

## Preparation of Chiral $\alpha$ -Oxy-[ $^2\text{H}_1$ ]methylolithiums of 99% ee and Determination of Their Configurational Stability

Dagmar Kapeller,<sup>†</sup> Roland Barth,<sup>†</sup> Kurt Mereiter,<sup>‡</sup> and Friedrich Hammerschmidt<sup>\*†</sup>

Contribution from the Institute of Organic Chemistry, University of Vienna, Währingerstrasse 38, A-1090 Vienna, Austria, and Institute of Chemical Technologies and Analytics, Vienna University of Technology, Getreidemarkt 9/164SC, A-1060 Vienna, Austria

Received August 25, 2006; E-mail: friedrich.hammerschmidt@univie.ac.at

**Abstract:** (Tributylstannyl)methyl 2,2,6,6-tetramethylpiperidine-1-carboxylate was metalated with *t*-BuLi/TMEDA at  $-78\text{ }^\circ\text{C}$  and borylated with the mixed borate derived from (*R,R*)-1,2-dicyclohexylethane-1,2-diol and *t*-butanol to give diastereomeric boronates **31/32** in equal amounts. Boronates **31** and **32** were reduced with  $\text{LiBEt}_3\text{D}$  and then oxidized with basic  $\text{H}_2\text{O}_2$  to give (*S*)- and (*R*)-tributylstannyl-[1- $^2\text{H}_1$ ]methanol of 99% ee, respectively. Treatment of their respective phosphates with *n*-BuLi at  $-78$  and  $0\text{ }^\circ\text{C}$  gave microscopically configurationally stable phosphinyloxy-substituted [ $^2\text{H}_1$ ]methylolithiums, which rearranged to hydroxy-[1- $^2\text{H}_1$ ]methylphosphonates of ee > 98% (phosphate–phosphonate rearrangement). The *N,N*-diisopropylcarbamates of the enantiomeric tributylstannyl-[1- $^2\text{H}_1$ ]methanols were transmetalated to give carbamoyloxy-substituted chiral [ $^2\text{H}_1$ ]methylolithiums, which were macroscopically configurationally stable for prolonged periods of time (up to 3 h, ee still 99%) at  $-78\text{ }^\circ\text{C}$ , deduced from trapping experiments with benzaldehyde. The chemical stability of these methylolithiums ended at  $-50\text{ }^\circ\text{C}$ . The stereochemistry of the monoprotected and monodeuterated 1-phenylethane-1,2-diols obtained was secured by spectroscopic comparison of their Mosher esters with that of all four stereoisomeric 1-phenyl-[1- $^2\text{H}_1$ ]ethane-1,2-diols synthesized independently. Furthermore, the configurations of the boronates and the chiral methylolithiums derived from them were deduced from a single-crystal X-ray structure analysis of a carbamate in which the tributylstannyl group had been replaced by the [(1*R*)-menthyl]dimethylstannyl group.

### Introduction

Organometallic reagents, especially those containing lithium and magnesium, play a pivotal role in organic chemistry, academia and industry alike.<sup>1</sup> Their preparations, the elucidation of their structures, and the fine-tuning of their reactivity by additives or other metal ions are attractive fields of research. Due to the importance of enantioselectivity in synthesis, the interest has shifted over the years from simple alkylmetals to versions containing functional groups derived from various heteroatoms and chiral centers. This is especially true for organolithiums, as lithium-carbanion pairs with three different substituents (alkyl groups, hydrogen) racemize as easily as the isoelectronic amines.<sup>2</sup>

In 1950, the first historic milestone for  $\text{sp}^3$  hybridized carbanions was set by Letsinger, who succeeded in the preparation of 1-methylheptyllithium as the first chiral, nonracemic alkylolithium from (–)-2-iodooctane and *s*-BuLi at  $-70\text{ }^\circ\text{C}$ .<sup>3</sup> Applequist and Peterson<sup>4</sup> and Walborsky et al.<sup>5</sup> showed that

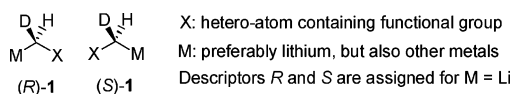
the incorporation of the carbanionic center into a cyclopropane conferred configurational stability in ether at ambient temperature. The same was true for the corresponding magnesium compound,<sup>6</sup> while the sodium compound<sup>7</sup> partly racemized. Still and Sreekumar were the first to prove that heteroatom substitution and intramolecular complexation raised the barrier to organolithium inversion.<sup>8</sup> They demonstrated that  $\alpha$ -alkoxyalkylolithiums were configurationally stable at low temperature in THF. This finding marked an upsurge of interest in  $\alpha$ -heteroatom (O, N, S, Se, halogen) substituted alkylolithiums and their configurational stability, which can be determined qualitatively by a simple test developed and used extensively by Hoffmann et al.<sup>9</sup> In general, the configurational stability decreases in those with an oxygen, stable up to  $-30\text{ }^\circ\text{C}$ , to nitrogen, sulfides (sulfoxides show exceptional stability), selenium, and bromine.<sup>1b</sup> Benzyl- and allyllithiums are less stable than alkylolithiums, and additional alkyl substituents as well as chelation slow down inversion. These experimental findings are

<sup>†</sup> University of Vienna.

<sup>‡</sup> Vienna University of Technology.

(1) Reviews: (a) Hanack, M. *Methoden der Organischen Chemie*; Houben-Weyl, E 19d: Carbanionen; George Thieme Verlag: Stuttgart, 1993. (b) Clayden, J. *Organolithiums: Selectivity for Synthesis*; Tetrahedron Organic Chemistry Series 23; Pergamon: Amsterdam, 2002. (c) *Organolithiums in Enantioselective Synthesis*; Hodgson, D. M., Ed.; Topics in Organometallic Chemistry 5; Springer: Berlin, 2003.  
(2) Review: Lambert, J. B. *Top. Stereochem.* **1971**, *6*, 19–105.  
(3) Letsinger, R. L. *J. Am. Chem. Soc.* **1950**, *72*, 4842.

(4) Applequist, D. E.; Peterson, A. H. *J. Am. Chem. Soc.* **1961**, *83*, 862–865.  
(5) Walborsky, H. M.; Impastato, F. J.; Young, A. E. *J. Am. Chem. Soc.* **1964**, *86*, 3283–3288.  
(6) Walborsky, H. M.; Young, A. E. *J. Am. Chem. Soc.* **1964**, *86*, 3288–3296.  
(7) Pierce, J. B.; Walborsky, H. M. *J. Org. Chem.* **1968**, *33*, 1962–1965.  
(8) Still, W. C.; Sreekumar, C. *J. Am. Chem. Soc.* **1980**, *102*, 1201–1202.  
(9) (a) Hoffmann, R. W.; Lanz, J.; Metternich, R.; Tarara, G.; Hoppe, D. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1145–1146. (b) Hirsch, R.; Hoffmann, R. W. *Chem. Ber.* **1992**, *125*, 975–982. (c) Hoffmann, R. W.; Rühl, T.; Harbach, J. *Liebigs Ann. Chem.* **1992**, 725–730.



**Figure 1.** Enantiomers of chiral methylolithiums.

nically supported by numerous calculations at different levels.<sup>10</sup> Hoppe et al.'s findings that carbamates with a shielded carbonyl group are metalated highly enantioselectively using (–)-sparteine/*s*-BuLi had a tremendous influence on the application of  $\alpha$ -oxyanions.<sup>11</sup> Beak et al. demonstrated the potential of chiral, nonracemic  $\alpha$ -aminoorganolithiums easily accessed by deprotonation of Boc-protected amines with (–)-sparteine/*s*-BuLi.<sup>12</sup>  $\alpha$ -Heteroatom-substituted carbanions react with a wide variety of electrophiles, preferentially in a retentive course.

Up to now only chiral, nonracemic secondary alkylolithiums with an  $\alpha$ -heteroatom have been prepared, but never primary ones of type **1** with two isotopes of hydrogen, for which we propose the term chiral methylolithiums (Figure 1). It was selected in analogy to the term chiral methyl group first mentioned by Cornforth<sup>13</sup> and Arigoni et al.<sup>14</sup> in their preparation of chiral acetic acid. Our direct synthesis of chiral methanol intrigued us to attack this unsolved challenge.<sup>15</sup>

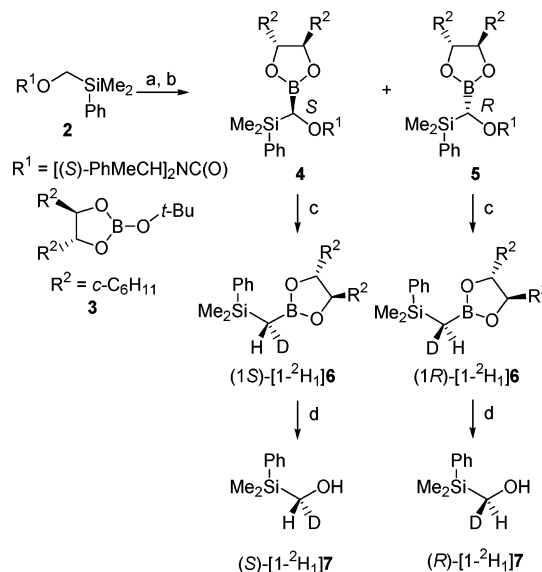
## Results and Discussion

As we envisaged to prepare chiral methylolithiums with various heteroatoms, the starting material of choice would be the chirally deuterated (tributylstannyl)methanol. It could be converted easily to the requisite precursors, which are amenable to tin lithium exchange to give chiral methylolithiums. We anticipated a lower barrier of inversion compared to the ones with an alkyl group in place of a hydrogen isotope. However, we were hoping that at least the oxymethylolithiums would be configurationally stable at (very) low temperatures, an assumption based on theoretical calculations.<sup>10</sup> Here, we present our results on the generation of the chiral (diisopropoxyphosphinyloxy- and *N,N*-diisopropylcarbamoyloxy)-substituted methylolithiums and the determination of their microscopic and macroscopic configurational stabilities, respectively.

### Preparation of (*R*)- and (*S*)-Tributylstannyl-[ $^2\text{H}_1$ ]methanol.

The preparation and the enantioselective reduction of acylstannanes are well-known reactions.<sup>16</sup> Unfortunately, this sequence cannot be extended to tributylformylstannane, which has been postulated as an unstable intermediate of the hydrolysis of ( $\alpha$ -chloro- $\alpha$ -ethoxymethyl)tributylstannane.<sup>17</sup> Therefore, we resorted to the method developed for the preparation of chiral

### Scheme 1. Preparation of (*R*)- and (*S*)-Dimethylphenylsilyl-[ $^2\text{H}_1$ ]methanol<sup>a</sup>



<sup>a</sup> (a) *s*-BuLi/TMEDA/–78 °C; (b) borylation with **3**; (c) LiAlD<sub>4</sub> or LiBEt<sub>3</sub>D; (d) H<sub>2</sub>O<sub>2</sub>/NaHCO<sub>3</sub>/H<sub>2</sub>O/THF/50 °C.

dimethylphenylsilyl-[ $^2\text{H}_1$ ]methanol.<sup>15</sup> The key steps are given for the sake of clarity (Scheme 1). Thus, carbamate **2** was prepared from homochiral (*S,S*)-bis(1-phenylethyl)amine and (dimethylphenylsilyl)methanol [easily available from commercial (chloromethyl)dimethylphenylsilane], metalated with *s*-BuLi/TMEDA, and borylated with borate **3** (or the one derived from (+)-pinane-2,3-diol) to give boronates **4** and **5**. Each diastereomer was reduced with LiBEt<sub>3</sub>D under inversion of configuration to a deuterated (dimethylphenylsilyl)methylboronate **6**, which in turn was oxidized (H<sub>2</sub>O<sub>2</sub>/THF/NaHCO<sub>3</sub>) to give dimethylphenylsilyl-[ $^2\text{H}_1$ ]methanol **7** (ee 99%). The seemingly simple switch from the dimethylphenylsilyl to the tributylstannyl substituent forced us to reshape the synthesis because of the reduced acidity of hydrogens  $\alpha$  to tin compared to silicon.

Additionally, we had to access the corresponding carbamate by a different route, because (chloromethyl)tributylstannane is not commercially available. To this end, carbamate **9** was prepared from methanol and (*S,S*)-bis(1-phenylethyl)amine (**8**) (Scheme 2). Metalation with *s*-BuLi/TMEDA and quenching with Bu<sub>3</sub>SnCl furnished an inseparable mixture of diastereomeric stannanes **11a/b** (ratio by <sup>1</sup>H NMR: 2.2:1) in 75% yield, containing at best 15% of stannylmethyl carbamate **10**. This result reflects the higher acidity of the secondary benzylic hydrogens  $\alpha$  to nitrogen compared to the primary ones  $\alpha$  to oxygen. To overcome this side reaction, the 1-phenylethyl groups were replaced by isopropyl groups. Metalation and stannylation of methyl *N,N*-diisopropylcarbamate gave the (tributylstannyl)methyl carbamate in about 50% yield as already found by Boche et al.<sup>18</sup> Alternatively, it was prepared by a one-pot procedure. Tributylstannylolithium<sup>19</sup> generated from hexabutylditin and *n*-BuLi was added to paraformaldehyde, and the lithium stannylmethoxide **13** was esterified with *N,N*-diisopro-

(10) (a) Rondan, G. N.; Houk, K. N.; Beak, P.; Zajdel, W. J.; Chandrasekhar, J.; Schleyer, P. v. R. *J. Org. Chem.* **1981**, *46*, 4108–4110. (b) Schleyer, P. v. R.; Clark, T.; Kos, A. J.; Spitznagel, G. W.; Rohde, C.; Arad, D.; Houk, K. N.; Rondan, N. G. *J. Am. Chem. Soc.* **1984**, *106*, 6467–6475. (c) Boche, G.; Opel, A.; Marsch, M.; Harms, K.; Haller, F.; Lohrenz, J. C. W.; Thümmel, C.; Koch, W. *Chem. Ber.* **1992**, *125*, 2265–2273.

(11) Reviews: (a) Hoppe, D.; Hense, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2282–2316. (b) Hoppe, D.; Marr, F.; Brüggemann, M. In *Organolithiums in Enantioselective Synthesis*; Hodgson, D. M., Ed.; Topics in Organometallic Chemistry 5; Springer: Berlin, 2003; pp 61–137.

(12) Reviews: (a) Beak, P.; Johnson, T. A.; Kim, D. D.; Lim, S. H. In *Organolithiums in Enantioselective Synthesis*; Hodgson, D. M., Ed.; Topics in Organometallic Chemistry 5; Springer: Berlin, 2003; pp 139–176. (b) Beak, P.; Basu, A.; Gallagher, D. J.; Park, Y. S.; Thayumanavan, S. *Acc. Chem. Res.* **1996**, *29*, 552–560. (c) Gawley, R. E. *Curr. Org. Chem.* **1997**, *1*, 71–94.

(13) Cornforth, J. W.; Redmond, J. W.; Eggerer, H.; Buckel, W.; Gutschow, C. *Nature* **1969**, *221*, 1212–1213.

(14) Lüthy, J.; Retej, J.; Arigoni, D. *Nature* **1969**, *221*, 1213–1215.

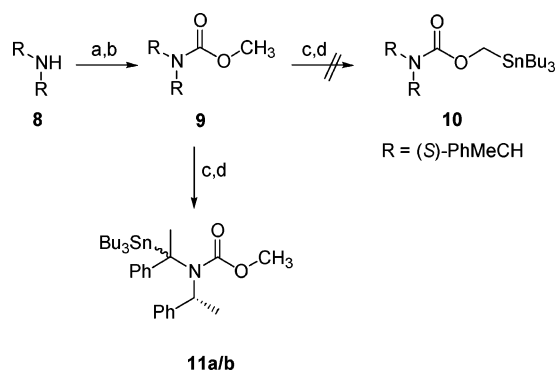
(15) Peric Simov, B.; Wuggenig, F.; Mereiter, K.; Andres, H.; France, J.; Schnell, P.; Hammerschmidt, F. *J. Am. Chem. Soc.* **2005**, *127*, 13934–13940.

(16) Chan, P. C.-M.; Chong, J. M. *J. Org. Chem.* **1988**, *53*, 5584–5586.

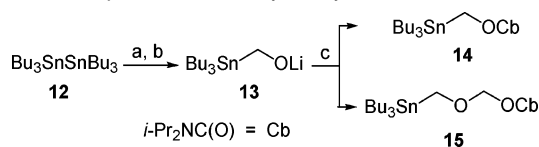
(17) Quintard, J.-P.; Elissondo, B.; Mouko-Mpegna, D. *J. Organomet. Chem.* **1983**, *251*, 175–187.

(18) Boche, G.; Bosold, F.; Lohrenz, J. C. W.; Opel, A.; Zulauf, P. *Chem. Ber.* **1993**, *126*, 1873–1885.

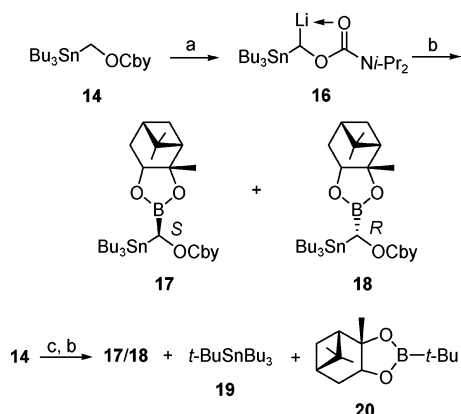
(19) Still, W. C. *J. Am. Chem. Soc.* **1978**, *100*, 1481–1487.

**Scheme 2.** Attempted Preparation of Stannylmethyl Carbamate **10**<sup>a</sup>

<sup>a</sup> (a)  $\text{COCl}_2/i\text{-Pr}_2\text{NEt/toluene}/0\text{ }^\circ\text{C}$ ; (b)  $\text{MeOH}/i\text{-Pr}_2\text{NEt/DMAP}/70\text{ }^\circ\text{C}$  (93%); (c)  $s\text{-BuLi/TMEDA/Et}_2\text{O}/-78\text{ }^\circ\text{C}$ ; (d)  $\text{Bu}_3\text{SnCl}$  (75%).

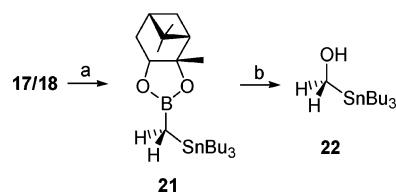
**Scheme 3.** Preparation of Stannylmethyl Carbamate **14**<sup>a</sup>

<sup>a</sup> (a)  $n\text{-BuLi}$ ; (b) paraformaldehyde; (c)  $i\text{-Pr}_2\text{NC(O)Cl}$  (55%).

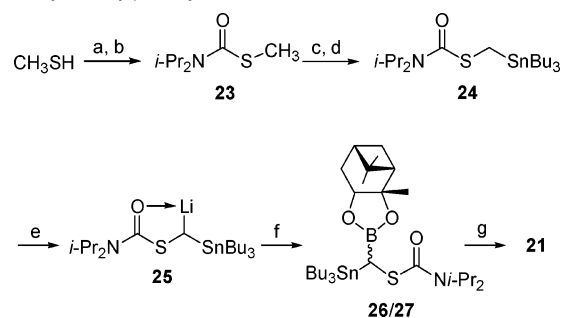
**Scheme 4.** Lithiation and Borylation of (Tributylstannyl)methyl Carbamate **14**<sup>a</sup>

<sup>a</sup> (a)  $\text{LiTMP/Et}_2\text{O}$ ; (b) mixed borate of (+)-pinane-2,3-diol and  $t$ -butanol (31%); (c)  $t\text{-BuLi/TMEDA/Et}_2\text{O}/-78\text{ }^\circ\text{C}/30\text{ min}$ , then (b) (29%).

pylcarbamoyle chloride in an overall yield of 55% along with carbamate **15** as side product in 8% yield (Scheme 3). Whereas the silyl analogue of **14** was metalated easily with  $s\text{-BuLi}$ /TMEDA at  $-78\text{ }^\circ\text{C}$  in diethyl ether, deprotonative lithiation of **14** was a major problem (Scheme 4). The use of  $n\text{-BuLi}$  and  $s\text{-BuLi}$  was not feasible because of tin–lithium exchange. Metalation was only effected when performed with  $\text{LiTMP}$  between  $-30$  and  $-20\text{ }^\circ\text{C}$  in diethyl ether for 1 h as evidenced by the formation of diastereomeric boronates **17** and **18** when the mixed borate<sup>15</sup> of (+)-pinane-2,3-diol and  $t$ -butanol was added. This cheap borate was also used extensively in the silyl series and furnished separable diastereomers, which qualified it for the preliminary experiments here as well. Unfortunately, the boronates that were formed in a combined yield of at best 31% in a ratio of 1:1 (by  $^1\text{H NMR}$ ) could not be separated by flash chromatography or HPLC. Neither could the yield be improved by performing the lithiation at  $-10\text{ }^\circ\text{C}$  for 1.5 h. Finally, we tested  $t\text{-BuLi}$  as base, knowing that tin–lithium exchange would likely interfere with deprotonation. The desired

**Scheme 5.** Synthesis of (Tributylstannyl)methanol from Boronates **17** and **18**<sup>a</sup>

<sup>a</sup> (a)  $\text{LiBEt}_3\text{H/Et}_2\text{O}/20\text{ }^\circ\text{C}/3\text{ h}$  (89%); (b)  $\text{H}_2\text{O}_2/\text{H}_2\text{O/NaOH/THF}/20\text{ }^\circ\text{C}$  (21%).

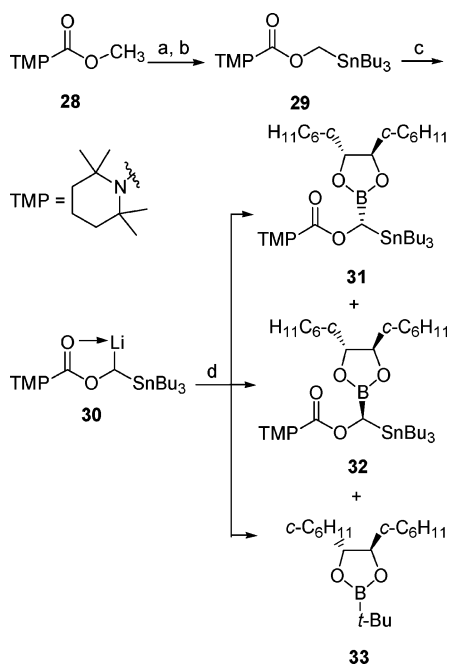
**Scheme 6.** Preparation and Borylation of  $S$ -(Tributylstannyl)methyl Thiocarbamate **23**<sup>a</sup>

<sup>a</sup> (a)  $n\text{-BuLi}$ ; (b)  $i\text{-Pr}_2\text{NC(O)Cl}$  (94%); (c)  $s\text{-BuLi/TMEDA/Et}_2\text{O}/-78\text{ }^\circ\text{C}/35\text{ min}$ ; (d)  $\text{Bu}_3\text{SnCl}$  (94%); (e)  $\text{LiTMP/Et}_2\text{O}/-50\text{ }^\circ\text{C}/1\text{ h}$ ; (f) mixed borate of (+)-pinane-2,3-diol and  $t$ -butanol/ $-50\text{ }^\circ\text{C}/1\text{ h}$  (94%); (g)  $\text{LiAlH}_4/\text{THF}/0\text{ }^\circ\text{C}/4\text{ h}$  (0%).

boronates **17/18** (ratio:1:1, by  $^1\text{H NMR}$ ) were isolated in consistently low yield (29%) along with tributyl- $t$ -butylstannane (**19**) in 65% yield, diagnostic for tin–lithium exchange.  $t$ -Butylboronate **20** resulted from excess  $t\text{-BuLi}$  and borate. To make sure that any lengthy optimization of metalation was justified, we decided to check whether this mixture of diastereomers could in principle be transformed into (tributylstannyl)methanol (Scheme 5). Indeed, the diastereomers were reduced with  $\text{LiBEt}_3\text{H}$  to (tributylstannyl)methylboronate **21** as cleanly as the silyl analogues in 89% yield.<sup>15</sup> The oxidative cleavage of the B–C bond necessitated the use of  $\text{H}_2\text{O}_2$  in a biphasic system of THF and sodium hydroxide instead of  $\text{NaHCO}_3$  used in the silyl series to furnish the desired (tributylstannyl)methanol<sup>20</sup> (**22**) although in only 21% yield. The neat conversion of boronates **17** and **18** to **21** in high yield encouraged us to resume the search for separable boronates or related precursors in better yields. As there is no stronger lithium amide base than  $\text{LiTMP}$ <sup>21</sup> easily available and  $t\text{-BuLi}$  was competing with tin–lithium exchange, the change of substituents at nitrogen was a viable option left to increase the yield. Alternatively, the oxygen of the carbamate could be replaced by sulfur to increase the acidity of the hydrogens  $\alpha$  to tin. The latter option seemed to be more effective, and thus thiocarbamate **23** was prepared (Scheme 6). Lithiation of thiocarbamate **23** with  $s\text{-BuLi}$ /TMEDA for 35 min compared to 4.5 h for the corresponding carbamate at  $-78\text{ }^\circ\text{C}$  followed by stannylation with  $\text{Bu}_3\text{SnCl}$  furnished  $S$ -(tributylstannyl)methyl thiocarbamate (**24**) in 94% yield. It was lithiated with  $\text{LiTMP}$  smoothly at  $-50\text{ }^\circ\text{C}$  for 1 h and borylated with the mixed borate of (+)-pinane-2,3-diol and  $t$ -butanol to give a mixture of boronates **26/27** (ratio 55:45) separable by HPLC in 94% yield. Unfortunately, none of the

(20) (a) Fernandez-Megía, E.; Ley, S. V. *Synlett* **2000**, 4, 455–458. (b) Meyer, N.; Seebach, D. *Chem. Ber.* **1980**, 113, 1290–1303.

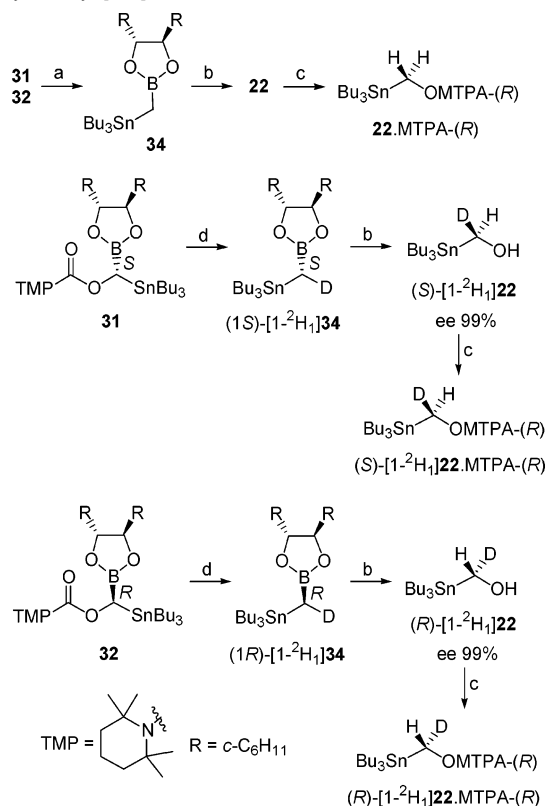
(21) Fraser, R. R.; Mansour, T. S. J. *Org. Chem.* **1984**, 49, 3442–3443.

**Scheme 7.** Preparation and Borylation of (Tributylstannyl)methyl Carbamate **29**<sup>a</sup>

<sup>a</sup> (a) *s*-BuLi/TMEDA/Et<sub>2</sub>O/−78 °C/1.5 h; (b) Bu<sub>3</sub>SnCl (69%); (c) *t*-BuLi/TMEDA/Et<sub>2</sub>O/−78 °C/30 min; (d) mixed borate of (*R,R*)-1,2-dicyclohexylethane-1,2-diol and *t*-butanol/−78 °C/30 min (ratio by <sup>1</sup>H NMR: 1:1; isolated, **31**: 35%, **32**: 30%).

diastereomers could be reduced with LiAlH<sub>4</sub>, and therefore we had to resort to the second option, the search for an analogue of the *N,N*-diisopropylcarbamoyl group. Our first choice was the symmetric 2,2,6,6-tetramethylpiperidine-1-carbonyl group, which seemed to be more attractive than the unsymmetrical 2,2,4,4-tetramethyl-1,3-oxazolidine-3-carbonyl group introduced by Hoppe and Hintze.<sup>22</sup> Deprotonative lithiation and stannylation of methyl carbamate<sup>23</sup> **28** with *s*-BuLi/TMEDA furnished (tributylstannyl)methyl carbamate **29** in 69% yield (Scheme 7). The second deprotonative lithiation was performed with *t*-BuLi/TMEDA at −78 °C, and the intermediate dipole-stabilized organolithium **30** was borylated with the homochiral borate<sup>15</sup> **3** derived from (*R,R*)-1,2-dicyclohexylethane-1,2-diol<sup>24</sup> and tri(*t*-butyl) borate. *s*-BuLi/TMEDA effected a clean tin–lithium exchange as expected. The combined yield of the diastereomeric boronates **31** and **32** formed in equal quantities (by <sup>1</sup>H NMR) was 65%. They could be separated easily by flash chromatography, as they differed very much in their polarity on silica (*R<sub>f</sub>* = 0.42 and 0.29 in hexanes/CH<sub>2</sub>Cl<sub>2</sub>, 2:1). Boronate **33** and tributyl-*t*-butylstannane (30%) were formed as well. Anticipating the latter results, the less polar diastereomer **31** had (*S*)-configuration and consequently the more polar one **32** had (*R*)-configuration.

In exploratory experiments, both diastereomeric boronates **31** and **32** were reduced smoothly with 1.2 equiv of LiBEt<sub>3</sub>H or LiAlH<sub>4</sub> to the same (tributylstannyl)methylboronate **34** in yields of 79–89% (Scheme 8). Oxidation of **34** in a basic solution of H<sub>2</sub>O<sub>2</sub> furnished (tributylstannyl)methanol (**22**) in 84% yield. The

**Scheme 8.** Conversion of Boronates to Enantiomers of Tributylstannyl- $[\text{H}_1]$ methanol<sup>a</sup>

<sup>a</sup> (a) LiBEt<sub>3</sub>H/Et<sub>2</sub>O/20 °C/2 h (84%); (b) H<sub>2</sub>O<sub>2</sub>/H<sub>2</sub>O/THF/NaOH, 20 °C/2 h (90%); (c) (*S*)-MTPACl/CH<sub>2</sub>Cl<sub>2</sub>/pyridine/20 °C (96–100%); (d) LiBEt<sub>3</sub>D/Et<sub>2</sub>O/20 °C/2 h (83–87%).

alcohol was esterified with (*S*)-MTPACl to give the Mosher ester,<sup>25</sup> whose <sup>1</sup>H NMR spectrum (400 MHz) showed an AB system ( $\delta$  = 4.39, *J*<sub>AB</sub> = 11.5 Hz) for the SnCH<sub>2</sub> group, suitable for the determination of the enantiomeric excesses in the deuterated series. The reactions in the labeled series were performed similarly, except that LiBEt<sub>3</sub>H was replaced by LiBEt<sub>3</sub>D (or LiAlD<sub>4</sub>), assuming that the carbamoyloxy group was replaced with inversion of configuration.<sup>15,26</sup> Thus, (*R*)- and (*S*)-tributylstannyl- $[\text{H}_1]$ methanol with an ee of 99% could be accessed easily and used for the preparation of a variety of heteroatom-substituted chiral methylolithiums.

**Determination of Microscopic Configurational Stability of Chiral  $\alpha$ -Oxymethylolithiums.** The microscopic stability of a carbanion refers to the rate of its inversion of configuration relative to the reaction with an electrophile. We selected the phosphate–phosphonate rearrangement,<sup>27</sup> a fast intramolecular isomerization, to study the microscopic configurational stability of the (diisopropoxyphosphinyl)oxy-substituted methylolithium as a first example of a chiral dipole-stabilized  $\alpha$ -oxy-methylolithium.<sup>28</sup> First, the feasibility of the sequence was established in the unlabeled series. Crude (tributylstannyl)-methanol was phosphorylated with diisopropyl bromophosphate/pyridine<sup>29</sup> to give stannylmethyl phosphate **35** in 44% overall yield (Scheme 9). Transmetalation<sup>29</sup> with excess *n*-BuLi/

(22) Hintze, F.; Hoppe, D. *Synthesis* **1992**, 1216–1218.

(23) Werchan, H. G.; Russew, R. I.; Held, P.; Schubert, H. J. *Prakt. Chem.* **1977**, 319, 516–521.

(24) (a) Hoffmann, R. W.; Ditrich, K.; Köster, G.; Stürmer, R. *Chem. Ber.* **1989**, 122, 1783–1789. (b) Hiscox, W. C.; Matteson, D. S. *J. Org. Chem.* **1996**, 61, 8315–8316.

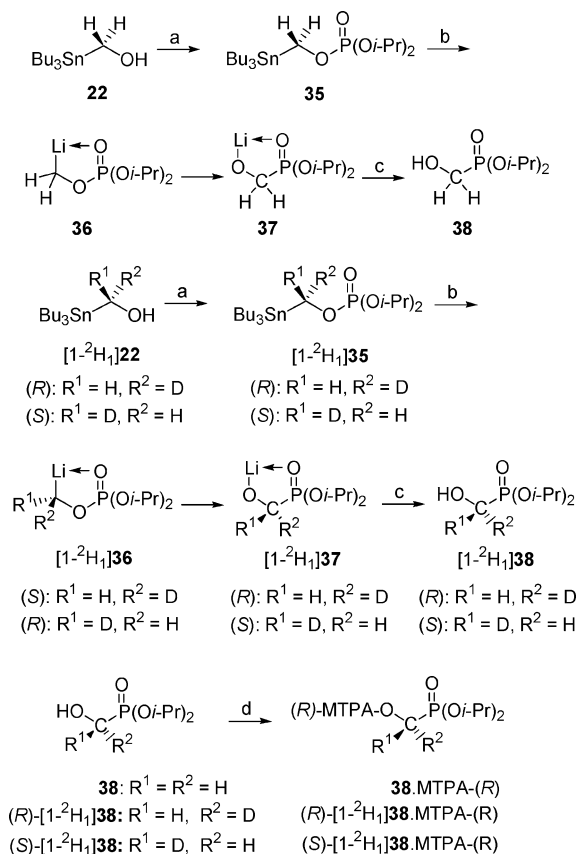
(25) Review: Seco, J. M.; Quiñoá, E.; Riguera, R. *Chem. Rev.* **2004**, 104, 17–117.

(26) Zweifel, G.; Brown, H. C. *Org. React.* **1963**, 13, 1–54.

(27) Hammerschmidt, F.; Schmidt, S. *Eur. J. Org. Chem.* **2000**, 2239–2245.

(28) Review: Beak, P.; Reitz, D. B. *Chem. Rev.* **1978**, 78, 275–316.

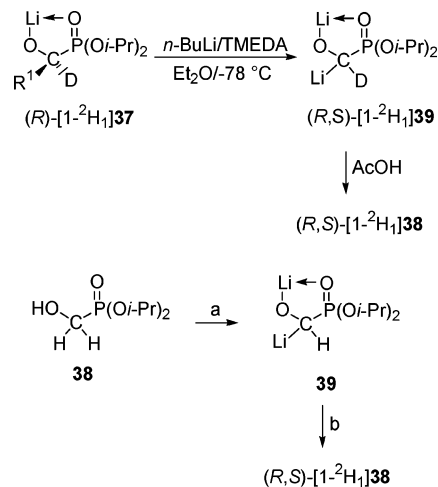
(29) Hammerschmidt, F.; Schmidt, S. *Monatsh. Chem.* **1997**, 128, 1173–1180.

**Scheme 9.** Preparation and Phosphate–Phosphonate Rearrangement of Stannymethyl Phosphates **35**<sup>a</sup>

<sup>a</sup> (a) (*i*-Pr)<sub>2</sub>P(O)Br/pyridine/CH<sub>2</sub>Cl<sub>2</sub>/20 °C/1 h (72–81%); (b) *n*-BuLi/TMEDA/Et<sub>2</sub>O/−78 or 0 °C/3 to 40 min; (c) AcOH (36–76%); (d) (*S*)-MTPACl/pyridine/20 °C (80–90%).

TMEDA in diethyl ether at −78 °C produced lithium-complexed α-oxymethyl lithium **36**, which rearranged to lithiated oxy-methylphosphonate **37** and gave hydroxymethylphosphonate **38** on workup in 67% yield. Esterification with (*S*)-MTPACl/pyridine produced the respective Mosher ester. Its <sup>1</sup>H NMR spectrum (400 MHz) revealed an AB system coupling with phosphorus for the two diastereotopic hydrogens of the PCH<sub>2</sub>O group, allowing the determination of the ee of deuterated samples.

Similarly, deuterated stannymethanol (*R*)-[<sup>2</sup>H<sub>1</sub>]**22** was phosphorylated and subjected to the phosphate–phosphonate rearrangement using 1.6 equiv of *n*-BuLi/TMEDA to give the hydroxymethylphosphonate (*R*)-[<sup>2</sup>H<sub>1</sub>]**38** in 74% yield. (*R*)-Configuration was assigned tentatively on the basis of previous work with alkyl<sup>27</sup> and benzyl phosphates<sup>30a</sup> and *N*-benzyl phosphoramidates<sup>30b</sup> rearranging with retention of configuration at the anionic carbon atom. The <sup>1</sup>H NMR spectrum of the Mosher ester of (*R*)-[<sup>2</sup>H<sub>1</sub>]**38** revealed that two broadened doublets (*J* = 8.5 Hz), a weak one at 4.59 and a strong one at 4.43 ppm, for the PCHD groups of the two diastereomers were present, indicating an ee of 83% for the underlying alcohol. The partial racemization could result from either the configurational instability of the (diisopropoxyphosphinyl)oxymethyl lithium (*S*)-[<sup>2</sup>H<sub>1</sub>]**36** or a side reaction caused by excess *n*-BuLi.

**Scheme 10.** Double Metalation of Hydroxymethylphosphonate and Quenching with AcOD<sup>a</sup>

<sup>a</sup> (a) 2 equiv of *n*-BuLi/TMEDA/Et<sub>2</sub>O/−78 °C/30 min; (b) AcOD (64%, D<sub>1</sub> by <sup>1</sup>H NMR: 23%).

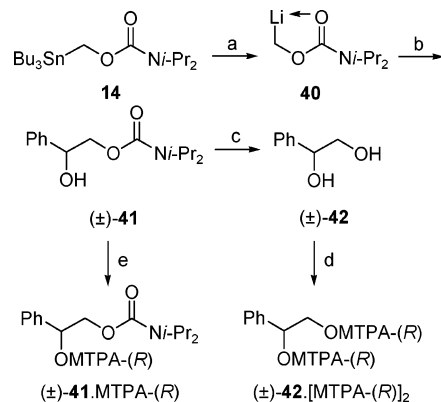
We suspected that the lithiated hydroxymethylphosphonate could have been deprotonated with a high primary kinetic isotope effect to give a dianion that racemized to (*R,S*)-[1-<sup>2</sup>H<sub>1</sub>]**39** rapidly before being quenched with water (Scheme 10).<sup>30</sup> To verify this, unlabeled hydroxymethylphosphonate **38** was treated with 2 equiv of *n*-BuLi/TMEDA in diethyl ether at −78 °C for 30 min. Quenching with AcOD and purification of the isolated product furnished hydroxymethylphosphonate **38**, which was in part (23%) monodeuterated. Therefore, the experiment with labeled stannymethyl phosphate (*R*)-[1-<sup>2</sup>H<sub>1</sub>]**35** was repeated using only 0.90 equiv of *n*-BuLi/TMEDA to preclude the possible double metalation and the ensuing racemization. Some starting material was recovered (15%), but the labeled hydroxymethylphosphonate (*R*)-[1-<sup>2</sup>H<sub>1</sub>]**38** obtained in 70% yield had an ee of 98%. Complementary results were obtained with the phosphate derived from (tributylstannyl)methanol (*S*)-[<sup>2</sup>H<sub>1</sub>]**22**. Finally, the phosphate–phosphonate rearrangement of both enantiomeric phosphates was performed again at 0 °C. Stannymethyl phosphate (*R*)-[1-<sup>2</sup>H<sub>1</sub>]**35** was transmetalated with 0.90 equiv of *n*-BuLi/TMEDA for 30 min. The isomeric phosphonate (*R*)-[1-<sup>2</sup>H<sub>1</sub>]**38** was isolated in 36% yield (ee 94%; 43% of the starting material was recovered). Here, the small amount of racemization is attributed to the retro-Abramov reaction,<sup>31</sup> the decomposition of (*R*)-[1-<sup>2</sup>H<sub>1</sub>]**37** to the lithium salt of diisopropyl phosphite and [1-<sup>2</sup>H<sub>1</sub>]formaldehyde, followed by the reverse process with the formation of both enantiomers of [1-<sup>2</sup>H<sub>1</sub>]**37**. Racemization via metalation of (*R*)-[1-<sup>2</sup>H<sub>1</sub>]**38** is not feasible, because the amount of *n*-BuLi (0.9 equiv) was not even sufficient for a complete transmetalation. When the rearrangement at 0 °C was repeated with the phosphate (*S*)-[1-<sup>2</sup>H<sub>1</sub>]**38** under identical conditions except the reaction time, which was 3 min, the phosphonate was formed in 76% yield and had an ee of 98%. These results prove unequivocally that the (diisopropoxyphosphinyl)oxy-substituted chiral methyl lithiums [2H<sub>1</sub>]-**36** are configurationally stable from −78 to 0 °C relative to the phosphate–phosphonate rearrangement (intramolecular reaction).

(30) (a) Hammerschmidt, F.; Hanninger, A. *Chem. Ber.* **1995**, *128*, 823–830. (b) Hammerschmidt, F.; Hanbauer, M. *J. Org. Chem.* **2000**, *65*, 6121–6131.

(31) (a) Abramov, V. S.; Semenova, L. P.; Semenova, L. G. *Dokl. Akad. Nauk* **1952**, *84*, 281–284; *Chem. Abstr.* **1953**, *47*, 3227i. (b) Horner, L.; Röder, H. *Chem. Ber.* **1970**, *103*, 2984–2986.

**Determination of Macroscopic Configurational Stability of Chiral  $\alpha$ -Oxymethylolithiums.** Tributylstannyl-[ $^2\text{H}_1$ ]methanol can be transformed into a variety of protected derivatives, which can be transmetalated to give chiral  $\alpha$ -oxymethylolithiums. We focused on carbamoyl groups most widely used as protective groups for alcohols, when a deprotonative metalation is envisaged. Furthermore, we planned to test the configurational stability of the chiral methylolithium from  $-78$  to  $0$  °C, if the chemical stability allowed it. Before we could embark on the generation of chiral carbamoyloxy-substituted methylolithiums, we had to (a) test the chemical stability in the unlabeled series for various periods of time up to  $0$  °C, (b) find a suitable electrophile, (c) determine the configurations at the chiral centers before tin–lithium exchange via X-ray structure analysis, and (d) prepare reference samples of known configuration. The *N,N*-diisopropylcarbamoyl group was selected as protective group and benzaldehyde as electrophile. Thus, carbamate **14** was transmetalated in diethyl ether with excess *n*-BuLi/TMEDA at  $-78$  °C and quenched after 3 min with benzaldehyde (Scheme 11). The racemic monoprotected diol ( $\pm$ )-**41** was isolated in 81% yield (Table 1). When the reaction time, the time elapsed between addition of *n*-BuLi and benzaldehyde, was increased to 60 min at  $-78$  °C, the yield dropped to 70%. When the reaction temperature was increased to  $-35$  and  $0$  °C, no product was isolated, despite a reaction time of only 30 s. However, the yield increased to 62% at  $-50$  °C, if the reaction time was shortened to 15 s. At  $0$  °C, some product (26 and 37%) could be obtained, if the transmetalations were performed with an

**Scheme 11.** Tin–Lithium Exchange in **14** and Trapping of the  $\alpha$ -Oxymethylolithium with Benzaldehyde<sup>a</sup>



<sup>a</sup> (a) 1.5 equiv of *n*-BuLi and 2.6 equiv of TMEDA in Et<sub>2</sub>O or 1.5 equiv of *n*-BuLi in THF (for temperature and time elapsed between addition of *n*-BuLi and PhCHO, see Table 1); (b) 1.6 equiv of PhCHO (for yields, see Table 1); (c) LiAlH<sub>4</sub>/THF/reflux/1 h (82%); (d) (*S*)-MTPACl/pyridine/ $20$  °C (96%); (e) (*S*)-MTPACl/pyridine/ $20$  °C (97%).

**Table 1.** Yield of ( $\pm$ )-**41** in Trapping Experiments of **40** as Function of Reaction Time and Temperature

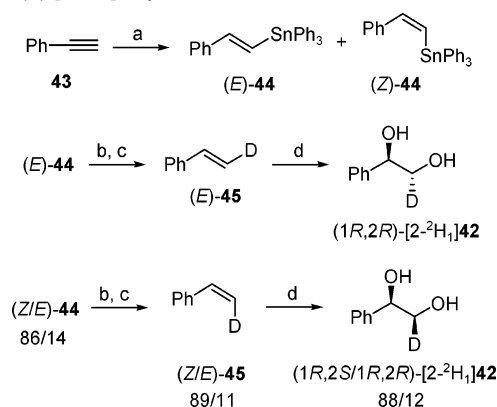
entry	temp (°C)	time (min)	yield (%)
1	$-78$	3	81
2	$-78$	60	70
3	0	1	—
4	0	0.5	—
5	$-35$	0.5	—
6	$-50$	0.25	62
7	0	—	26 <sup>a</sup>
8	0	—	37 <sup>b</sup>

<sup>a</sup> Benzaldehyde (3 equiv) was present on addition of *n*-BuLi (3 equiv).

<sup>b</sup> Benzaldehyde (5 equiv) was present on addition of *n*-BuLi (3 equiv).

excess (3 equiv) of *n*-BuLi in the presence of various amounts of benzaldehyde (3 or 5 equiv). Tin–lithium exchange was complete in all cases and proceeded even faster than the addition of *n*-BuLi to benzaldehyde as shown by the last two experiments (entries 7 and 8). The upper limit for the chemical stability of methylolithium **40** in Et<sub>2</sub>O/TMEDA was reached at  $-50$  °C. The mode of its decomposition, possibly formation of methylene and in part rearrangement<sup>32</sup> to the *N,N*-diisopropyl hydroxyacetamide, is unknown. Reductive removal of the carbamoyl group with LiAlH<sub>4</sub> gave diol ( $\pm$ )-**42**, which was esterified with (*S*)-MTPACl to a mixture of two diesters. The <sup>1</sup>H NMR spectrum (400 MHz) showed two sets of resonances for the O–CHPh–CH<sub>2</sub>–O groups of the diastereomers. The AB portions of the resonances of the CH<sub>2</sub>O groups were in part overlapping. However, the unequivocal assignment of signals and their integrations was possible, prerequisite for the experiments in the labeled series to determine the relative quantities of diastereomers. It was found later that Mosher ester ( $\pm$ )-**41**.MTPA-(*R*) could have been possibly used in very much the same way, when the spectra were recorded in toluene-*d*<sub>8</sub> instead of CDCl<sub>3</sub>.

**Scheme 12.** Preparation and Enantioselective Dihydroxylation of (*E*)- and (*Z*)-[ $^2\text{H}_1$ ]Vinylbenzene<sup>a</sup>



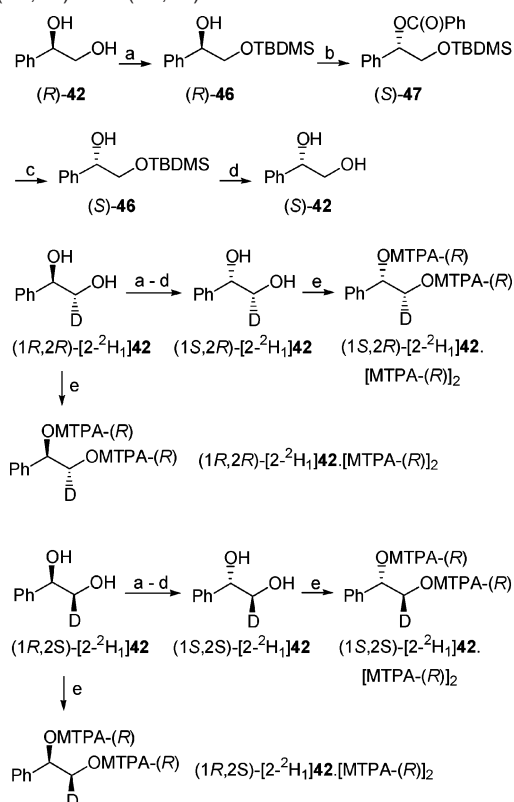
<sup>a</sup> (a) Ph<sub>3</sub>SnH [41% of (*E*)-**44**, 45% of (*Z/E*)-**44** with a ratio of 86/14]; (b) *n*-BuLi/THF/ $-78$  to  $-15$  °C; (c) MeOD [73% for (*E*)-**42** consisting of 98% (*E*), 1.5% unlabeled, 0.5% (*Z*); 58% for (*Z*)-**42** consisting of 86% (*Z*), 11% (*E*), and 3% unlabeled]; (d) AD-mix- $\beta$  (yield for (1*R*,2*R*)-[ $^2\text{H}_1$ ]**46**: 82%, containing 3% of (*R*)-**42**, ee > 97%; yield for (1*R*,2*S*)-[ $^2\text{H}_1$ ]**42**: 84%, consisting of (1*R*,2*S*)-[ $^2\text{H}_1$ ]**42**/(1*R*,2*R*)-[ $^2\text{H}_1$ ]**42**/(*R*)-**42** in a ratio of 85/12/3).

A major task was the preparation of the four reference samples, the Mosher esters of the four stereoisomeric 1-phenyl-[ $^2\text{H}_1$ ]ethane-1,2-diols with known configurations at C-1 and C-2. The latter can be accessed via Sharpless dihydroxylation<sup>33</sup> of (*E*)- and (*Z*)-[ $^2\text{H}_1$ ]vinylbenzene (**45**), giving 97% ee for the diol derived from styrene. The deuterated styrenes were obtained from phenylacetylene by literature procedures (Scheme 12). Freshly prepared triphenyltin hydride<sup>34</sup> was added to the triple bond, giving a mixture of vinylstannanes (*E*)- and (*Z*)-**44** in a ratio of 54:46. Surprisingly, Baldwin and Carter reported

(32) The analogue compound formed from the TMP derivative was isolated in 2% as a side product when carbamate **28** was stannylated according to Scheme 7.

(33) (a) Review: Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483–2547. (b) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768–2771.

(34) v. d. Kerk, G. J. M.; Noltes, J. G.; Luijten, J. G. A. *J. Appl. Chem.* **1957**, *7*, 366–369.

**Scheme 13.** Inversion of Configuration of (*R*)-**42** and Deuterated Diols (*1R,2R*)- and (*1R,2S*)-**42** at C-1<sup>a</sup>

<sup>a</sup> (a) TBDMSCl/Et<sub>3</sub>N/DMAP {for (*R*)-**46**: 87%; (*1R,2R*)-[2-<sup>2</sup>H<sub>1</sub>]**46**: 93%; (*1R,2S*)-[2-<sup>2</sup>H<sub>1</sub>]**46**: 88%}; (b) Ph<sub>3</sub>P/DIAD/PhCO<sub>2</sub>H/THF {for (*S*)-**47**: 97%; (*1S,2R*)-[2-<sup>2</sup>H<sub>1</sub>]**47**: 94%; (*1S,2S*)-[2-<sup>2</sup>H<sub>1</sub>]**47**: 95%}; (c) LiEt<sub>3</sub>BH/Et<sub>2</sub>O {for (*S*)-**46**: 85%; (*1S,2R*)-[2-<sup>2</sup>H<sub>1</sub>]**46**: 72%; (*1S,2S*)-[2-<sup>2</sup>H<sub>1</sub>]**46**: 88%}; (d) TBAF/CH<sub>3</sub>CN {for (*S*)-**42**: 99%; (*1S,2R*)-[2-<sup>2</sup>H<sub>1</sub>]**42**: 73%; (*1S,2S*)-[2-<sup>2</sup>H<sub>1</sub>]**42**: 87%, contained 12% (*1S,2R*)-[2-<sup>2</sup>H<sub>1</sub>]**42**}; (e) (*S*)-MTPACl/pyridine (81–99%).

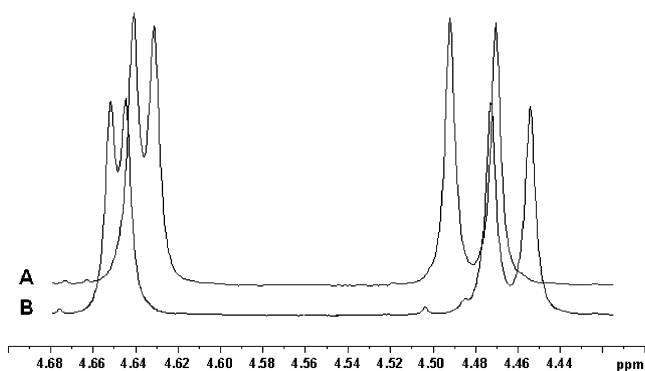
the highly selective formation of (*E*)-**44** in 74% yield.<sup>35</sup> This was advantageous in our case, as we needed both isomers, if they could be separated. It was found that crystallization from pentane furnished homogeneous (*E*)-isomer in 41% yield. Flash chromatography of the mother liquor gave an (*E/Z*)-mixture (ratio by <sup>1</sup>H NMR: 14:86) in 45% yield, sufficiently enriched in the (*Z*)-isomer. Vinylstannanes (*E*)- and (*Z/E*)-**44** were transmetalated with *n*-BuLi in THF, and the configurationally stable vinylolithiums were quenched with MeOD to give (*E*)- and (*Z/E*)-**42** in yields of 73 and 58%, respectively.<sup>35</sup> The deuterated vinylbenzenes were immediately Sharpless-dihydroxylated using AD-mix-β to furnish diols (*1R,2R*)- and (*1R,2S*)-[2-<sup>2</sup>H<sub>1</sub>]**42**, the latter in admixture with 12% of (*1R,2R*)-[2-<sup>2</sup>H<sub>1</sub>]**42**.<sup>33</sup>

The missing two stereoisomers, diols (*1S,2R*)- and (*1S,2S*)-[2-<sup>2</sup>H<sub>1</sub>]**42**, were obtained by inverting the configuration at the benzylic position of the diols accessed by dihydroxylation, which was established in the unlabeled series first (Scheme 13). Selective protection of the primary hydroxyl group of diol (*R*)-**42** with TBDMSCl/Et<sub>3</sub>N/DMAP<sup>36</sup> gave silyl ether (*R*)-**46** in 87% yield. The ensuing Mitsunobu reaction with Ph<sub>3</sub>P/diisopropyl azodicarboxylate (DIAD)/PhCO<sub>2</sub>H<sup>37</sup> produced benzoate (*S*)-**47**

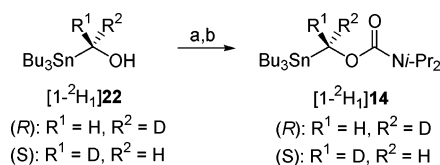
(35) Baldwin, J. E.; Carter, C. G. *J. Am. Chem. Soc.* **1982**, *104*, 1362–1368.

(36) Moreno-Dorado, F. J.; Guerra, F. M.; Ortega, M. J.; Zubía, E.; Massanet, G. M. *Tetrahedron: Asymmetry* **2003**, *14*, 503–510.

(37) Reviews: (a) Mitsunobu, O. *Synthesis* **1981**, 1–28. (b) Hughes, D. L. *Org. Prep. Proced. Int.* **1996**, *28*, 127–164.



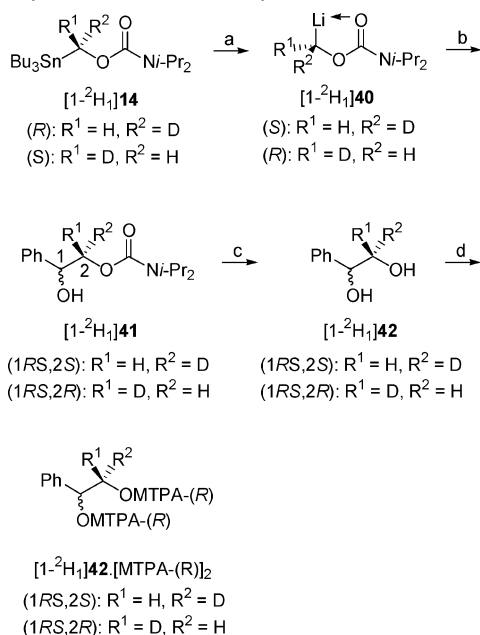
**Figure 2.** Portions of <sup>1</sup>H NMR spectra of bis(Mosher ester) recorded in CDCl<sub>3</sub> at 400 MHz. Only the doublets of the CHD groups are given. (A) Mixture of (*1S,2R*)-[2-<sup>2</sup>H<sub>1</sub>]**42**. [MTPA-(*R*)]<sub>2</sub>: δ = 4.64, *J* = 3.9 Hz and (*1R,2R*)-[2-<sup>2</sup>H<sub>1</sub>]**42**. [MTPA-(*R*)]<sub>2</sub>: δ = 4.48, *J* = 8.6 Hz. (B) Mixture of (*1R,2S*)-[2-<sup>2</sup>H<sub>1</sub>]**42**. [MTPA-(*R*)]<sub>2</sub>: δ = 4.67, *J* = 2.8 Hz and (*1S,2S*)-[2-<sup>2</sup>H<sub>1</sub>]**42**. [MTPA-(*R*)]<sub>2</sub>: δ = 4.46, *J* = 7.3 Hz.

**Scheme 14.** Transformation of Deuterated Stannylmethanols **22** into Carbamates **14**<sup>a</sup>

<sup>a</sup> (a) LiTMP/THF/−78 °C; (b) *i*-Pr<sub>2</sub>NC(O)Cl {78% for (*R*)-[1-<sup>2</sup>H<sub>1</sub>]**14**; 76% for (*S*)-[1-<sup>2</sup>H<sub>1</sub>]**14**}.

in high yield (97%). The ester was deprotected with lithium triethylborohydride and the silyl group with TBAF to give diol (*S*)-**42** of 98% ee compared to 97% of the starting diol. Basic removal of the benzoyl group resulted in partial silyl migration. Using the same sequence, we transformed the labeled diols obtained by Sharpless dihydroxylation into diols (*1S,2R*)- and (*1S,2S*)-[2-<sup>2</sup>H<sub>1</sub>]**42** containing some (*1S,2R*)-[2-<sup>2</sup>H<sub>1</sub>]**42** (12%). Finally, all four stereoisomeric diols were converted to bis-(Mosher ester). Their <sup>1</sup>H NMR (400 MHz) spectra showed that the resonances were separated enough to allow the quantitation and assignment of the configuration of the stereoisomers in a mixture, especially when recorded at 600 MHz (Figure 2).

Finally, deuterated stannylmethanols (*R*)- and (*S*)-[1-<sup>2</sup>H<sub>1</sub>]**22** were converted to carbamates **14** in yields of 78 and 76%, respectively, using LiTMP for the generation of the lithium alkoxides and commercially available *N,N*-diisopropylcarbamoyl chloride for esterification (Scheme 14). Transmetalation was routinely effected with *n*-BuLi in Et<sub>2</sub>O/TMEDA, Et<sub>2</sub>O, or THF at various temperatures to generate the corresponding chiral α-oxymethylolithiums, which were trapped with benzaldehyde after certain periods of time (Scheme 15). The derivatized diol [1-<sup>2</sup>H<sub>1</sub>]**41** was deblocked and transformed into the bis(Mosher ester). The results are summarized in Table 2. When benzaldehyde was added 3 min after the addition of *n*-BuLi, the yield of [1-<sup>2</sup>H<sub>1</sub>]**41** was 99% (entry 1). 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 chiral carbanion [1-<sup>2</sup>H<sub>1</sub>]**40** was 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 configuration at C-2 was (*S*) and the “ee” 99%. Assuming that

**Scheme 15.** Transmetalation of Carbamates **14** and Trapping of  $\alpha$ -Oxymethylolithium with Benzaldehyde<sup>a</sup>

<sup>a</sup> (a) *n*-BuLi (for solvent and temperature, see Table 2); (b) PhCHO (for yield, see Table 2); (c) LiAlH<sub>4</sub>/THF/reflux; (d) (*S*)-MTPACl/pyridine/20 °C (for ee, see Table 2).

**Table 2.** Generation of Chiral  $\alpha$ -Oxymethylolithiums **40** and Their Trapping with Benzaldehyde

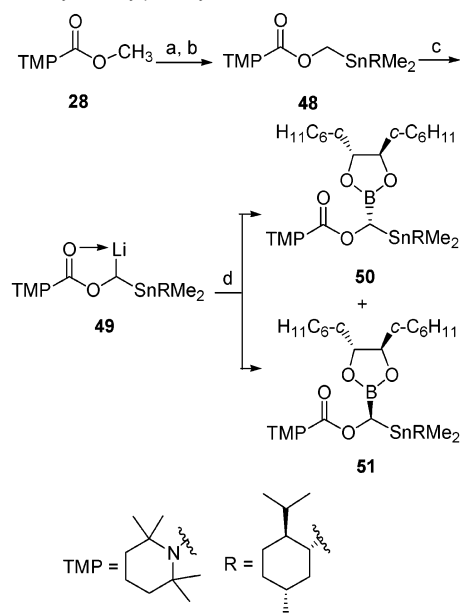
entry	[1- <sup>2</sup> H <sub>1</sub> ] <b>14</b>	solvent	temp (°C)	time (min)	yield <sup>a</sup> (%)	ee <sup>b</sup> (%)
1	( <i>R</i> )	Et <sub>2</sub> O TMEDA	-78	3	99	99
2	( <i>R</i> )	Et <sub>2</sub> O TMEDA	-78	180	79	85
3	( <i>S</i> )	Et <sub>2</sub> O TMEDA	-50	30	7	81
4	( <i>S</i> )	Et <sub>2</sub> O TMEDA	0	—	53 <sup>c</sup>	94
5	( <i>S</i> )	Et <sub>2</sub> O	-78	10	67	99
6	( <i>S</i> )	Et <sub>2</sub> O	-78	180	10	97
7	( <i>S</i> )	THF	-78	10	88	99
8	( <i>S</i> )	THF	-78	180	55	99

<sup>a</sup> Yield of carbamate [1-<sup>2</sup>H<sub>1</sub>]**41**. <sup>b</sup> Configuration at C-2. <sup>c</sup> Benzaldehyde present on addition of *n*-BuLi.

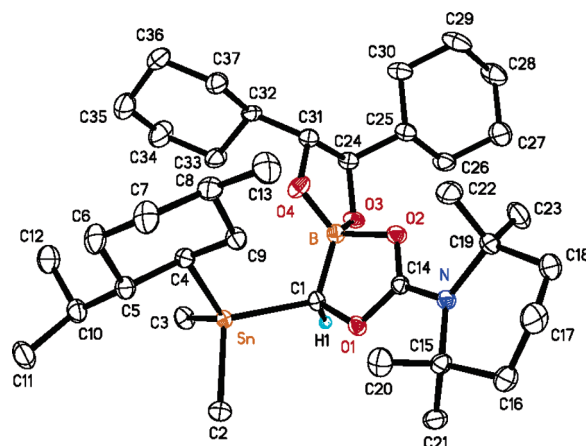
tin–lithium exchange proceeded with retention<sup>8,38,39</sup> of configuration, a cornerstone for stereochemical correlations, the  $\alpha$ -oxymethylolithium obtained from carbamate (*R*)-[1-<sup>2</sup>H<sub>1</sub>]**14** would have (*S*)-configuration. It is configurationally stable and will add to benzaldehyde with retention of configuration. Increasing the time from 3 to 180 min before the addition of the aldehyde caused the yield and “ee” to decrease to 79 and 85%, respectively (entry 2). These findings indicate that the chemical and configurational stabilities were eroding, which became very significant at -50 °C (entry 3). At 0 °C, the product could be isolated only if benzaldehyde was added to the stannane prior to *n*-BuLi. Under these conditions, the short-lived chiral  $\alpha$ -oxymethylolithium could be intercepted by the electrophile before decomposition and inverting its configuration (entry 4). To study the influence of the ligand, the next two experiments were conducted in Et<sub>2</sub>O without TMEDA with reaction times of 10 and 180 min (entries 5 and 6). In general,

(38) (a) Sawyer, J. S.; Kucerovy, A.; Macdonald, T. L.; McGarvey, G. J. *J. Am. Chem. Soc.* **1988**, *110*, 842–853. (b) Reich, H. J.; Borst, J. P.; Coplien, M. B.; Phillips, N. H. *J. Am. Chem. Soc.* **1992**, *114*, 6577–6579.

(39) Hammerschmidt, F.; Hanninger, A.; Völlenkle, H. *Chem.–Eur. J.* **1997**, *3*, 1728–1732.

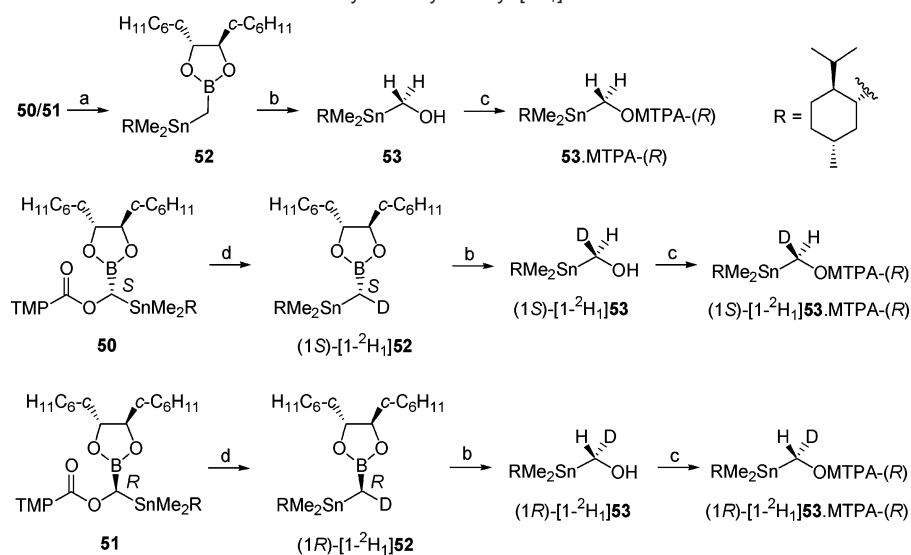
**Scheme 16.** Preparation and Borylation of (Menthylidimethylstannyl)methyl Carbamate **48**<sup>a</sup>

<sup>a</sup> (a) *s*-BuLi/TMEDA/Et<sub>2</sub>O/-78 °C/1.5 h; (b) (–)-menthylidimethyltin bromide (55%); (c) *t*-BuLi/TMEDA/Et<sub>2</sub>O/-78 °C, 1 h; (d) mixed borate of (*R,R*)-1,2-dicyclohexylethane-1,2-diol and *t*-butanol (**3**)/-78 °C/0.5 h (ratio by <sup>1</sup>H NMR: 1:1; isolated **50**: 35%, **51**: 31%).

**Figure 3.** Molecular structure of **50** in the solid state (40% ellipsoids, all hydrogen atoms except H(1) omitted for clarity).

the yields dropped to 67 and 10% compared to 99 and 79% with TMEDA. Surprisingly, the “ee” was influenced only marginally. The last two experiments performed in THF showed that the “ee” after 180 min was still unchanged (99%) and the yields were higher than in Et<sub>2</sub>O (entries 7 and 8). The low chemical stability of the  $\alpha$ -oxymethylolithium in Et<sub>2</sub>O compared to that in Et<sub>2</sub>O/TMEDA and THF is attributed to the reduced solvation of lithium by Et<sub>2</sub>O compared to TMEDA or THF. Consequently, intramolecular complexation by the carbamoyloxy group is increased, which possibly facilitates elimination of lithium *N,N*-diisopropylcarbamidate and therefore formation of methylene. From a preparative point of view, THF seems to be the solvent of choice for chiral  $\alpha$ -oxymethylolithium [1-<sup>2</sup>H<sub>1</sub>]-**40**, in which it is macroscopically configurationally stable for at least 3 h at -78 °C. The yield of the addition to an electrophile might suffer from a long reaction time because of an interfering chemical decomposition of the  $\alpha$ -oxymethylolithium.



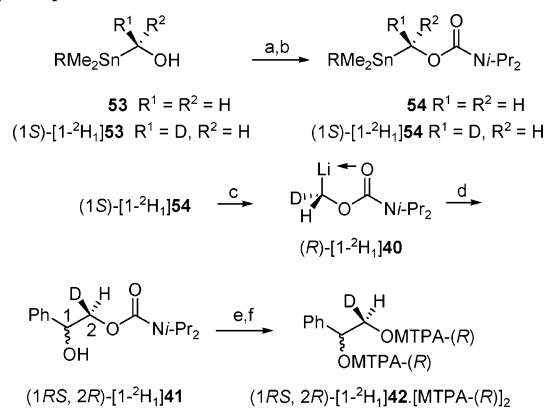
**Scheme 17.** Conversion of Boronates **50** and **51** to Menthylidimethylstannyl-[<sup>2</sup>H<sub>1</sub>]methanols **53**<sup>a</sup>

<sup>a</sup> (a) LiEt<sub>3</sub>H/Et<sub>2</sub>O/20 °C/2 h (70%); (b) H<sub>2</sub>O<sub>2</sub>/H<sub>2</sub>O/THF/NaOH/20 °C {yield for **52**: 75%; for (1*S*)-[1-<sup>2</sup>H<sub>1</sub>]**52**: 58%; for (1*R*)-[1-<sup>2</sup>H<sub>1</sub>]**52**: 85%}; (c) (S)-MTPACl/pyridine/20 °C (quantitative yields); (d) LiEt<sub>3</sub>D/Et<sub>2</sub>O/20 °C/2 h {yield for (1*S*)-[1-<sup>2</sup>H<sub>1</sub>]**52**: 69%; for (1*R*)-[1-<sup>2</sup>H<sub>1</sub>]**52**: 81%}.

### Determination of Absolute Configuration of Deuterated (Tributylstannyl)methanols.

The configuration of the deuterated (tributylstannyl)methanols can be deduced from the configuration of the corresponding boronates, plausibly assuming that the reductive removal of the carbamoyloxy group and the oxidative cleavage of the B–C bond follow an invertive and retentive course, respectively.<sup>15</sup> Unfortunately, boronates **31** and **32** were oils that could not be induced to crystallize because of the butyl substituents on tin. Therefore, the configuration of the diastereomers could not be secured by a single-crystal X-ray structure analysis. As a first option, the tributylstannyl group was replaced by the menthylidimethylstannyl one.<sup>39</sup> Thus, carbamate **28** was transformed into stannylmethyl carbamate **48** in 55% yield using (–)-menthylidimethyltin bromide<sup>40</sup> in place of tributyltin chloride for stannylation (Scheme 16). As in the tributylstannyl series, carbamate **48** was metalated with *t*-BuLi/TMEDA and borylated to give a 1:1 mixture of oily boronates **50** (*R<sub>f</sub>* = 0.55) and **51** (*R<sub>f</sub>* = 0.34) separable by flash chromatography (hexanes/ethyl acetate = 20:1). Each diastereomer contained an impurity (about 10%), which could not be removed at that stage, but at the next one. On the basis of the spectroscopic data, the impurities are related to **50** and **51** and seem to contain a *t*-butyl group instead of one of the geminal methyl groups. The less polar diastereomer **50** started to crystallize when kept neat for several weeks in the refrigerator. The (*S*)-configuration at the boron-bearing carbon atom was secured by a single-crystal X-ray structure analysis showing a noteworthy tetracoordinated boron atom (Figure 3).<sup>15,41</sup>

Consequently, the configuration of **51** at the same center is (*R*). If the two diastereomeric pairs of boronates, **31/32** and **48/49**, behave similarly, the less polar boronate **31** could also have (*S*)-configuration. To verify that, boronates **50** and **51** were subjected to the same reaction sequences as their analogues **31** and **32**. Both carbamoyloxy-substituted boronates were reduced with LiEt<sub>3</sub>H to the same boronate **52** (Scheme 17). This was

**Scheme 18.** Conversion of (Menthylidimethylstannyl)methanols to Carbamates **52** and Preparation of Chiral α-Oxymethyl lithium (*R*)-[1-<sup>2</sup>H<sub>1</sub>]**40**<sup>a</sup>

<sup>a</sup> (a) LiTMP/THF/−78 °C; (b) *i*-Pr<sub>2</sub>NC(O)Cl {84% for **54**, 80% for (1*S*)-[1-<sup>2</sup>H<sub>1</sub>]**54**}; (c) *n*-BuLi/TMEDA/Et<sub>2</sub>O/−78 °C/3 min; (d) benzaldehyde (81%); (e) LiAlH<sub>4</sub>/THF/reflux/1 h (90%); (f) (*S*)-MTPACl/pyridine/20 °C (76%).

converted first to the (menthylidimethylstannyl)methanol (**53**) and then to the Mosher ester showing in the <sup>1</sup>H NMR spectrum a diagnostic AB system ( $\delta = 4.38$ ,  $J = 11.5$  Hz). Analogously, each diastereomer was reduced with LiEt<sub>3</sub>D to give diastereomeric boronates [1-<sup>2</sup>H<sub>1</sub>]**52** under inversion of configuration (substitution of TMPCO<sub>2</sub><sup>−</sup> by D<sup>−</sup>), which ended up as diastereomeric Mosher esters of 99% de. The CHD group of the Mosher ester derived from stannylmethanol (1*S*)-[1-<sup>2</sup>H<sub>1</sub>]**53** resonated in the <sup>1</sup>H NMR spectrum as a singlet at higher field ( $\delta = 4.31$ ) than that derived from (1*R*)-[1-<sup>2</sup>H<sub>1</sub>]**51** ( $\delta = 4.41$ ), paralleling the finding in the tributylstannyl series.

To finish the chemical correlation, stannylmethanols **53** and (1*S*)-[1-<sup>2</sup>H<sub>1</sub>]**53** were esterified with *N,N*-diisopropylcarbamoyl chloride to give carbamates **54** (Scheme 18). The latter was transmetalated with *n*-BuLi in Et<sub>2</sub>O/TMEDA for 3 min at −78 °C, and the intermediate α-oxymethyl lithium was reacted with benzaldehyde. The monoprotected diol obtained in 81% yield was converted to the bis(Mosher ester). Comparison of its <sup>1</sup>H NMR spectrum with those of the reference compounds showed that the configuration at C-2 was exclusively (*R*) (“ee” 99%).

(40) Schumann, H.; Wassermann, B. C. *J. Organomet. Chem.* **1989**, 365, C1–C5.

(41) Peric Simov, B.; Rohn, A.; Brecker, L.; Giester, G.; Hammerschmidt, F. *Synthesis* **2004**, 2704–2710.

The same bis(Mosher ester) was obtained from boronate **31**, which is less polar than its diastereomer **32**. Consequently, (tributylstannyl)methylboronate **31** has (*S*)-configuration at the boron-bearing carbon atom and **32** (*R*). The configurations of the corresponding deuterated boronates **34** and the deuterated (tributylstannyl)methanols **22** can be deduced as given in Scheme 8. Therefore, we have proven independently that tin–lithium exchange and addition of the  $\alpha$ -oxymethylolithium to benzaldehyde result in net retention of configuration, best rationalized by assuming retention for both steps.

### Conclusions

We have shown that lithiated carbamates of stannylmethanols are configurationally stable at the time scale of their reaction with borates derived from (*R,R*)-1,2-dicyclohexylethane-1,2-diol and *t*-butanol. The diastereomeric boronates were stereospecifically transformed into deuterated stannylmethanols, used to prepare two types of dipole-stabilized chiral  $\alpha$ -oxymethylolithiums, the (diisopropoxy)phosphinyl- and *N,N*-diisopropylcarbamoyl-substituted ones. The former are short-lived and (microscopically) configurationally stable up to 0 °C and rearrange to  $\alpha$ -hydroxymethylphosphonates with (presumably) retention of configuration. The latter are macroscopically configurationally stable at –78 °C in Et<sub>2</sub>O/TMEDA for at least 10 min and in Et<sub>2</sub>O and THF even for 3 h, although their chemical instability

interferes heavily with increasing temperature. These  $\alpha$ -oxymethylolithiums behave as carbanions, despite their carbenoid nature.<sup>42</sup> More experiments are necessary to show whether the partial racemization of the chiral carbamoyloxy-substituted methylolithiums reflects inversion of configuration or disintegration into methylene and lithium carbamate and formation thereof. The syntheses of the chirally deuterated stannylmethanols of 99% ee will make chiral heteroatom-substituted methylolithiums a general tool in organic chemistry.

**Acknowledgment.** This work was supported by Grant No. P14985-N03 from the Fonds zur Förderung der wissenschaftlichen Forschung. We are grateful to Dr. A. Woschek for performing part of the experiments concerning the phosphate–phosphonate rearrangement, S. Felsing and C. Tyl for recording the NMR spectra and Dr. L. Brecker for help with the interpretation of NMR spectra.

**Supporting Information Available:** All experimental procedures and spectroscopic data. X-ray crystallographic data of **24** in PDF and CIF formats. This material is available free of charge via the Internet at <http://pubs.acs.org>.

JA066183S

(42) Köbrich, G. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 473–485.