 = 23).[26] Consequently, the rearrangement of the naphthyl derivative proceeded even at −95 °C, while the phenyl derivative rearranged only at temperatures above −50 °C. The reaction rate of the former was (much) higher than of the latter, so that the lifetime of carbanion **13c** was (much) shorter than that of **13b**. Therefore at −50 °C only the benzyl-substituted thio[D$_1$]methyllithium [D$_1$]**13b** had enough time to racemize completely, while in the case of the naphthylmethyl-substituted one 80% of the molecules did not enantiomerize, resulting in an ee of 60%.

Synthesis and Configurational Stability of Homochiral Bromo[D$_1$]methyllithium. *α*-Haloalkyllithiums, also termed lithium carbenoids, have nucleophilic and electrophilic properties, depending on the solvent and the reaction temperature.[27] They are usually prepared in LiX-complexed form by halogen−lithium exchange in *α*,*α*-dihaloalkanes,[28,29] *α*,*α*-dihalocyclopropanes,[30] or preferably dihalomethanes,[29,31] at low temperatures (−78 to −120 °C) and are reacted with a variety of electrophiles, especially aldehydes and ketones to obtain epoxides. As chloro- and bromomethyllithiums decompose easily, they are trapped in situ. Chiral *α*-chloroalkyllithiums and *α*-chloroalkylmagnesium halides have also been prepared elegantly, the latter being the configurationally more stable species (below −20 °C).[32] The experimental results are nicely supplemented with theoretical calculations.[14] Hoffmann et al. showed that *α*-bromoalkyllithiums are macroscopically configurationally stable at −110 °C.[7,28] Enantiopure chloro-[D$_1$]methyllithium was prepared in our group and found to be micro- and macroscopically configurationally stable at −78 °C, but chemically very labile.[6] Fluoromethyllithium has to the best of our knowledge not yet been prepared.[14a,33]

Here we address the configurational stability of enantiopure bromo[D$_1$]methyllithiums similarly to the chloro analogues. However, the preparation of starting bromo[D$_1$]methylstannanes of ee ≥99% and the high propensity of BrCHDLi to decomposition were challenging obstacles on the way to success. We reasoned that we could generate bromomethyllithium from bromomethyltributylstannane by tin−lithium exchange and trap it in situ with benzaldehyde, resulting in the formation of the lithium salt of the corresponding bromohydrin. To check whether it is chemically stable and whether its (*R*)-Mosher ester is suitable for the determination of the ee in the labeled series, some exploratory experiments were performed (Scheme 8). Phenacyl bromide was reduced with DIBALH to bromohydrin (±)-**23**. When it was converted to the lithium alkoxide in THF with MeLi at −78 °C and then quenched with CF$_3$CO$_2$H after 5 min, it was recovered unchanged in 95% yield. No epoxide **24** could be detected in the ^{1}H NMR spectrum (400 MHz) of the crude product as evidenced by spiking with an authentic sample. Samples of (±)-**23** and (*S*)-**23** obtained by enantioselective reduction of phenacyl bromide with (+)-DIP-chloride[34] were converted to diastereomeric (*R*)-Mosher esters and investigated by ^{1}H NMR spectroscopy. The CH$_2$Br groups resonated as overlapping AB parts of two ABX systems. The ee of (*S*)-**23** was found to be 94%.

Bromomethyltributylstannane was prepared from tributylstannylmethanol (**2**) in yields of up to 91% using Ph$_3$P/NBS[35] (Scheme 9). When it was transmetalated at −78 °C in THF and the reaction quenched with CF$_3$CO$_2$H 30 s after the addition of 1 M MeLi, the crude product was methyltributyl-

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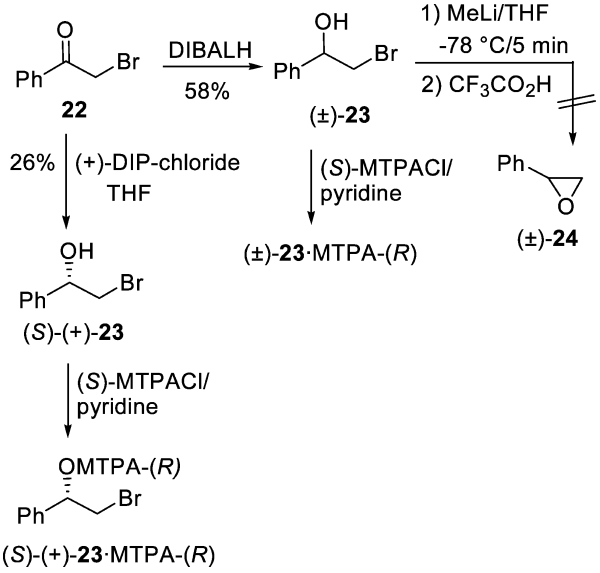
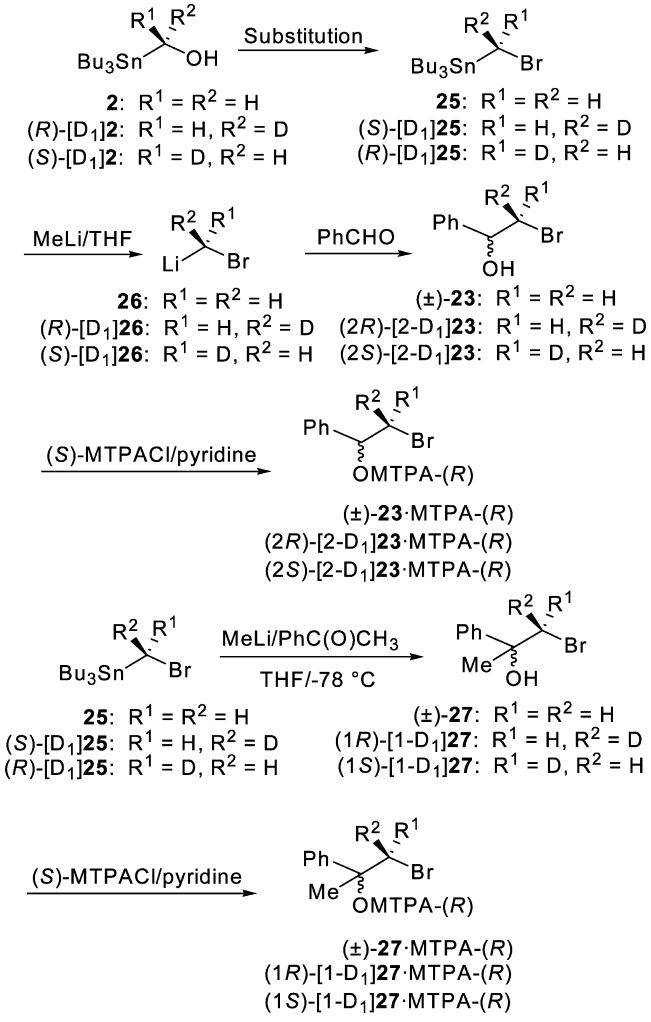
Scheme 8. Exploratory Experiments for Determination of Configurational Stability of BrCHDLi



Scheme 9. Preparation of Bromomethyllithiums and in Situ Trapping with Benzaldehyde and Acetophenone



stannane containing no starting material. Tin–lithium exchange was therefore a rapid process. Anticipating fast decomposition of bromomethyllithium, we decided to do two in situ trappings using 4 equiv of benzaldehyde in admixture with bromomethylstannane in dry THF at −78 °C in analogy to the experiments with chloromethyllithium. Four equiv of MeLi (1 M in cumene/THF/diethoxymethane) were added dropwise and the reaction was quenched with CF_3CO_2H after 5 and 15 min, respectively. In both cases, only 25% of the starting material was transmetalated, of which 80% formed bromohydrin (±)-**23** in 19% yield for both experiments as evidenced by ^{1}H NMR spectroscopy of the crude product. MeLi underwent two competing reactions, tin–lithium exchange and addition to benzaldehyde, which was faster and resulted in (±)-1-phenylethanol as major side product. To slow down addition of MeLi to the electrophile relative to transmetalation, acetophenone was tested as alternative electrophile. The desired bromohydrin (±)-**27** was obtained in 13% yield along with the tertiary alcohol derived from addition of MeLi to acetophenone, and recovered starting material. Bromohydrin (±)-**27** although a tertiary alcohol could be converted to diastereomeric (*R*)-Mosher esters under forcing conditions (50 °C, 1,4-dioxane, 8 h). The ^{1}H NMR spectrum (400 MHz) showed AB systems for the CH_2Br groups, demonstrating the feasibility to determine the ee in the deuterated series.

Chiral bromo[D_1]methylstannane (*R*)-[D_1]**25** was prepared from (*S*)-[D_1]**2** at first by the procedure used for the preparation of the unlabeled compound in 92% yield. Transmetalation and in situ trapping (with retention of configuration) of the intermediate bromo[D_1]methyllithium [(*S*)-[D_1]**26**] with benzaldehyde at −78 °C furnished bromohydrin (2*S*)-[2-D_1]**23** in 11% yield with an ee of 57% at C-2, determined by ^{1}H NMR spectroscopy of the corresponding (*R*)-Mosher ester. Being unsure about the ee of the starting bromide, we determined it in the same way as that of the chloride, using a homochiral thiol as derivatizing agent and ^{1}H NMR spectroscopy and found it to be 57%.[6] This proved that the chiral bromo[D_1]methylstannane was not enantiomerically pure and that it seemingly produced microscopically configurationally stable bromo[D_1]methyllithium, which we wanted to corroborate by more experiments. Apparently, the starting bromo[D_1]methylstannane racemized partly under the reaction conditions for the substitution reaction, under which the chloro compound was configurationally stable. Bromide ions in the reaction mixture replaced bromide of the substrate by a S_N2 mechanism, resulting in partial enantiomerization.[36] Then we switched to a modified Mitsunobu reaction[37] with Ph_3P/DIAD (diisopropyl azodicarboxylate)/Ph_3PHBr in toluene, optimized it, and finally obtained (*R*)-bromo[D_1]methylstannane of ≥99% ee in 35% yield.[38] Chiral bromo[D_1]methylstannanes with ee ranging from 77 to ≥99% were transmetalated in the presence of benzaldehyde or acetophenone at −78 or −95 °C. The bromohydrins formed were derivatized and the ee were determined. The results are compiled in Table 4 (see also Figure 2). The data show that the ee of the bromohydrins reflect the ee of the respective starting bromo[D_1]-methylstannanes being microscopically configurationally stable, irrespective of whether benzaldehyde or acetophenone was used for the in situ trapping (Table 4, entries 3–5). In the case of entry 5, the ^{1}H NMR spectrum of the crude product revealed the following molar ratios: (*S*)-[D_1]**2**/PhCHO/bromohydrin (2*R*)-[2-D_1]**23**/Bu_3SnCH_3/$PhCH(OH)CH_3$ = 2:1.62:0.1:0.35:4.18. The major portion [85%; 2/(2 + 0.35) = 0.85] of the starting material was recovered and only about

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Table 4. Conditions, Yields, and ee of Bromohydrins [D_1]23 and [D_1]27 Obtained by in Situ Trapping of Chiral Bromo[D_1]methyllithiums

entry	substrate (% ee)/product	temp (°C)	yield (%)	ee[a] (%)
1[b]	(*R*)-[D_1]**2** (77)/(2*S*)-[2-D_1]**23**	−78	18	76
2[c]	(*R*)-[D_1]**2** (77)/(1*S*)-[1-D_1]**27**	−78	12	75
3[b]	(*S*)-[D_1]**2** (94)/(2*R*)-[2-D_1]**23**	−78	9	94
4[c]	(*S*)-[D_1]**2** (94)/(1*R*)-[1-D_1]**27**	−95	31	93
5[b]	(*S*)-[D_1]**2** (99)/(2*R*)-[2-D_1]**23**	−78	14	≥99

[a]Determined by ^{1}H NMR spectroscopy of (*R*)-Mosher esters. [b]Benzaldehyde was used as electrophile. [c]Acetophenone was used as electrophile.

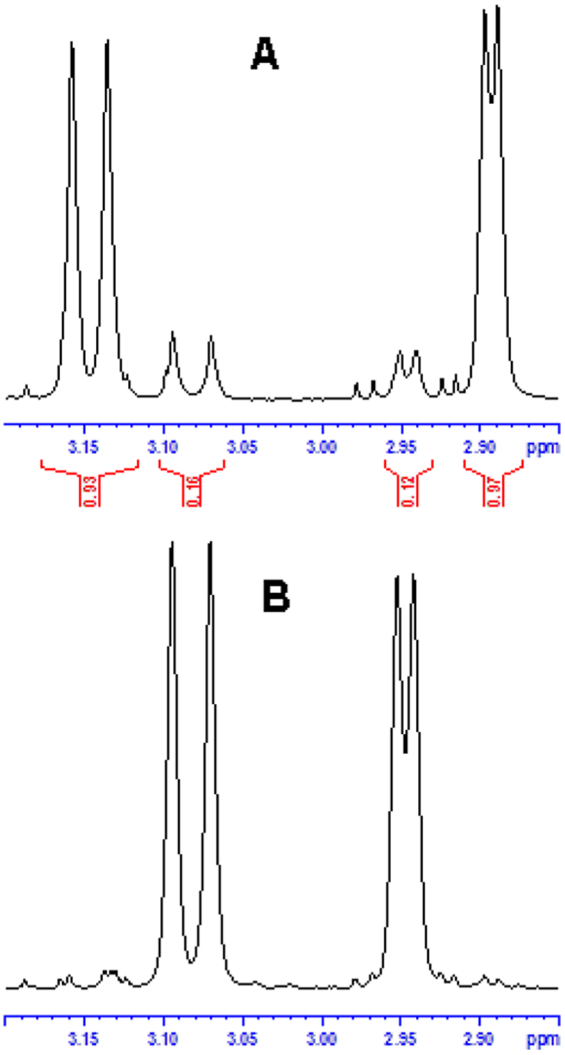

Figure 2. Signals of CHDBr groups in the ^{1}H NMR spectra (400 MHz, toluene-d_8) of (*R*)-Mosher esters derived from (A) (2*S*)-[2-D_1]**23** of 76% ee and (B) (2*R*)-[2-D_1]**23** of 99% ee (D ≥96%).

one-third (0.1:0.35 = 0.29) of the chiral bromomethyllithium as deduced from the formed tributylmethylstannane gave bromohydrin. Evidently, the other two-thirds decomposed because of low chemical stability. When acetophenone was used as electrophile, the ratios for entry 4 of Table 4 in the crude product were for (*S*)-[D_1]**2**/$PhC(O)CH_3$/bromohydrin (1*R*)-[1-D_1]**27**/Bu_3SnCH_3/$PhC(OH)(CH_3)_2$ = 0.0:0.93:-0.39:1.0:0.72. This time transmetalation was complete as addition of MeLi to acetophenone was slowed down compared to benzaldehyde. Surprisingly, again only about one-third of the bromo[D_1]methyllithium generated was intercepted by acetophenone. However, two-thirds decomposed apparently. We expected a higher percentage of decomposition because the lifetime of BrCHDLi will be longer in the presence of acetophenone than benzaldehyde as the addition to the electrophile will be slower. We cannot exclude that some of the bromomethyllithiums reacted with the starting bromomethylstannanes to give finally tributylmethylstannane and ethene as found for α-haloalkylstannanes.[39] The main product was (±)-1-phenylethanol formed by addition of MeLi to benzaldehyde. These results demonstrate that chiral bromo-[D_1]methyllithiums are microscopically stable on the time scales of the addition to benzaldehyde and acetophenone, but extremely labile.

CONCLUSIONS

Four chiral thio[D_1]methyllithiums with different substituents at sulfur were prepared by tin−lithium exchange and their microscopic configurational stability was determined relative to the thiophosphate-α-mercaptophosphonate and thia-[2,3]-Wittig rearrangements, respectively (Figure 3). The configurational stability of chiral thio[D_1]methyllithiums is delicately influenced by their lifetime depending on the substitutent at sulfur. The chances for enantiomerization of a thiomethyllithium will increase with its lifetime, which is inversely proportional to the rate of the rearrangement. While **13a** is configurationally stable at −95 °C, **13b** underwent the thia-[2,3]-rearrangement only down to −50 °C and racemized completely. In case of **13b**, the microscopic configurational stability was also evaluated on the time scale of its addition to benzaldehyde. Unfortunately, the solution structures of the respective methyllithiums and their mechanism of enantiomerization are unknown. Hoffmann et al.[40] and Reich and Dykstra[41] found for α-selenium- and α-sulfur-substituted alkyllithiums that rotation about the C−heteroatom bond is

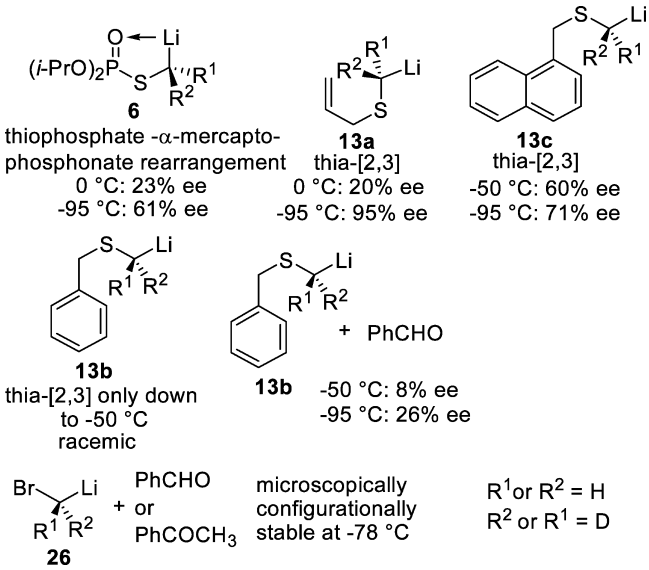

Figure 3. Microscopic configurational stability of various thio[D_1]-methyllithiums on the time scale of rearrangements for **6** and **13a−c** and on the time scale of addition of **13b** and bromo[D_1]-methyllithiums **26** to benzaldehyde.

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the rate-determining step of enantiomerization. Chiral bromo-[D_1]methyllithiums generated by tin−lithium exchange (salt free?) proved to be chemically very labile but microscopically configurationally stable on the time scale of the addition to benzaldehyde and acetophenone at −78 °C. In summary, we assume that the rearrangements of **6** and **13a,c** follow a retentive and invertive course, respectively, in analogy to chiral, nonracemic organolithiums with the same heteroatom, but an alkyl group instead of the deuterium atom. Analogously, thiomethyllithium **13b** and bromomethyllithium **26** add to benzaldehyde with retention of configuration. Thiomethyllithium **13b** enantiomerizes down to −50 °C prior to [2,3]-rearrangement.

EXPERIMENTAL SECTION

$^1H/^{13}C$ (J modulated) NMR spectra were measured at 300 K at 400.13, 400.27, 600.13 MHz/100.61, 100.65, 150.92 MHz, respectively. ^{31}P NMR spectra were recorded at 161.98, 162.03, or 242.94 MHz. All chemical shifts (δ) are given in ppm. They were referenced either to residual $CHCl_3$ (δ_H 7.24)/toluene-d_8 (CHD_2: δ_H 2.09)/CD_3OD (CHD_2: δ_H 3.31)/DMSO-d_6 (CHD_2: δ_H 2.50) or $CDCl_3$ (δ_C 77.00)/toluene-d_8 (CD_3: δ_C 21.04)/CD_3OD (CD_3: δ_C 49.00)/DMSO-d_6 (CD_3: δ_C 39.50). IR spectra of films on a silicon disk were recorded on FT-IR spectrometers or by using ATR.[42] Optical rotations were measured at 20 °C with a polarimeter in a 1 dm cell. Melting points are uncorrected.

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

Improved Preparation of (*S*)- and (*R*)-Tributylstannyl[D_1]-methanol {(*S*)- and (*R*)-[D_1]2}.[2] The two diastereomeric boronates **31** and **32** were reduced with $LiBEt_3D$ to (1*S*)-[1-$^2H_1$]- and (1*R*)-[1-$^2H_1$]**34**, respectively (compound numbers are taken from the literature[2]). 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 (1*S*)-[1-$^2H_1$]**34** (1.689 g, 3.13 mmol) dissolved in dry THF (15.7 mL). After the biphasic mixture was stirred vigorously for 1 h, more NaOH (2.27 mL) and H_2O_2 (1.0 mL) were added. Stirring was continued for another 1 h, and then water (18 mL) and pentaerythritol (600 mg) were added. The reaction mixture was stirred for 30 min. The organic phase was separated, and the aqueous phase was extracted with EtOAc (3 × 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, R_f 0.48) to give (*S*)-[D_1]**2** (826 mg, 82%, D 96−98%).

Similarly, (1*R*)-[1-$^2H_1$]**34** (1.617 g, 2.99 mmol) was converted to (*R*)-[D_1]**2** (731 mg, 76%, D 96−98%).

Preparation of (*R*)-Mosher Esters of Secondary Alcohols: 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) in dry CH_2Cl_2 (2 mL) was left at rt (for bromohydrins 4 h, for all other alcohols 4−18 h). Afterward, CH_2Cl_2 (10 mL) and HCl (10 mL, 1 M) were added. The organic phase was separated, washed with saturated aq $NaHCO_3$, dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was purified by flash chromatography to furnish oily (*R*)-Mosher esters.

Diisopropyl *S*-Tributylstannylmethyl Thiophosphate, (*R*)- and (*S*)-Diisopropyl *S*-Tributylstannyl[D_1]methyl Thiophosphate {5, (*R*)- and (*S*)-[D_1]5}. TMP (432 mg, 3.07 mmol) was dissolved in dry THF (12.4 mL) under argon and the solution cooled to −10 °C. *n*-BuLi (1.93 mL, 3.07 mmol, 1.6 M in hexane) was added. After 15 min, the solution was cooled to −78 °C, tributylstannylmethanol (**2**) (826 mg, 2.56 mmol) in dry THF (4.2 mL) was added, and the solution was stirred for 15 min. MsCl (258 μL, 3.33 mmol) was added, the solution was stirred for another 20 min, and then freshly prepared triethylammonium salt of *O,O*-diisopropyl thiophosphoric acid (3.84 mmol, 10.68 mL of solution prepared from 10 mmol of phosphite in 25 mL of *i*-PrOH)[17] was added. Stirring was continued for 18 h at rt. The mixture was concentrated under reduced pressure, and water (26 mL) was added. The aq phase was extracted with CH_2Cl_2 (2 × 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 **5** as a colorless oil (1.014 g, 79% for two steps). IR (Si): ν 2958, 2927, 1253, 979 cm^{-1}. ^1H NMR (400.27 MHz, $CDCl_3$): δ 4.72 (dsept, J = 8.9, 6.2 Hz, 2H), 2.04 (d, J = 9.0 Hz, $J(^{117/119}Sn)$ = 35.4 Hz, 2H), 1.60−1.38 (m, 6H), 1.36 (d, J = 6.3 Hz, 6H), 1.33 (d, J = 6.3 Hz, 6H), 1.29 (sext, J = 7.3 Hz, 6H), 1.04−0.87 (m, $J(^{117/119}Sn)$ = 50.8 Hz, 6H), 0.87 (t, J = 7.3 Hz, 9H). ^{13}C NMR (100.61 MHz, $CDCl_3$): δ 72.1 (d, J = 6.0 Hz, 2C), 28.9 ($J(^{117/119}Sn)$ = 21.8 Hz, 3C), 27.2 ($J(^{117/119}Sn)$ = 56.5 Hz, 3C), 23.9 (d, J = 4.2 Hz, 2C), 23.7 (d, J = 5.6 Hz, 2C), 13.6 (3C), 9.7 ($J(^{117/119}Sn)$ = 323.4 Hz, 3C), 4.5 (d, J = 4.9 Hz). ^{31}P NMR (161.98 MHz, $CDCl_3$): δ 29.5. Anal. Calcd for $C_{19}H_{43}O_3PSSn$: C, 45.52; H, 8.65; S, 6.40. Found: C, 45.93; H, 8.85; S, 6.10.

Similarly, (*S*)-tributylstannyl[D_1]methanol {(*S*)-[D_1]**2**} (826 mg, 2.56 mmol) and (*R*)-[D_1]**2** (731 mg, 2.27 mmol) were converted to thiophosphates (*R*)-[D_1]**5** (1.014 g, 79%) and (*S*)-[D_1]**5** (947 mg, 83%), respectively. Their ^1H NMR spectra (400.27 MHz, $CDCl_3$) were identical to that for **5** except for δ 2.04 (br d, J = 9.0 Hz, $J(^{117/119}Sn)$ = 35.4 Hz, 1H).

Diisopropyl Mercaptomethylphosphonate, (*S*)- and (*R*)-Diisopropyl Mercapto[D_1]methylphosphonate {8, (*S*)- and (*R*)-[D_1]8}. *Experiment 1.* MeLi (0.52 mL, 0.52 mmol, 1 M in THF/cumene) was added to a solution of *S*-stannylmethyl thiophosphate **5** (217 mg, 0.43 mmol) in dry THF (3 mL) under argon at −78 °C dropwise every 3 s. After 2 min, AcOH (0.5 mL, 2 M, in THF) was added, and the solution was warmed and concentrated under reduced pressure. Water (4 mL) was added, and the aq phase was extracted with EtOAc (3 × 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 **8** as a colorless oil (55 mg, 60%). The spectroscopic data are identical to those of the literature.[17]

Experiment 2. Similarly, thiophosphate **5** (202 mg, 0.40 mmol) was converted to mercaptophosphonate **8** (28 mg, 33%) except that MeLi was added dropwise every 1 s and that the reaction was quenched after 1 min with AcOH (0.48 mL, 2 M, in THF).

Experiment 3. Similarly to experiment 1, (*S*)-[D_1]**5** (280 mg, 0.56 mmol) was converted to (*R*)-[D_1]**8** (48 mg, 41%, ee 23%) except that the reaction was performed at 0 °C and quenched with AcOH 15 s after the addition of MeLi, added dropwise every 1 s. The spectroscopic data were identical to that of **8** except as follows. ^1H NMR (400.27 MHz, $CDCl_3$): δ 2.60 (tdd, J = 13.4, 8.2, 2.1 Hz, 1H), 1.79 (dd, J = 8.5, 8.2 Hz, 1H). ^{13}C NMR (100.61 MHz, $CDCl_3$): δ 18.3 (dt, J = 151.8, 21.2 Hz).

Experiment 4. Similarly to experiment 1, (*S*)-[D_1]**5** (229 mg, 0.46 mmol) was converted to (*R*)-[D_1]**8** (22 mg, 22%, ee 77%) except that the reaction was performed in Et_2O at −95 °C, using 1.05 equiv of MeLi. The reaction was quenched after 1 min.

Experiment 5. Similarly to experiment 4, (*S*)-[D_1]**5** (218 mg, 0.43 mmol) was converted to (*R*)-[D_1]**8** (52 mg, 56%, racemic), except that the reaction was performed in dry Et_2O at 0 °C. The reaction was quenched with AcOH after 15 s.

Experiment 6. Similarly to experiment 4, thiophosphate (*R*)-[D_1]**5** (286 mg, 0.57 mmol) was converted to deuterated (*S*)-mercaptophosphonate (*S*)-[D_1]**8** (31 mg, 25%, ee 61%) except that the reaction was performed in dry THF and quenched with AcOH 3 min after the addition of MeLi.

Experiment 7. Similarly to experiment 6, (*R*)-[D_1]**5** (249 mg, 0.50 mmol) was converted to (*S*)-[D_1]**8** (73 mg, 68%, ee 52%) except that MeLi was replaced by *n*-BuLi.

***S*-(Diisopropoxyphosphinyl)methyl (*R*)-1-(1-Naphthyl)-ethylthiocarbamate, (*R*)- and (*S*)-*S*-(diisopropoxyphosphinyl)-**

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[D$_1$]methyl (*R*)-1-(1-naphthyl)ethylthiocarbamate {10b, (*R*)- and (*S*)-[D$_1$]10b}. A solution of mercaptomethylphoshonate[24] **8** (76 mg, 0.36 mmol) and (*R*)-(−)-1-(1-naphthyl)ethyl isocyanate (0.62 mL, 0.72 mmol, ee 95%) in dry THF (3 mL) under argon was stirred for 5 h at rt. Afterward, water (0.25 mL) was added, and the mixture was stirred for another 2.5 h and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/EtOAc, 1:2, R_f 0.61) to yield thiocarbamate **10b** (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), 7.85−7.75 (m, 1H), 7.74 (d, J = 7.9 Hz, 1H), 7.55−7.35 (m, 4H), 6.59 (br s, 1H, NH), 5.85 (br s, 1H), 4.61 (dsept, J = 7.7, 6.3 Hz, 2H), 3.18 (AB-syst, J_{AB} = 15.0 Hz, J = 12.9 Hz, 2H), 1.63 (d, J = 6.8 Hz, 3H), 1.27 (d, J = 6.0 Hz, 3H), 1.26 (d, J = 5.7 Hz, 3H), 1.23 (d, J = 6.2 Hz, 3H), 1.21 (d, J = 6.2 Hz, 3H). ^{13}C NMR (100.61 MHz, $CDCl_3$): δ 164.3 (br s), 137.9, 133.8, 130.7, 128.8, 128.8, 128.3, 126.4, 125.7, 125.2, 123.0, 122.6, 71.40 (d, J = 6.7 Hz), 71.38 (d, J = 6.7 Hz), 60.3, 24.0 (d, J = 153.2 Hz), 23.94 (d, J = 4.5 Hz), 23.91 (d, J = 4.4 Hz), 23.79 (d, J = 4.8 Hz), 23.77 (d, J = 5.2 Hz), 21.1 (br s). ^{31}P NMR (161.98 MHz, $CDCl_3$): δ 22.5. Anal. Calcd for $C_{20}H_{28}NO_4PS$: 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.

Similarly, (*R*)-[D$_1$]**8** (48 mg, 0.22 mmol) was converted to (*R*)-[D$_1$]**10b** (66 mg, 73%, ee 23%). The ^{1}H NMR spectrum (400.27 MHz, $CDCl_3$) was identical to that of **10b** except for δ 3.22 (d, J = 13.3 Hz, 0.38H), 3.17 (d, J = 13.2 Hz, 0.61H).

Similarly, (*S*)-[D$_1$]**8** (31 mg, 0.14 mmol) was converted to (*S*)-[D$_1$]**10b** (50 mg, 86%, ee 51%). The ^{1}H NMR spectrum (400.27 MHz, $CDCl_3$) was identical to that of (*R*)-[D$_1$]**10b** except for the different integration of the two doublets δ 3.22 (d, J = 13.3 Hz, 0.74H), 3.17 (d, J = 13.2 Hz, 0.23H).

(Allylthiomethyl)tributylstannane, (*S*)- and (*R*)-(Allylthio[D$_1$]-methyl)tributylstannane {12a, (*S*)-and (*R*)-12a}. Allylmercaptan (0.20 mL, 2.37 mmol) was added to a solution of *t*-BuONa (228 mg, 2.37 mmol) in dry THF (5.0 mL) and stirred under argon for 10 min. The reaction mixture was cooled to −30 °C, and tributylstannylmethyl mesylate (**3**) (632 mg, 1.58 mmol) in dry THF (3 mL) was added. After the mixture was stirred for 15 min, 1 M HCl (8 mL) 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, 30:1, R_f 0.54) to yield tributylstannylmethyl sulfide (**12a**) (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 = 17.2, 10.0, 7.3 Hz, 1H), 5.07 (tdd, J = 10.0, 1.7, 0.8 Hz, 1H), 5.03 (tdd, J = 17.2, 1.7, 1.2 Hz, 1H), 3.06 (ddd, J = 7.3, 1.2, 0.8 Hz, 2H), 1.80 (s, J($^{117/119}$Sn) = 41.3 Hz, 2H), 1.60−1.38 (m, 6H), 1.30 (sext, J = 7.3 Hz, 6H), 1.10−0.82 (m, J($^{117/119}$Sn) = 50.6 Hz, 6H), 0.87 (t, J = 7.3 Hz, 9H). ^{13}C NMR (100.61 MHz, $CDCl_3$): δ 133.9, 116.7, 41.0, 29.0 (J($^{117/119}$Sn) = 20.9 Hz, 3C), 27.3 (J($^{117/119}$Sn) = 55.2 Hz, 3C), 13.7 (3C), 9.5 (J($^{117/119}$Sn) = 334.7, 319.6 Hz, 3C), 7.5. Anal. Calcd for $C_{16}H_{34}SSn$: C, 50.94; H, 9.08. Found: C, 51.16; H, 9.14.

Similarly, mesylates[4] (*R*)- and (*S*)-[D$_1$]**3** (690 mg, 1.72 mmol and 635 mg, 1.59 mmol) were converted to sulfides (*S*)-[D$_1$]**12a** (537 mg, 83%) and (*R*)-[D$_1$]**12a** (375 mg, 63%), respectively. The ^{1}H NMR spectra (400.27 MHz, $CDCl_3$) were identical to that of **12** except for δ 1.78 (br s, J($^{117/119}$Sn) = 40.7 Hz, 1H).

Benzylthiomethyl- and (*R*)- and (*S*)-Benzylthio[D$_1$]-methyltributylstannane {12b, (*R*)- and (*S*)-[D$_1$]12b}. Benzylmercaptan (0.35 mL, 3.0 mmol) was alkylated with mesylate **3** (798 mg, 2.0 mmol) by the procedure used for the preparation of allylthiomethylstannane **12a**. The crude product was first heated (45 °C, 0.5 mbar) to remove excess benzylmercaptan and then purified by flash chromatography (hexane/CH_2Cl_2, 30:1, R_f 0.33) to yield benzylthiomethylstannane **12b** (786 mg, 92%) as a colorless oil. IR (Si): ν 2955, 2923, 2851, 1493, 1453, 1376, 1071 cm^{-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 × CH_2CH_2Sn), 1.30 (sext, J = 7.3 Hz, 6H, 3 × $CH_2(CH_2)_2Sn$), 0.97−0.80 (m, J($^{117/119}$Sn) = 49.6 Hz, 6H, 3 × CH_2Sn), 0.85 (t, J = 7.3 Hz, 9H, 3x $CH_3(CH_2)_3Sn$). ^{13}C NMR (100.61 MHz, $CDCl_3$): δ Cq not detected, 129.0 (2C, C_{arom}), 128.3 (2C, C_{arom}), 126.6 (C_{arom}), 42.5 (CH_2S), 29.0 (J($^{117/119}$Sn) = 20.6 Hz, 3C, 3 × $CH_2(CH_2)_2Sn$), 27.2 (J($^{117/119}$Sn) = 55.2 Hz, 3C, 3 × CH_2-CH_2Sn), 13.7 (3C, 3 × $CH_3(CH_2)_3$), 9.5 (J($^{117/119}$Sn) = 334.4 Hz, 3C, 3 × $SnCH_2(CH_2)_2$), 8.3 (t, J($^{117/119}$Sn) = 223.0 Hz, SCH_2Sn). Anal. Calcd for $C_{20}H_{36}SSn$: C, 56.22; H, 8.49; S, 7.50. Found: C, 56.48; H, 8.45; S, 7.26.

Similarly, mesylates (*R*)-[D$_1$]**3** (1.0 g, 2.49 mmol) and (*S*)-[D$_1$]**3** (1.690 g, 4.22 mmol) were converted to benzylthio-[D$_1$]-methylstannanes (*S*)-[D$_1$]**12b** (870 mg, 82%) and (*R*)-[D$_1$]**12b** (1.535 g, 85%), respectively. Their ^{1}H NMR spectra (400.27 MHz, $CDCl_3$) were identical to that of **12b** except for δ 1.77 (s, J($^{117/119}$Sn) = 41.6 Hz, 1H).

(1-Naphthylmethyl)thiomethyl- and (*R*)-(1-naphthylmethyl)-thio[D$_1$]methyltributylstannane {12c, (*R*)-[D$_1$]12c}. 1-Naphthylmethanethiol[43] (745 mg, 4.66 mmol) was alkylated with mesylate **3** (1.240 g, 3.11 mmol) by the procedure used for the preparation of allylthiomethylstannane **12a**. The combined organic layers were washed with brine (25 mL) and 2 M NaOH (3 × 25 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was purified by flash chromatography (hexane/CH_2Cl_2, 30:1, R_f 0.33) to yield (1-naphthylmethyl)thiomethylstannane **12c** (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), 7.85−7.68 (m, 2H), 7.55−7.42 (m, 2H), 7.41−7.33 (m, 2H), 4.12 (s, 2H), 1.83 (s, J($^{117/119}$Sn) = 40.1 Hz, 2H), 1.49−1.33 (m, 6H), 1.21 (sext, J = 7.3 Hz, 6H), 0.98−0.83 (m, 6H), 0.81 (t, J = 7.3 Hz, 9H). ^{13}C NMR (100.61 MHz, $CDCl_3$): δ 134.1, 133.7, 131.6, 128.6, 127.7, 127.2, 125.8, 125.6, 125.0, 124.3, 40.4, 28.9 (J($^{117/119}$Sn) = 20.9 Hz, 3C), 27.2 (J($^{117/119}$Sn) = 55.1 Hz, 3C), 13.6 (3C), 9.5 (J($^{117/119}$Sn) = 319.6 Hz, 3C), 9.1 (J($^{117/119}$Sn) = 214.4 Hz). Anal. Calcd for $C_{24}H_{38}SSn$: C, 60.39; H, 8.02. Found: C, 60.34; H, 7.76.

Similarly, mesylate (*S*)-[D$_1$]**3** (678 mg, 1.69 mmol) was converted to thiomethylstannane (*R*)-[D$_1$]**12c** (642 mg, 79%). The spectroscopic data were identical to that of **12c** except for the following. ^{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, $SCHDSn$).

[2,3]-Rerrangement of (Allylthiomethyl)stannanes 12, (*R*)- and (*S*)-[D$_1$]12a, and Derivatization of 3-Butenethiols Formed from Thiocarbamate 16. *Experiment 1.* *n*-BuLi (0.25 mL, 0.39 mmol) was added to the solution of sulfide **12a** (131 mg, 0.33 mmol) in dry THF (2.5 mL) at −95 °C under argon. After 10 min, 2 M CF_3CO_2H (70 μL, 0.13 mmol) was added and the mixture was used immediately for the derivatization as thiol **15** cannot be isolated because of its low boiling point.[25]

(*R*)-(+)-1-Phenylethyl isocyanate (0,10 mL, 0.66 mmol, ee 99%) was added at −95 °C. The cooling bath was removed and stirring was continued at rt. After 45 min a saturated aqueous solution of $NaHCO_3$ (10 mL) was added and the mixture was extracted with EtOAc (2 × 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 derived from isocyanate 0.45; second: hexane/CH_2Cl_2, 1:1, R_f 0.29, side product derived from isocyanate 0.68) to yield thiocarbamate **16** (64 mg, 83%) as colorless crystals. Mp: 46−47 °C (hexane). $[\alpha]^{20}_D$ = −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 = 17.0, 10.2, 6.7 Hz, 1H, CH═CH_2), 5.54 (br s, 1H, NH), 5.06 (qd, J = 17.0, 1.6 Hz, 1H, CH═CH_2), 5.05 (br s, 1H, $CHCH_3$), 5.01 (tdd, J_{ci} = 10.2, 1.6, 1.2 Hz, 1H, CH═CH_2), 2.95 (AB-sys, J_{AB} = 13.4 Hz, J = 7.1 Hz, 2H, CH_2S), 2.35 (tddd, J = 7.1, 6.7, 1.6, 1.2 Hz, 2H, CH_2CH_2S), 1.49 (d, J = 6.9 Hz, 3H, CH_3CH). ^{13}C NMR (100.61 MHz, $CDCl_3$): δ 142.8, 136.3, 128.7 (2C), 127.5 (2C), 126.0, 116.3, 51.1, 34.5, 29.2, 22.0. Anal. Calcd for $C_{13}H_{17}NOS$: C, 66.34; H, 7.28; N, 5.95; S, 13.62. Found: C, 66.16; H, 7.25; N, 6.04; S, 13.40.

The ^{1}H NMR spectra (400.27 MHz, $CDCl_3$) of (*R*)- and (*S*)-[D$_1$]**16** were identical to that of **16**, except for δ 2.95 (t, J = 7.2 Hz, 1H, CHD), 2.34 (t, J = 6.9 Hz, CH_2CHD). To determine the ee of derivatives [D$_1$]**16** the ^{1}H NMR experiments were performed in

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DMSO-d_6 (600.13 MHz) with irradiation at 2.24 ppm (decoupling of SCHDCH_2). Two broad singlets (δ 2.79 and 2.82) were observed for the two diastereotopic protons of the SCHD group. (*S*)-[D_1]**12a** gave the carbamate with the broad singlet at δ 2.82.

Experiment 2. Allylthio[D_1]methylstannane (*S*)-[D_1]**12a** (174 mg, 0.46 mmol) was converted to thiocarbamate (*S*)-[D_1]**16** (90 mg, 83%, ee ≥95%) by the procedure used for experiment 1.

Experiment 3. Stannane (*S*)-[D_1]**12a** (161 mg, 0.43 mmol) was converted to (*S*)-[D_1]**16** (95 mg, 95%, ee 91%) by the procedure used for experiment 1 except that it was performed at −78 °C.

Experiment 4. Stannane (*S*)-[D_1]**12a** (172 mg, 0.45 mmol) was converted to (*S*)-[D_1]**16** (104 mg, 99%, ee 83%) by the procedure used for experiment 1 except that it was performed at −40 °C.

Experiment 5. Stannane (*S*)-[D_1]**12a** (164 mg, 0.43 mmol) was converted to (*S*)-[D_1]**16** (73 mg, 72%, ee 71%) by the procedure used for experiment 1 except that it was performed at 0 °C and that the reaction was quenched with CF_3CO_2H 3 min after the addition of *n*-BuL.

Experiment 6. Stannane (*R*)-[D_1]**12a** (189 mg, 0.50 mmol) was converted to (*R*)-[D_1]**16** (74 mg, 62%, ee 50%) by the procedure used for experiment 3 except that it was performed in dry Et_2O.

Experiment 7. Stannane (*R*)-[D_1]**12a** (184 mg, 0.49 mmol) was converted to (*R*)-[D_1]**16** (51 mg, 45%, ee 20%) by the procedure used for experiment 5 except that it was performed in dry Et_2O.

[2,3]-Rearrangement of Benzylthiomethylstannanes 12b and (*R*)-[D_1]12b, Derivatization of 2-Methylphenylmethanethiols Formed, and Determination of ee. *n*-BuLi (0.41 mL, 0.65 mmol) was added to a solution of **12b** (231 mg, 0.54 mmol) in dry THF (3.8 mL) at −30 °C under argon. After 30 min, 2 M CF_3CO_2H (0.11 mL, 0.22 mmol) was added, and the mixture was used directly for the derivatization. The 2-methylphenylmethanethiol **17** (detectable by TLC: hexane/CH_2Cl_2, 10:1, R_f 0.54) was not isolated because of its volatility (bp 97 °C/14 mm[44]). (*R*)-(+)-1-Phenylethyl isocyanate (0.17 mL, 1.08 mmol) was added. After the mixture was stirred for 1.5 h at rt, 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 **18** (66 mg, 43%) as colorless crystals; mp 92−93 °C (*i*-Pr_2O). IR (ATR): ν 3277, 2972, 2926, 1643, 1527, 1493, 1446, 1216 cm^{-1}. ^1H 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, $CHCH_3$), 5.08 (br s, 1H, NH), 4.16 (AB-sys, J_{AB} = 13.7 Hz, 2H, CH_2S), 2.33 (s, 3H, CH_3Ph), 1.49 (d, J = 6.9 Hz, 3H, CH_3CH). ^{13}C NMR (100.61 MHz, $CDCl_3$): δ CO n. d., 142.7 ($C_{q\ arom}$), 136.6 ($C_{q\ arom}$), 136.1 ($C_{q\ arom}$), 130.4 (C_{arom}), 129.9 (C_{arom}), 128.7 (2C, C_{arom}), 127.6 (2C, C_{arom}), 127.5 (C_{arom}), 126.2 (C_{arom}), 126.0 (C_{arom}), 51.2 ($CHCH_3$), 32.4 (CH_2S), 22.0 (br s, CH_3CH), 19.4 (CH_3Ph). Anal. Calcd for $C_{17}H_{19}NOS$: 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.

Similarly, (*S*)-benzylthio[D_1]methylstannane (*S*)-[D_1]**12b** (232 mg, 0.54 mmol) was converted to thiocarbamate [D_1]**18** (92 mg, 59%) except that the reaction temperature was −50 C and the reaction time 20 min. The ^1H NMR spectrum (400.27 MHz, $CDCl_3$) was identical to that of the unlabeled species **18** except for δ 4.17 (s, 1H, CHD), 4.13 (s, 1H, CHD) (thiol [D_1]**17** was racemic).

Experiments To Test Macroscopic and Microscopic Configurational Stability of (*S*)-Benzylthio[D_1]methyllithium. Generation of Benzylthiomethyllithiums 13b and (*S*)-[D_1]13b and Their Addition to Benzaldehyde To Give 2-Benzylthio-1-phenylethanol[45] (19) and Benzylthio-1-phenyl[2-D_1]ethanol {(2*S*)-[2-D_1]19}. *Experiment 1.* *n*-BuLi (0.17 mL, 0.26 mmol) was added to a solution of benzylthiomethylstannane **12b** (92 mg, 0.22 mmol) in dry THF (1.6 mL) at −78 °C under argon. After 10 min, benzaldehyde (0.17 mL, 0.33 mmol, 2 M in dry THF) was added, followed by saturated aq $NaHCO_3$ (3 mL) 5 min later. The mixture was extracted with EtOAc (3 × 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[43] **19** (42 mg, 77%) as a colorless oil. ^1H NMR (400.27 MHz, $CDCl_3$): δ 7.40−7.18 (m, 10H), 4.66 (X-part of ABX-syst J = 9.2, 3.7 Hz, 1H), 3.71 (s, 2H), 2.78 (A-part of ABX-syst, J_{AB} = 14.0 Hz, J = 3.7 Hz, 1H), 2.65 (B-part of ABX-syst, J_{AB} = 14.0 Hz, J = 9.2 Hz, 1H), 2.47 (br s, 1H, OH).

Experiment 2. Similarly, stannane (*R*)-[D_1]**12b** (233 mg, 0.54 mmol) was transformed into alcohol (±)-[2-D_1]**19** (95 mg, 72%) by the procedure used for experiment 1 except that benzaldehyde (0.54 mL, 1.08 mmol, 2 M in dry THF), was added 1 min after the addition of MeLi (0.27 mL, 0.82 mmol, 3 M in diethoxymethane).

The spectroscopic data of (2*S*)-[2-D_1]**19** were identical to that of **19** except for the following. ^1H NMR (400.13 MHz, $CDCl_3$): δ 4.59 (2 overlapping d, J = 9.2, 3.7 Hz, 1H), 2.82 (br s, 1H, OH), 2.68 (br s, 1H, SCHD), 2.58 (br d, J = 9.2 Hz, 1H, SC*H*D). ^{13}C NMR (100.61 MHz, $CDCl_3$): δ 40.4 (t, J = 21.5 Hz, 1C, SCHD).

Experiment 3. (*R*)-Benzylthio[D_1]methylstannane [(*R*)-[D_1]**12b**] (213 mg, 0.50 mmol) was transformed into alcohol (*S*)-[D_1]**19** (30 mg, 24%, ee 16%) by the procedure used for the preparation of the racemic alcohols except that the benzaldehyde (0.50 mL, 1.0 mmol, 2 M in dry THF) was present in the reaction mixture when MeLi was added dropwise every 3 s.

Experiment 4. Similarly, (*R*)-[D_1]**12b** (228 mg, 0.53 mmol) was transformed into (2*S*)-[2-D_1]**19** (11 mg, 9%, ee 26%) by the procedure used for experiment 3 except that it was performed at −95 °C and that 2 equiv of 12-crown-4 were present in the reaction mixture.

Experiment 5. Similarly, (*R*)-[D_1]**12b** (237 mg, 0.55 mmol) was transformed into (*S*)-[D_1]**19** (34 mg, 25%, ee 8%) by the procedure used for experiment 3, except that the experiment was performed at −50 °C. Part of starting stannane was recovered (50%).

Experiment 6. Similarly, (*R*)-[D_1]**12b** (228 mg, 0.53 mmol) was transformed into (±)-[D_1]**19** (26 mg, 21%) by the procedure used for experiment 3, except that the experiment was performed at 0 °C.

(*R*)-Mosher Esters of Alcohols 19 and (2*S*)-[2-D_1]19. Racemic alcohol **19** (mg, mmol) was converted to a 1:1 mixture of diastereomeric (*R*)-Mosher esters according to general procedure A. The crude product was purified by flash chromatography (hexane/EtOAc, 10:1, R_f 0.51) to yield esters **19**·(*R*)-MTPA (28 mg, 94%) as a colorless oil. ^1H NMR (600.13 MHz, $CDCl_3$): δ 7.48−7.07 (m, 30H), 5.97 (X-part of ABX-syst, J = 8.2, 5.7 Hz, 1H, diastereomer A), 5.86 (X-part of ABX-syst, J = 9.0, 4.8 Hz, 1H, diastereomer B), 3.66 (AB-syst, J_{AB} = 13.5 Hz, 2H), 3.60 (t, J = 1.2 Hz, 3H, 3.52 (s, 2H), 3.45 (t, J = 1.2 Hz, 3H), 2.87 (A-part of ABX-syst, J_{AB} = 14.4 Hz, J = 9.0 Hz, 1H, B), 2.83 (A-part of ABX-syst, J_{AB} = 14.4 Hz, J = 8.2 Hz, 1H, A), 2.70 (B-part of ABX-syst, J_{AB} = 14.4 Hz, J = 4.8 Hz, 1H, B), 2.69 (B-part of ABX-syst, J_{AB} = 14.4 Hz, J = 5.7 Hz, 1H, A).

Similarly, alcohol (2*S*)-[2-D_1]**19** (11 mg, 0.045 mmol), obtained by determination of microscopic configurational stability of chiral benzylthiomethyllithium by experiment 5 was converted to (*R*)-Mosher esters (*S*)-[D_1]**19**·(*R*)-MTPA (18 mg, 87%).

The ^1H NMR spectrum (600.13 MHz, $CDCl_3$) was identical to that of **19**·(*R*)-MTPA except for 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); ee of underlying alcohol 26%.

(1-Methylnaphth-2-yl)methanethiol and (1-Methylnaphth-2-yl)[D_1]methanethiol {20 and (*S*)-[D_1]20}. *n*-BuLi (0.50 mL, 0.79 mmol) was added to the solution of (1-naphthylmethylthiomethyl)-tributylstannane (**12c**) (314 mg, 0.66 mmol) in dry THF (4.6 mL) at −78 °C under argon. After 10 min, CF_3CO_2H (0.43 mL, 0.87 mmol, 2 M in CH_2Cl_2) was added, and the mixture was extracted with EtOAc (3 × 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 **20** (57 mg, 45%) as a colorless oil. IR (Si): ν 3050, 2924, 1597, 1510, 1382, 1264, 1248, 1210, 1060 cm^{-1}. ^1H NMR (400.27 MHz, $CDCl_3$): δ 8.04 (d, J = 8.5 Hz, 1H), 7.79 (d, J = 8.1 Hz, 1H), 7.67 (d, J = 8.4 Hz, 1H), 7.55−7.40 (m, 2H), 7.38−7.33 (m, 1H), 3.94 (d, J = 7.0 Hz, 2H), 2.69 (s, 3H), 1.71 (t, J = 7.0 Hz, 1H). ^{13}C NMR (100.61 MHz, $CDCl_3$): δ 136.1, 133.1, 132.8, 131.1, 128.5, 127.3, 126.7, 126.1, 125.4, 124.1, 27.7, 14.2. Anal. Calcd for $C_{12}H_{12}S$: C, 76.55; H, 6.42; S, 17.03. Found: C, 76.38; H, 6.39; S, 16.76.

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Similarly, (*R*)-[D_1]**12c** (206 mg, 0.43 mmol) was rearranged to (*R*)-[D_1]**20** (22 mg, 28%, ee 60%) except that transmetalation was performed with MeLi (3 M, in diethoxymethane) at −50 °C. The ^{1}H NMR spectrum (400.27 MHz, $CDCl_3$) was identical to that of **20** except for δ 3.92 (dt, J = 7.0, 1.8 Hz, 1H, *CHDSH*), 1.69 (d, J = 7.0 Hz, 1H, CHD*SH*).

Similarly, stannane (*R*)-[D_1]**12c** (208 mg, 0.43 mmol) was rearranged to thiol (*R*)-[D_1]**20** (49 mg, 60%, ee 72%) except that transmetalation was performed with *n*-BuLi at −95 °C.

***S*-(1-Methylnaphth-2-yl)methyl (*R*)-*N*-(1-Phenylethyl)-thiocarbamate and (*R*)-(1-Methylnaphth-2-yl)[D_1]methyl (*R*)-*N*-(1-Phenylethyl)thiocarbamate {21 and (*R*)-[D_1]21}.** A solution of (*R*)-(+)-1-phenylethyl isocyanate (67 μL, 0.48 mmol) and thiol **20** (46 mg, 0.24 mmol) in dry THF (1.2 mL) was left for 1 h under argon at rt. Water (1 mL) was added, and the mixture was extracted with EtOAc (3 × 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 **21** (39 mg, 50%) as colorless crystals. Mp: 134−135 °C (*i*-Pr_2O). 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), 7.78 (d, J = 8.3 Hz, 1H), 7.63 (d, J = 8.4 Hz, 1H), 7.53−7.39 (m, 3H), 7.38−7.19 (m, 5H), 5.46 (br s, 1H), 5.10 (br s, 1H), 4.38 (AB-sys, J_{AB} = 13.2 Hz, 2H), 2.65 (s, 3H), 1.50 (d, J = 6.9 Hz, 3H). ^{13}C NMR (100.61 MHz, $CDCl_3$): δ C═O (n. d.), 142.7, 133.0, 132.9, 132.4, 128.8, 128.5, 128.2, 127.6, 126.4, 126.0, 125.4, 124.1, 51.3, 33.3, 22.1 (br s), 14.5. Anal. Calcd for $C_{21}H_{21}NOS$: 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, thiol (*R*)-[D_1]**20** (49 mg, 0.26 mmol, obtained by rearrangement at −95 °C with *n*-BuLi) was converted to thiocarbamate (*R*)-[D_1]**21** (36 mg, 42%).

The spectroscopic data were identical to that of **21** except for the following. ^{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 (100.61 MHz, $CDCl_3$): δ 33.1 (t, J = 21.9 Hz, 1C, CHDS).

(±)- and (*S*)-(+)-2-Bromo-1-phenylethanol [(±)-23 and (*S*)-(+)-23]. (±)-**23**: A solution of DIBALH (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 h at −78 °C and then 1 h at −50 °C. The reaction was quenched with MeOH (0.5 mL) and water (2.5 mL) and stirred for another 30 min at rt. A solution of HCl (12 mL, 2 M) was added at 0 °C. The organic phase was separated, and the aqueous phase was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with water (15 mL) and satd aq $NaHCO_3$ (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 [(±)-**23**] (591 mg, 59%) as a colorless oil. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.39−7.29 (m, 5H), 4.92 (dd, X-part of an ABX-syst, J = 9.1, 3.5 Hz, 1H), 3.58 (AB-part of an ABX-syst, J_{AB} = 10.4 Hz, J = 9.1, 3.5 Hz, 2H), 2.59 (br s, 1H).

(*S*)-(+)-**23**: (+)-DIP-chloride[34] (1.8 g, 5.61 mmol, dissolved in 5 mL of dry THF) was added to ω-bromoacetophenone (744 mg, 3.74 mmol, dissolved in 5 mL of dry THF) under argon at 0 °C. The solution was stirred overnight at rt. 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 min at rt. The organic phase was separated and the aqueous one was extracted with Et_2O (3 × 15 mL). The combined organic layers were washed with water (2 × 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 5 mL of water) was added. The solution was stirred overnight at rt. The organic phase was separated and the aqueous one was extracted with Et_2O (3 × 15 mL). The combined organic layers were washed with water (2 × 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*)-(+)-**23**] as a colorless oil (193 mg, 26%), ee 94% (by ^{1}H NMR of (*R*)-Mosher ester), $[\alpha]^{20}_D$ +39.24 (*c* 1.975, CH_2Cl_2) [lit.[46] $[\alpha]^{20}_D$ +40.10, (*c* 1.81, $CHCl_3$), ee 92%]. The ^{1}H NMR spectrum was identical to that of the racemate.

(*R*)-Mosher Esters of (±)-23 and (*S*)-(+)-23. (±)-2-Bromo-1-phenylethanol [(±)-**23**] (20 mg, 0.10 mmol) was converted to (*R*)-Mosher esters using general procedure A. The crude product was purified by flash chromatography (hexane/EtOAc,10:1, R_f 0.66) to yield a mixture of diastereomeric Mosher esters (±)-**23**·(*R*)-MTPA (39 mg, 94%). ^{1}H NMR (400.13 MHz, toluene-d_8): δ 7.59−7.55 [m, 2H, (*R*,*S*)-diastereomer], 7.51−7.47 [m, 2H, (*R*,*R*)], 7.08−6.91 [m, 14H, 8H of (*R*,*S*), 6H of (*R*,*R*)], 6.78−6.75 [m, 2H, (*R*,*R*)], 6.04 [X-part of an ABX-syst, J = 8.8, 4.2 Hz, 1H, (*R*,*S*)], 5.90 [X-part of an ABX-syst, J = 9.6, 3.3 Hz, 1H, (*R*,*R*)], 3.58 [q, J = 1.0 Hz, 3H, (*R*,*R*)], 3.32 [q, J = 1.0 Hz, 3H, (*R*,*S*)], 3.07 [AB-part of an ABX-syst, J_{AB} = 11.1 Hz, J = 8.8, 4.2 Hz, 2H, (*R*,*S*)], 3.01 [AB-part of an ABX-syst, J_{AB} = 11.4 Hz, J = 9.6, 3.3 Hz, 2H, (*R*,*R*)].

Similarly, (*S*)-(+)-**23** [20 mg, 0.10 mmol, $[\alpha]^{20}_D$ +39.24, (*c* 1.98, CH_2Cl_2)] was converted to (*R*)-Mosher esters (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.

Test of Chemical Stability of Lithium Alkoxide Derived from (±)-2-Bromo-1-phenylethanol toward Formation of Phenyloxirane at −78 °C. A solution of MeLi (0.60 mL, 0.60 mmol, 1 M in cumene/THF) was added quickly at −78 °C to the (±)-bromohydrin (±)-**23** (100 mg, 0.5 mmol) dissolved in dry THF (2.5 mL) under argon atmosphere. After the mxiture was stirred for 5 min, CF_3CO_2H (75 mg, 0.65 mL, 0.65 mmol, 1.3 equiv, 1 M in dry CH_2Cl_2) and water (5 mL) 3 min later were added. The organic phase was separated and the aqueous one was extracted with Et_2O (3 × 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 recover bromohydrin (±)-**23** (95 mg, 95%). Its R_f value and ^{1}H NMR spectrum were identical to that of the starting material.

Bromomethyl- and (*R*)- and (*S*)-(Bromo[D_1]methyl)-tributylstannane Tributylstannane {25, (*R*)- and (*S*)-[D_1]25} and Determination of ee by the Method[6] Used for Chloro-[D_1]methylstannane except That Reaction Was Performed at −50 °C Instead of 0 °C. Using NBS/Ph_3P:[6] 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 min tributylstannylmethanol (**2**) (787 mg, 2.45 mmol) dissolved in dry CH_2Cl_2 (4 mL) was added, and the reaction mixture was stirred rt for 30 min. A few drops of MeOH were added, and the mixture was concentrated under reduced pressure. The residue was flash chromatographed (hexane/CH_2Cl_2, 1:1, R_f 0.98) to yield bromomethylstannane[47] **25** (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), 1.55−1.46 (m, 6H), 1.30 (sext, J = 7.3 Hz, 6H), 1.00−0.95 (m, J($^{117/119}$Sn) = 51.4 Hz, 6H), 0.88 (t, J = 7.3 Hz, 9H).

Similarly, (*S*)-[D_1]**2** (197 mg, 0.61 mmol, prepared by an improved procedure, see below) was converted to (*R*)-[D_1]**25** (205 mg, 92%, ee 60%). The ^{1}H NMR spectrum (400.13 MHz, $CDCl_3$) was identical to that of **25** except for δ 2.61 (t, J = 1.5 Hz, 1H, CHD).

When the reaction was performed in the same way as before, except that two instead of 1.2 equiv of Ph_3P/NBS were used, (*R*)-[D_1]**2** (251 mg, 0.78 mmol) were converted to (*S*)-[D_1]**25** (230 mg, 77%, ee 18%).

Using Mitsunobu reaction with Ph_3P·HBr: Ph_3P (109 mg, 0.62 mmol), Ph_3P·HBr (845 mg, 2.46 mmol), and stannylmethanol **2** (657 mg, 2.05 mmol) were dissolved in dry toluene (8.2 mL) under argon. After stirring for 5 min at 0 °C DIAD (0.71 mL, 4.47 mmol) was added and the reaction mixture was stirred for another 90 min. The reaction was quenched with a few drops of MeOH. The mixture was

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purified by flash chromatography (hexane/CH_2Cl_2, 1:1, R_f 0.98) to give bromomethylstannane **25** (383 mg, 49%) as a colorless oil.

Similarly, (*R*)-[D_1]**2** (852 mg, 2.65 mmol, prepared by an improved procedure, see below) was converted to (*S*)-D_1]**25** (491 mg, 48%, ee[6] 74%) except that the reaction time was 10 min. After the addition of methanol, the reaction mixture was immediately applied to the silica column for flash chromatography. The entire procedure (also flash chromatography) was performed in the cold room (3 °C). No bath was used during concentration of bromide-containing solutions under reduced pressure.

Similarly, (*R*)-[D_1]**2** (958 mg, 2.98 mmol) was converted to (*S*)-[D_1]**25** (521 mg, 45%, ee 94%) as before except that the reaction was performed at −10 °C for 10 min.

Similarly, (*R*)-[D_1]**2** (417 mg, 1.30 mmol) was converted to (*S*)-[D_1]**25** (179 mg, 35%, ee ≥99%) as before except that the reaction was performed at −25 °C for 10 min.

Determination of Ease of Transmetalation of (Bromomethyl)tributylstannane. 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 **25** (163 mg, 0.42 mmol) dissolved in dry THF (2 mL) under argon atmosphere. After 30 s, CF_3CO_2H (64 mg, 0.55 mL, 0.55 mmol, 1.3 equiv, 1 M in dry CH_2Cl_2) was added, followed by water (5 mL) 1 min later. The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with water (15 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was virtually homogeneous tributylmethylstannane as determined by ^{1}H NMR spectroscopy, which did not contain starting material.

Determination of Chemical Stability of Bromomethyllithium under the Conditions of Evaluation of Its Microscopic Configurtional Stability. *(±)-2-Bromo-1-phenylethanol [(±)-**23**].* A solution of MeLi (1.85 mL, 1.85 mmol, 1 M in cumene/THF) was quickly added to a solution of bromomethylstannane **25** (178 mg, 0.46 mmol) and benzaldehyde (194 mg, 0.93 mL, 1.85 mmol, freshly distilled, 2 M in THF) in dry THF (2 mL) under argon atmosphere at −78 °C. After 5 min, CF_3CO_2H (232 mg, 2 mL, 2 mmol, 1 M in CH_2Cl_2) and water (5 mL) were added. The organic phase was separated, and the aqeous phase was extracted with CH_2Cl_2 (3 × 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 bromohydrin (±)-**23** as a colorless oil (17 mg, 19%). The spectroscopic data were identical to those of the authentic sample.

Determination of Microscopic Configurational Stability of Chiral Bromo[D_1]methyllithiums: Preparation of 2-Bromo-1-phenyl[2-D_1]ethanols {(2*S*)- and (2*R*)-[2-D_1]23**} and 1-Bromo-2-phenyl-2-[1-D_1]propanols {(1*S*)- and (1*R*)-[1-D_1]**27**}.** *Experiment 1.* A solution of benzaldehyde (198 mg, 0.94 mL, 1.87 mmol, freshly distilled, 2 M in dry THF) was added at −78 °C to the (*R*)-bromo[1-D_1]methylstannane (*R*)-[D_1]**2** (180 mg, 0.47 mmol, ee 50%) in dry THF (2 mL) under argon atmosphere, followed dropwise by MeLi (1.87 mL, 1.87 mmol, 1 M in cumene/THF). After 10 min, the reaction was quenched with CF_3CO_2H (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 × 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 bromohydrin (2*S*)-[2-D_1]**23** (7 mg, 11%, ee 57%) as a colorless oil; impure fractions (estimated product about 10 mg) were discarded.

Experiment 2. (*R*)-[D_1]**2** (157 mg, 0.41 mmol, ee 77%) was converted to (2*S*)-[2-D_1]**23** (15 mg, 18%, ee 76%) by procedure used for experiment 1 except using 2 equiv of benzaldehyde and MeLi (1 M solution obtained by dilution of 3 M MeLi in diethoxymethane with dry THF) which was added dropwise every 5 s. If 3 M MeLi in diethoxymethane was used or it was added more rapidly, no product or only product traces were obtained.

Experiment 3. (*R*)-[D_1]**2** (161 mg, 0.42 mmol, ee 77%) was converted to (1*S*)-[1-D_1]**27** (11 mg, 12%, ee 75%) by the procedure used for experiment 2 except that acetophenone was used as electrophile. The bromhydrine was isolated by flash chromatography (hexane/EtOAc, 15:1; TLC: hexane/EtOAc, 10:1, R_f 0.34).

Experiment 4. (*S*)-[D_1]**2** (218 mg, 0.57 mmol, ee 94%) was converted to (2*R*)-[2-D_1]**23** (10 mg, 9%, ee 94%) by the procedure used for experiment 2.

Experiment 5. (*S*)-[D_1]**2** (259 mg, 0.67 mmol, ee 94%) was converted to (1*R*)-[1-D_1]**27** (45 mg, 31%, ee 93%) by the procedure used for experiment 3 except that the reaction was performed at −95 °C.

Experiment 6. (*S*)-[D_1]**2** (179 mg, 0.46 mmol, ee ≥99%) was converted to (2*R*)-[2-D_1]**23** (13 mg, 14%, ee ≥99%) by procedure used for experiment 2.

Determination of Enantiomeric Excess at C-2 of Deuterated Bromohydrins [2-D_1]23, Using Their (*R*)-Mosher Esters [2-D_1]23 (*R*)-MTPA. They were prepared in quantitative yield from alcohols [1-D_1]**23** according to general procedure A and they were purified by flash chromatography (hexane/EtOAc, 10:1, R_f 0.78). The two diastereomeric (*R*)-Mosher esters obtained in quantitative yield were separated by preparative TLC chromatography (hexane/CH_2Cl_2, 3:1) in one case. The less polar one (R_f 0.56) was derived from (1*R*,2*S*)-[2-D_1]**23** (56% ee) and the more polar one (R_f 0.35) from (1*S*,2*S*)-[2-D_1]**23** (57% ee) in quantitative yield.

Significant resonances of (*R*)-Mosher ester derived from (1*R*,2*S*)-[2-D_1]**23**. ^{1}H NMR (400.13 MHz, toluene-d_8): δ 5.89 (br d, J = 2.5 Hz, 1H), 2.89 (d, J = 2.5 Hz, 1H, CHD). Significant resonances of (*R*)-Mosher ester derived from (1*S*,2*S*)-[2-D_1]**23**. ^{1}H NMR (400.13 MHz, toluene-d_8): δ 5.94 (d, J = 8.8 Hz, 1H), 3.05 (d, J = 8.8 Hz, 1H, CHD).

Bromohydrins (±)-27 and [1-D_1]27 and Their (*R*)-Mosher Esters (±)-27·MTPA-(*R*) and [1-D_1]27·MTPA-(*R*). (±)-**27**: ^{1}H NMR (400.27 MHz, $CDCl_3$): δ 7.47−7.42 (m, 2H), 7.39−7.33 (m, 2H), 7.31−7.25 (m, 1H), 3.71 (AB-sys, J_{AB} = 10.4 Hz, 2H), 2.52 (br s, 1H), 1.67 (s, 3H).

[1-D_1]**27**: The ^{1}H NMR spectra (400.27 MHz, $CDCl_3$) were identical to that of (±)-**27** except for δ 3.73 (br s, 0.5H, CHD), 3.68 (t, J = 1.4 Hz, 0.5H, CHD).

The (*R*)-Mosher esters of (±)-**27** and [1-D_1]**27** were prepared by a modified general procedure As exemplified for (1*R*)-[1-D_1]**27**·MTPA-(*R*): A solution of bromohydrin (1*R*)-[1-D_1]**27** (16 mg, 0.074 mmol), (*S*)-Mosher chloride (0.15 mmol, 2 equiv, 0.29 mL of a 0.53 M solution in dry 1,4-dioxane), and DMAP (37 mg, 0.30 mmol, 4 equiv) in dry dioxane (1 mL) was heated at 50 °C for 8 h (no starting material present). After the solution was cooled to rt, a few drops of water were added and stirring was continued for 5 min. CH_2Cl_2 (3 mL) and HCl (3 mL, 1 M) were added. The mixture was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layers were washed with saturated aq $NaHCO_3$, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was flash chromatographed (hexane/EtOAc, 15:1, R_f 0.56) to yield (1*R*)-[1-D_1]**27**·MTPA-(*R*) (20 mg, 62%).

(±)-**27**·MTPA-(*R*): ^{1}H NMR (400.27 MHz, $CDCl_3$): δ 7.59−7.51 (m, 4H), 7.45−7.35 (m, 6H), 7.35−7.26 (m, 8H), 7.23−7.18 (m, 2H), 3.97 (AB-sys, J_{AB} = 11.0 Hz, 2H), 3.77 (AB-sys, J_{AB} = 11.0 Hz, 2H), 3.62 (q, J = 1.3 Hz, 3H), 3.57 (q, J = 1.2 Hz, 3H), 2.10 (s, 3H), 2.02 (s, 3H).

(1*R*)-[1-D_1]**27**·MTPA-(*R*): The ^{1}H NMR spectrum (400.27 MHz, $CDCl_3$) was identical to that of (±)-**27**·MTPA-(*R*) except for δ 3.91 (br s, 0.85H, CHD), 3.81 (br s, 0.85H, CHD) and 4.00 (br s, 0.02H), 3.71 (br s, 0.03H); 93% ee for bromohydrin at C-1.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

NMR spectra or segments of NMR spectra of selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: friedrich.hammerschmidt@univie.ac.at.

Notes

The authors declare no competing financial interest.

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