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Enantiopure Chiral (2,4,6-Triisopropylbenzoyl)oxy-[D_1]methyllithium: Configurational Stability, Reactions, and Mechanistic Studies

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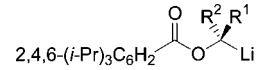

1: $R^1 = R^2 = H$

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

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

The configurational stability of enantiopure chiral (2,4,6-triisopropylbenzoyl)oxy-[D_1]methyllithium generated by a tin−lithium exchange was tested on the macroscopic time scale, employing trapping experiments with benzaldehyde. It was found to be configurationally stable for minutes at −78 °C and to be an appropriate substitute for the carbamoyloxy-substituted analogue in terms of cleavage. Its addition to several electrophiles was studied, leading to a protocol for the preparation of chiral primary deuterated alcohols, exemplified by the synthesis of 2-phenyl-[1-D_1]ethanol of 98% enantiomeric excess (ee). Furthermore, the mechanisms of enantiomerization and decomposition of this aroyloxymethyllithium were addressed by spectroscopic investigations of labeled substrates. It decomposed by formation of ethylene (minor pathway) and homologation of *n*-BuLi by up to three methylene units, followed by an exchange for a butyl group of Bu_4Sn.

Introduction

Organolithiums of diverse structures are the most important of all organometallic reagents, due to their easy availability, secure handling, and high reactivity with many functional groups. Their selectivity has led to multifold applications, made even more attractive by the development of configurationally stable species. The first to report on an enantiomerically enriched organolithium was Letsinger, who described the preparation of 2-lithiooctane in 1951.[1] The breakthrough came when Still and Sreekumar found that α-oxy-substituted organolithiums were configurationally stable up to −30 °C.[2] They turned out to be more configurationally stable than their nitrogen- and sulfur-substituted analogues. Finally, Hoppe's group discovered that primary alcohols with a carbamoyl protecting group (e.g., Cbx, Cby) based on an oxazolidine could be metalated highly enantioselectively α to oxygen by using *s*-BuLi/(−)-sparteine.[3,4] Beak et al. reported the synthesis of 2,6-disubstituted benzoates of primary alcohols, their lithiation to dipole-stabilized carbanions such as **1** (Figure 1), their reaction with various electrophiles, and their reductive cleavage with $LiAlH_4$.[5,6] Later studies focused on the configurational stability and stereochemistry of reactions of tertiary benzyllithiums **2**,[7,8] **3**,[9] and **4**,[9] which proved

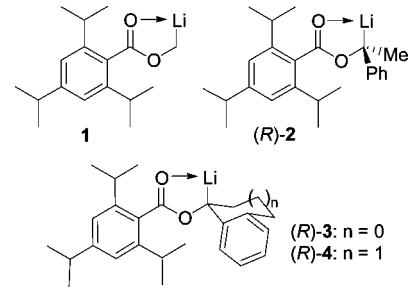

FIGURE 1. Known (2,4,6-triisopropylbenzoyl)oxy-substituted alkyllithiums.

(1) Letsinger, R. L. *J. Am. Chem. Soc.* **1950**, *72*, 4842.
(2) Still, W. C.; Sreekumar, C. *J. Am. Chem. Soc.* **1980**, *102*, 1201–1202.
(3) Hoppe, D.; Hintze, F.; Tebben, P. *Angew. Chem.* **1990**, *102*, 1457−1459; *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1422−1424.
(4) (a) Hoppe, D.; Hense, T. *Angew. Chem.* **1997**, *109*, 2376−2410; *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2282−2316. (b) Hoppe, D.; Christoph, G. In *The Chemistry of Organolithium Compounds,* Rappoport, Z., Marek, I., Eds.; John Wiley & Sons Ltd.: Chichester, U.K., 2004; Part 2, pp 1055−1164.
(5) Beak, P.; McKinnie, B. G. *J. Am. Chem. Soc.* **1977**, *99*, 5213.
(6) Beak, P.; Carter, L. G. *J. Org. Chem.* **1981**, *46*, 2363–2373.
(7) Hammerschmidt, F.; Hanninger, A. *Chem. Ber.* **1995**, *128*, 1069–1077.

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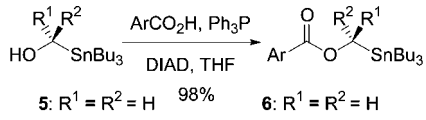
SCHEME 1. Preparation of Stannane Precursors 6 and [D$_1$]6[a]



[a] DIAD = diisopropyl azodicarboxylate; Ar = 2,4,6-(*i*-Pr)$_3$C$_6$H$_2$.

to be less configurationally stable than their (*N*,*N*-diisopropylcarbamoyl)oxy-substituted analogues.[10,11]

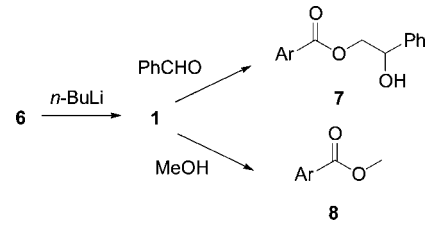
To expand the scope of the chiral heteroatom-substituted methyllithiums (XCHDLi), which so far include carbamoyloxy,[12] silyloxy-,[13] germyloxy-,[13] 2-alkenyloxy-,[13] and chloro-substituted[14] ones, we decided to prepare the (2,4,6-triisopropylbenzoyl)oxy-substituted version [1-D$_1$]**1** as well.

Besides studying its macroscopic configurational stability and reactions with several electrophiles, we wanted to explore its potential for the preparation of enantiopure chiral primary deuterated alcohols. Finally, we addressed its mechanisms of enantiomerization and decomposition.

Results and Discussion

Macroscopic Configurational Stability of (2,4,6-Triisopropylbenzoyl)oxy-[D$_1$]methyllithium. In analogy to previous studies, we wanted to prepare enantiopure [1-D$_1$]**1** from the corresponding tributylstannane precursor via tin−lithium exchange, easily accessible from enantiopure (99% enantiomeric excess (ee)) (*R*)- and (*S*)-tributylstannyl-[D$_1$]methanol ([D$_1$]**5**).[12] For the optimization of reaction conditions, unlabeled **5** was reacted with 2,4,6-triisopropylbenzoic acid in a Mitsunobu reaction[15] (S_N2) in almost quantitative yield (Scheme 1). The esterification in the deuterated series proceeded with inversion of configuration. To investigate the macroscopic configurational stability of [1-D$_1$]**1**, we intended to perform several experiments involving the aging of the organolithium before trapping it with benzaldehyde as an electrophile. This would allow a direct comparison with the previously tested carbamoyloxy-substituted analogue.[12] But beforehand, the feasibility of transmetalation and quenching was established in the unlabeled series (Scheme 2). Therefore, various conditions were tested by changing the temperature and the solvent (Table 1). The first experiment was performed in Et$_2$O/TMEDA at −78 °C, and benzaldehyde was added 3 min after the addition of *n*-BuLi, which gave racemic alcohol **7** in an 80% yield. Unfortunately, monoprotected diol **7** could not be separated by flash chromatography from 1-phenylpentanol, which was formed from excess *n*-BuLi and benzaldehyde. It did not matter here as the side product could be removed at a later stage. To ensure that tin−lithium exchange was complete before addition of benzaldehyde, the experiment was repeated with methanol as the trapping agent to give methyl ester **8** quantitatively (entry 2, Table 1). Otherwise, some transmetalation could have occurred after the addition of benzaldehyde. The overall result would then reflect a combination of macroscopic and microscopic configurational stability in the labeled series.

SCHEME 2. Testing of Transmetalation/Quenching in the Unlabeled Series[a]



[a] Ar = 2,4,6-(*i*-Pr)$_3$C$_6$H$_2$.

TABLE 1. Reaction Conditions and Yields of 7

entry	solvent	temp (°C)	time (min)	yield[a] (%)
1	Et$_2$O/TMEDA	−78	3	80
2[b]	Et$_2$O/TMEDA	−78	3	93
3	Et$_2$O/TMEDA	−50	3	55
4	THF	−50	3	78
5[c]	Et$_2$O/TMEDA	0		53

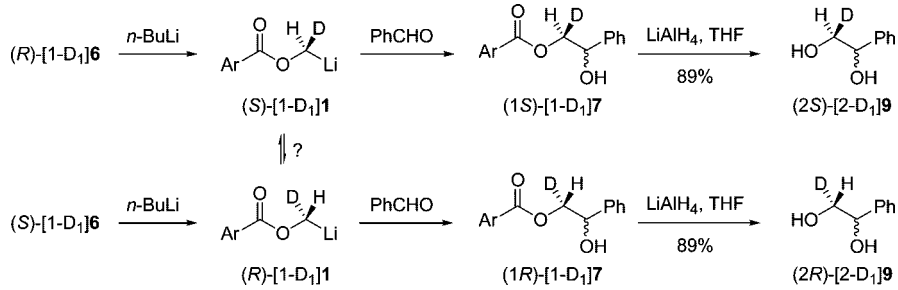
[a] Determined from ^{1}H NMR spectra of the chromatographed products (contaminated with 1-phenylpentanol). [b] With MeOH as electrophile. [c] Benzaldehyde (5 equiv) already present on addition of *n*-BuLi (5 equiv).

When transmetalation and addition to benzaldehyde were performed at −50 °C in Et$_2$O/TMEDA or THF, the yield was higher in the latter solvent, having a stabilizing effect on **1** (entries 3 and 4, Table 1). When the reaction temperature was increased to 0 °C, no alcohol **7** could be isolated, because carbanion **1** had already decomposed on addition of the aldehyde. Therefore, the microscopic configurational stability was addressed at 0 °C by intercepting the short-lived carbanion with benzaldehyde, which was added before *n*-BuLi, each in large excess (entry 5, Table 1). The yield of **7** was 53% and indicated that the tin−lithium exchange was faster than the addition of *n*-BuLi to benzaldehyde and that the carbanion was long-lived enough at 0 °C to add to benzaldehyde before chemical decomposition.

The experiments in the labeled series were performed similarly. To determine the configuration at the deuterium bearing carbon atom, benzoate [1-D$_1$]**7** derived from ester (*R*)-[1-D$_1$]**6** was converted to diol [2-D$_1$]**9**. The side product 1-phenylpentanol could now be removed easily by flash column chromatography from the diol, which was esterified with (*S*)-MTPACl to give the bis-(*R*)-Mosher ester for ^{1}H NMR spectroscopic analysis (Scheme 3).[12] For the sake of clarity it is more convenient here to give the enantiomeric excess (ee) for each chiral center individually. As the addition of chiral carbanion [1-D$_1$]**1** to benzaldehyde is not enantioselective, the benzylic center of [2-D$_1$]**9** is always racemic, resulting in a product with zero diastereomeric excess (de). However, the configuration at C-2 of [2-D$_1$]**9** for entry 1 (Table 2) was mainly (*S*) (>97%), resulting in an ee of 95%. Assuming that the tin−lithium exchange proceeds with retention[16] of configuration,

(8) Hammerschmidt, F.; Hanninger, A.; Völlenkle, H. *Chem.−Eur. J.* **1997**, *3*, 1728–1732.
(9) Hammerschmidt, F.; Hanninger, A.; Peric Simov, B.; Völlenkle, H.; Werner, A. *Eur. J. Org. Chem.* **1999**, 3511–3518.
(10) (a) Hoppe, D.; Carstens, A.; Krämer, T. *Angew. Chem.* **1990**, *102*, 1455−1456; *Angew. Chem., Int. Ed. Engl.* **1990** *29*, 1424−1425. (b) Carstens, A.; Hoppe, D. *Tetrahedron* **1994**, *50*, 6097–6108.
(11) Derwing, C.; Frank, H.; Hoppe, D. *Eur. J. Org. Chem.* **1999**, 3519–3524.
(12) Kapeller, D.; Barth, R.; Mereiter, K.; Hammerschmidt, F. *J. Am. Chem. Soc.* **2007**, *129*, 914–923.
(13) Kapeller, D. C.; Brecker, L.; Hammerschmidt, F. *Chem.−Eur. J.* **2007**, *13*, 9582–9588.
(14) Kapeller, D. C.; Hammerschmidt, F. *J. Am. Chem. Soc.* **2008**, *130*, 2329–2335.
(15) (a) Reviews: Mitsunobu, O. *Synthesis* **1981**, 1−28. (b) Hughes, D. L. *Org. Prep. Proc. Int.* **1996**, *28*, 127–164.

SCHEME 3. Testing of the Configurational Stability of [D$_1$]1[a]



[a] Ar = 2,4,6-(*i*-Pr)$_3$C$_6$H$_2$.

TABLE 2. Reaction Conditions and Yields of [1-D$_1$]7

entry	substrate	solvent	temp (°C)/time (min)	yield[a]/ee (%)
1	(*R*)-[D$_1$]**6**	Et$_2$O/TMEDA	−78/3	88/95
2	(*S*)-[D$_1$]**6**	Et$_2$O/TMEDA	−78/180	75/73
3	(*S*)-[D$_1$]**6**	Et$_2$O/TMEDA	−50/3	70/78
4	(*R*)-[D$_1$]**6**	Et$_2$O/TMEDA	0/−	59/86
5	(*S*)-[D$_1$]**6**	THF	−78/10	76/98
6	(*S*)-[D$_1$]**6**	THF	−78/180	70/50

[a] Determined from ^{1}H NMR spectra of the chromatographed products (contaminated with 1-phenylpentanol).

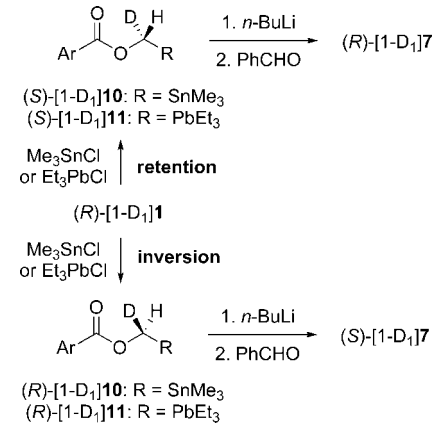
benzoyloxymethyllithiums obtained from benzoates (*R*)-[1-D$_1$]**6** and (*S*)-[1-D$_1$]**6,** should have (*S*) and (*R*) configurations, respectively. As they are configurationally stable, they will have to add to benzaldehyde with retention of configuration as proven by entry 1 (Table 2). It was found that [1-D$_1$]**1** did not racemize in Et$_2$O/TMEDA and THF for short periods of time (3 and 10 min, respectively) at −78 °C (entries 1 and 5 in Table 2). When the carbanion was aged for 3 h before adding benzaldehyde, the yields were only slightly reduced, but the ee's were significantly lower, in THF even more so than in Et$_2$O/TMEDA (entries 2 and 6, Table 2). Raising the temperature to −50 °C caused an erosion of the ee to 78% within only 3 min of aging of the carbanion (entry 3, Table 2). When the transmetalation was performed at 0 °C under microscopic conditions, the ee at C-2 was still 86% (entry 4, Table 2), demonstrating that chiral oxymethyllithium [1-D$_1$]**1** was microscopically configurationally labile.

In summary, aroyloxy-substituted chiral [1-D$_1$]methyllithiums were found to be slightly less configurationally stable than their *N*,*N*-diisopropylcarbamoyl analogues but could, under the appropriate conditions, form monoprotected diols [2-D$_1$]**9** with an ee of up to 98% at the deuterated center on addition to benzaldehyde.

Trimethyltin and Triethyllead Chloride as Electrophiles. The stereochemistry concerning the trapping of an organolithium species is strongly influenced by the electrophile used.[16] Aldehydes or H$^+$ usually react under retention of configuration, while inversion is observed with alkyl, acyl, or stannyl halides. This effect is especially pronounced with benzyllithiums having a flattened carbanion.[16] In the case of benzaldehyde, we found exclusive retention of configuration on reaction with (2,4,6-triisopropylbenzoyl)oxy-[D$_1$]methyllithium. Would this change if a reagent known to prefer inversion of configuration was used, even though our carbanion was not a stabilized one? To test this, we decided to employ trimethyltin and triethyllead chloride

(16) (a) Reich, H. J.; Borst, J. P.; Coplien, M. B.; Phillips, N. H. *J. Am. Chem. Soc.* **1992**, *114*, 6577–6579. (b) Clayden, J. *Organolithiums: Selectivity for Synthesis*; Tetrahedron Organic Chemistry Series; Pergamon (An imprint of Elsevier Science): Oxford, 2002; Vol. 23.

SCHEME 4. Trapping of Oxymethyllithium [1-D$_1$]1 with Me$_3$SnCl or Et$_3$PbCl, Followed by Transmetalation and Addition of the Regenerated [1-D$_1$]1 to PhCHO, Starting from (*R*)-[1-D$_1$]1[a]



[a] Ar = 2,4,6-(*i*-Pr)$_3$C$_6$H$_2$.

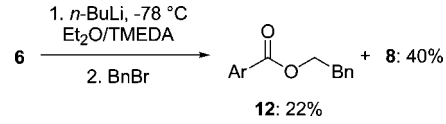
TABLE 3. Reaction Conditions and Yields of [1-D$_1$]7 Prepared via Stannane [1-D$_1$]10 or Plumbane [1-D$_1$]11

entry	substrate/intermediate	solvent	temp (°C)/time (min)	yield[a]/ee (%)
1	(*R*)-[D$_1$]**6**/(*R*)-[D$_1$]**9**	Et$_2$O/TMEDA	−78/3	62/96
2	(*S*)-[D$_1$]**6**/(*S*)-[D$_1$]**9**	THF	−78/10	77/38
3	(*S*)-[D$_1$]**6**/(*S*)-[D$_1$]**10**	THF	−78/5	53/8

[a] Determined from ^{1}H NMR spectra of the chromatographed products (contaminated with 1-phenylpentanol).

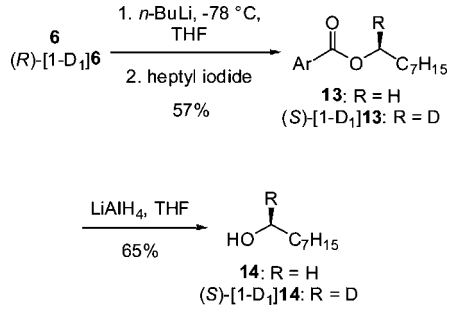
as electrophiles in a two step reaction sequence (Scheme 4). Thus, enantiopure stannane [1-D$_1$]**6** was transmetalated using *n*-BuLi at −78 °C in the respective solvent, and the intermediate oxymethyllithium [1-D$_1$]**1** was trapped with either trimethyltin or triethyllead chloride (Table 3). To determine whether retention or inversion of configuration had occurred, stannane [1-D$_1$]**10** and plumbane [1-D$_1$]**11** were not isolated but immediately transmetalated, and the oxymethyllithium formed was quenched with benzaldehyde under conditions where no enantiomerization had been observed before (−78 °C, 5 min). This gave alcohols [1-D$_1$]**7**, whose ee's were secured by reductive deprotection of [1-D$_1$]**7** and esterification of the diols with (*S*)-Mosher chloride in pyridine (Scheme 3). Surprisingly, complete overall retention of configuration (ee of 96%) was observed, when Et$_2$O/TMEDA was used as the solvent and trimethyltin chloride as the electrophile, added 3 min after addition of *n*-BuLi (entry 1 in Table 3). Consequently, stannylation followed a retentive course, the same as addition of [1-D$_1$]**1** to benzaldehyde. Changing the solvent to THF, which was found to lower the configurational stability of [1-D$_1$]**1**, the ee of diol [1-D$_1$]**7**

SCHEME 5. Transmetalation/Alkylation Sequence with Stannane 6[a]



[a] Ar = 2,4,6-(*i*-Pr)$_3$C$_6$H$_2$.

SCHEME 6. Transmetalation/Alkylation Sequence with Heptyl Iodide[a]



[a] Ar = 2,4,6-(*i*-Pr)$_3$C$_6$H$_2$.

was significantly reduced to 38% with aging of the carbanion for 10 min (entry 2, Table 3). This result underlines that the solvent has a significant influence on the configurational stability of the intermediate oxymethyllithium. Anticipating later results, we think that one reason for that might be the opening of the five-membered chelate ring by the stronger lithium-coordinating effect of THF rather than Et_2O in combination with TMEDA, which is a prerequisite for inversion of configuration of the carbanion.[17] When this experiment was repeated, except that trimethyltin chloride was replaced by triethyllead chloride, almost racemic monoprotected diol [1-D$_1$]**7** was formed having an ee of 8% at the deuterium-bearing carbon atom with retention still predominating slightly.

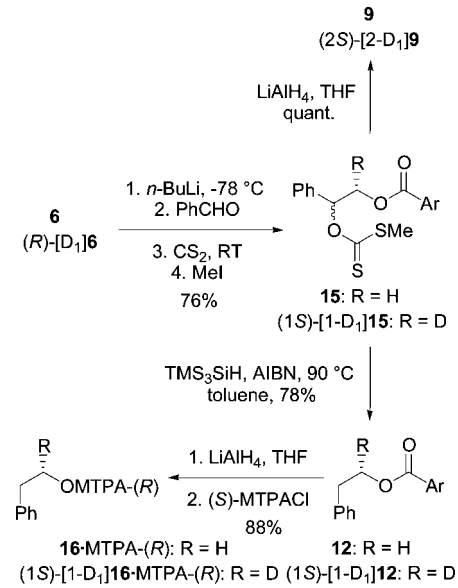
Preparation of Chirally Labeled Primary Alcohols. We also envisaged the synthesis of enantiopure primary deuterated alcohols of known configuration by alkylation of oxymethyllithium [1-D$_1$]**1** with alkyl halides. In a preliminary experiment benzyl bromide was used as a highly reactive electrophile (Scheme 5).

When performing the transmetalation for 3 min in Et_2O/TMEDA with the nondeuterated stannane **6** and waiting with the workup for 30 min after addition of benzyl bromide, we isolated the desired benzyl ester **12** in merely 22% yield. However, the main product (40%) was methyl ester **8**, indicating that alkylation of methyllithium was possibly slow and not yet finished before aqueous workup. When THF was used as solvent and the reaction time for alkylation extended to 3 h, the yield of 2-phenylethyl benzoate **12** did not improve either (28%). These disencouraging results induced us to try heptyl iodide as an alternative electrophile with chiral oxymethyllithim [1-D$_1$]**1** (Scheme 6).

In an exploratory experiment with the unlabeled oxymethyllithium, we were able to isolate 57% of unlabeled **13**, which seemed enough to repeat the reaction with labeled stannane (*R*)-[D$_1$]**6**. Transmetalation was performed at −78 °C in THF for 10 min as usual before addition of heptyl iodide, followed by an aqueous workup 1 h later. The octyl ester [D$_1$]**13** could be

(17) Basu, A.; Thayumanavan, S. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 717–738.

SCHEME 7. Preparation of Enantiopure 2-Phenyl-[1-D$_1$]ethanol−Xanthogenate Route[a]



[a] Ar = 2,4,6-(*i*-Pr)$_3$C$_6$H$_2$.

isolated in a 57% yield. $LiAlH_4$-mediated reduction finally gave C-1 deuterated 1-octanol, whose ee could be determined via its (*R*)-Mosher ester. Comparison of its ^{1}H NMR spectra with those reported in the literature[13] revealed an ee of 29%, which was probably mainly due to an interfering radical mechanism[18] and to a lesser extent to some enantiomerization on aging of the enantiopure carbanion before alkylation.

These findings effectively ruled out the preparation of enantiomerically pure primary deuterated alcohols by alkylation of aroyloxy-[1-D$_1$]methyllithium with alkyl halides and by deprotection. To avoid alkylation, we thought of a sequence involving addition of chiral oxymethyllithium [1-D$_1$]**1** to an aldehyde, followed by deoxygenation to give the 2,4,6-triisopropylbenzoate of a primary deuterated alcohol. The most promising route seemed to be the intermediate formation of a xanthogenate in a one-pot reaction, reminiscent of the Barton−McCombie protocol.[19]

To this end, stannane **6** and later (*R*)-[D$_1$]**6** were transmetalated (THF, −78 °C, 5 min) and the intermediate carbanion was trapped with benzaldehyde. The lithium alkoxide formed was reacted with carbon disulfide and subsequently methyl iodide to give xanthogenate (1*S*)-[1-D$_1$]**15** in an average yield of 79% (Scheme 7).

But before optimizing deoxygenation, we checked if enantiomerization had occurred at the deuterated center. Therefore, xanthogenate (1*S*)-[1-D$_1$]**15** was quantitatively reduced with $LiAlH_4$ to deuterated 1-phenylethane-1,2-diol of 98% ee at C-2 as determined by ^{1}H NMR spectroscopy of the bis-(*R*)-Mosher ester.[12] Then, unlabeled and labeled **15** were treated with tris(trimethylsilyl)silane/AIBN[20] in toluene at 90 °C to afford esters **12** and (1*S*)-[1-D$_1$]**12** in 78% yield, which were in turn deprotected to finally yield 2-phenylethanols (**16**) (Scheme 7). At this stage we again determined the ee of deuterated (*S*)-[1-D$_1$]**16** to rule out enantiomerization during the radical

(18) Ashby, E. C. *Acc. Chem. Res.* **1988**, *21*, 414–421.

(19) (a) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574–1585. For a review see: (b) Hartwig, W. *Tetrahedron* **1983**, *39*, 2609–2645.

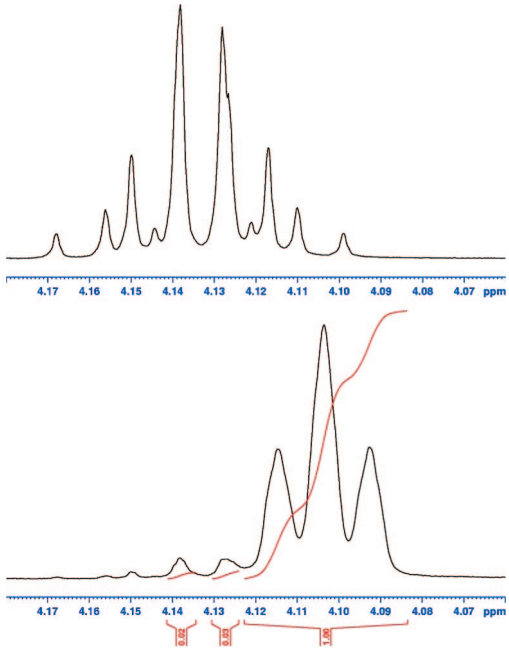


FIGURE 2. Sections of ^{1}H NMR spectra (400 MHz, toluene-d_8) of **16**·MTPA-(*R*) (top) and (1*S*)-[1-D$_1$]**16**·MTPA-(*R*) (bottom).

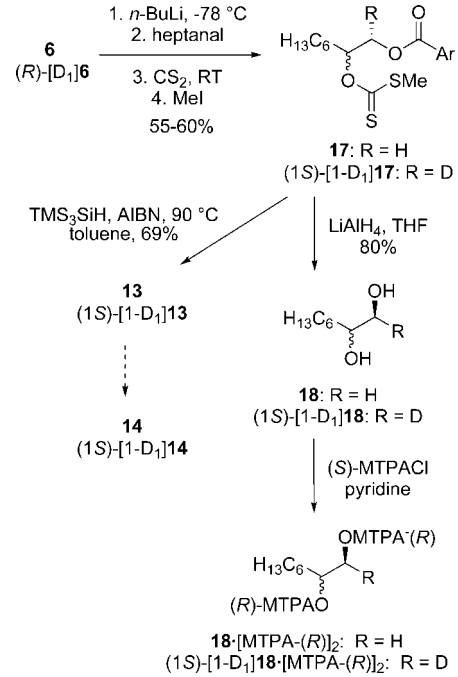
mediated step of deoxygenation. Again, the (*R*)-Mosher esters were formed and investigated by ^{1}H NMR spectroscopy. Unlabeled **16**·MTPA-(*R*) showed a tripletic AB system at δ = 4.13 (J_{AB} = 10.9 Hz, J = 7.1 Hz). In the labeled series, a broadened triplet at δ = 4.10 (J = 6.6 Hz) was found for the CHD group. Decoupling of the neighboring CH_2 group did not bring any further information, as the peaks were too broad to be well separated. No signal was found that could be attributed to the diastereomeric Mosher ester, indicating that 2-phenyl-[1-D$_1$]ethanol was enantiomerically pure (Figure 2). This claim was supported by calculating the relative chemical shifts for the hydrogens of the AB system in the unlabeled series and subtracting the deuterium induced isotope shift.[21] Chemical shifts of ν_A = 4.123 ppm and ν_B = 4.101 ppm were found, the latter in good agreement with the 4.104 ppm of labeled (1*S*)-[1-D$_1$]**16**·MTPA-(*R*). There was no significant peak at 4.12 ppm apart from resonances of the unlabeled compound (2−3%).

After our success with benzaldehyde, we wanted to test this procedure on an aliphatic aldehyde as well and decided to use heptanal, as we had a reference sample of the (*R*)-Mosher ester for the resulting [1-D$_1$]octanol.[13] Thus, the same sequence was repeated, except that benzaldehyde was replaced by heptanal (Scheme 8). This time, the yield of xanthogenate **17** was lower (55−60%) which could be likely due to the enolization of heptanal by the oxymethyllithium, giving methyl ester **8** isolated as well (16%). Believing that we did not have to determine the ee of the xanthogenate directly after our success with 2-phenylethanol, we immediately deoxygenated it, which gave octyl ester **13** and its deuterated analogue in a 69% yield. Surprisingly, the latter had an ee of 89% as determined by ^{1}H NMR spectroscopy of the (*R*)-Mosher ester of the respective 1-[1-D$_1$]-octanol {[1-D$_1$]**14**} obtained after reductive removal of the 2,4,6-triisopropylbenzoyl group (Scheme 6).

(20) For a review see: (a) Chatgilialoglu, C. *Acc. Chem. Res.* **1992**, *25*, 191–194. (b) Schummer, D.; Höfle, G. *Synlett* **1990**, 705–706.

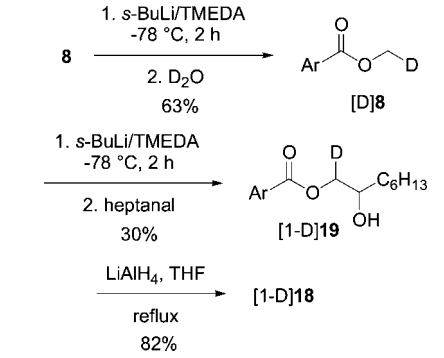
(21) Günther, H. *NMR-Spektroskopie*; Georg Thieme Verlag: Stuttgart, 1973, 163−165.

SCHEME 8. Preparation of Labeled Octanol (1*S*)-[1-D$_1$]14−Xanthogenate Route[a]



[a] Ar = 2,4,6-(*i*-Pr)$_3$C$_6$H$_2$.

SCHEME 9. Synthesis of Labeled Octane-1,2-diol [1-D]18[a]



[a] Ar = 2,4,6-(*i*-Pr)$_3$C$_6$H$_2$.

We reasoned that perhaps in this instance the fault lay with the deoxygenation. Thus, again a sample of xanthogenate (*S*)-[D$_1$]**13** was reduced to (1*S*)-[1-D$_1$]octane-1,2-diol, which was converted to the bis-(*R*)-Mosher esters (1*S*,2*RS*)-[1-D$_1$]**18**·[MTPA-(*R*)]$_2$ (Scheme 8). The Mosher esters diastereomeric at C-2 could be separated by flash column chromatography. Additionally, we prepared unlabeled and racemic deuterated reference samples of diol **18**. Therefore, methyl ester **8** was deprotonated with *s*-BuLi/TMEDA and quenched with D_2O to give 63% of a 5:4 mixture of [D$_1$]**8** and **8** (Scheme 9).

This mixture was again treated with *s*-BuLi and trapped with heptanal (−78 °C, 2 h), yielding 30% of [1-D]**19** (labeled/unlabeled compound 5:4), which was reduced to diol [1-D]**18**, a mixture of four stereoisomeric deuterated octane-1,2-diols and racemic nondeuterated octane-1,2-diol, with $LiAlH_4$ (see Scheme 8) and transformed into the bis-(*R*)-Mosher esters for recording reference ^{1}H NMR spectra. Comparison of these spectra with those of the bis-(*R*)-Mosher ester of the 1,2-diol derived from xanthogenate (1*S*)-[1-D$_1$]**17** allowed unequivocal assignment of the peaks, especially after reducing the number of relevant signals by irradiation at 2-H of the diol portion (Figure 3). The

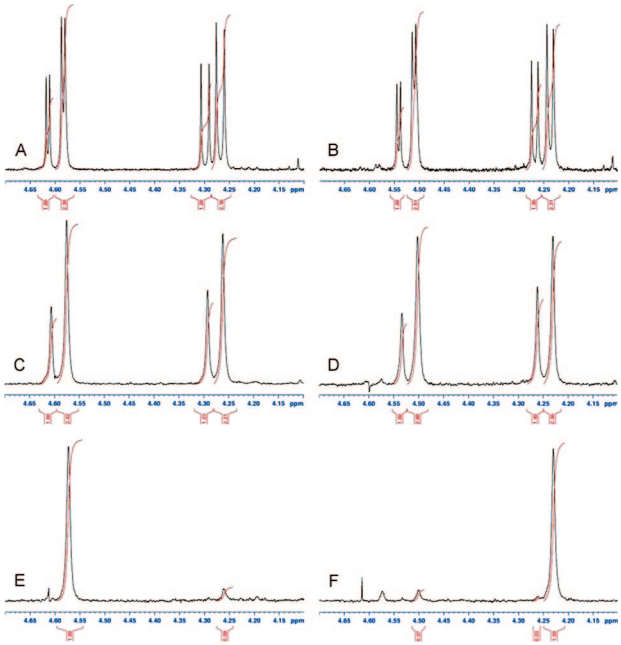
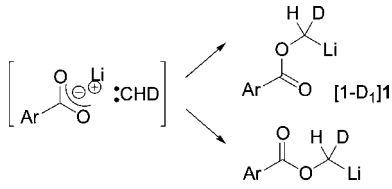


FIGURE 3. Signals of CH_2O/CHDO groups in the ^{1}H NMR spectra (400 MHz, $CDCl_3$) of [1-D]**18**·[MTPA-(*R*)]$_2$ and (1*S*)-[1-D$_1$]**18**·[MTPA-(*R*)]$_2$ derived from stannane (*R*)-[1-D$_1$]**6**. (A) (1*R*/*S*,2*R*)-[D]**18**·[MTPA-(*R*)]$_2$. (B) (1*R*/*S*,2*S*)-[D]**18**·[MTPA-(*R*)]$_2$. (C) (1*R*/*S*,2*R*)-[D]**18**·[MTPA-(*R*)]$_2$ after irradiation at 4.3 ppm. (D) (1*R*/*S*,2*S*)-[D]**18**·[MTPA-(*R*)]$_2$ after irradiation at 4.3 ppm. (E) (1*S*,2*R*)-[1-D$_1$]**18**·[MTPA-(*R*)]$_2$ of 85% ee at C-1 after irradiation at 4.3 ppm. (F) (1*S*,2*S*)-[1-D$_1$]**18**·[MTPA-(*R*)]$_2$ of 89% ee at C-1 after irradiation at 4.3 ppm.

SCHEME 10. Proposed Mechanism for Enantiomerization Of (*R*)-[1-D$_1$]1[a]



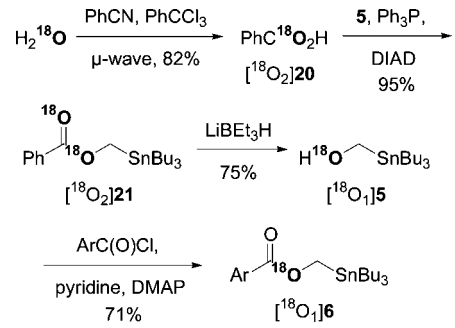
[a] Ar = 2,4,6-(*i*-Pr)$_3$C$_6$H$_2$.

ee of 85% at C-1 was found for (1*S*)-[1-D$_1$]**18**·[MTPA-(*R*)]$_2$, proving that enantiomerization did not occur during radical deoxygenation but evidently during addition of the carbanion to heptanal. We do not have a plausible explanation for this finding, as intermediate oxymethyllithium [D$_1$]**1** is configurationally stable under these conditions. The mechanism that initially comes to mind is a single electron transfer between heptanal and oxymethyllithium, which caused enantiomerization before radical combination. But if that was indeed the case, one would expect even more enantiomerization with benzaldehyde as the electrophile, which is not supported by our experiments.

Mechanistic Studies toward the Enantiomerization of [1-D$_1$]1. None of the mechanisms concerning enantiomerization of organolithiums in the literature seemed to describe this particular species, and thus we hypothesized that inversion of configuration could involve the intermediate formation of lithium 2,4,6-triisopropylbenzoate and deuteromethylene, which could recombine with either oxygen of the benzoate to give enantiomers of [1-D$_1$]**1** (Scheme 10).

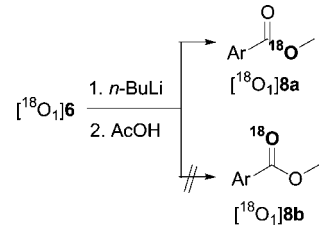
To demonstrate that, regiospecifically ^{18}O-labeled stannane **6** was prepared starting from oxygen-18 labeled water (87% ^{18}O). It was reacted with a mixture of benzonitrile and trichloromethylbenzene in a microwave reactor to give doubly ^{18}O-labeled benzoic acid[22] in an 80% yield (79% [^{18}O$_2$], 17% [^{18}O$_1$], 4% unlabeled, by MS) (Scheme 11).

SCHEME 11. Synthesis of Regiospecificly ^{18}O Labeled 6[a]



[a] Ar = 2,4,6-(*i*-Pr)$_3$C$_6$H$_2$.

SCHEME 12. Transmetalation of [^{18}O$_1$]6 and Quenching of Intermediate Oxymethyllithium with AcOH[a]



[a] Ar = 2,4,6-(*i*-Pr)$_3$C$_6$H$_2$.

TABLE 4. Conditions and Yields for Transmetalation of [^{18}O$_1$]6 and Quenching of Carbanion with AcOH

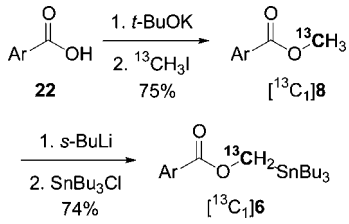
entry	solvent	temp (°C)	time	yield (%)
1	THF	−78	5 h	61
2	Et_2O/TMEDA	−50	5 min	76
3	THF	−30	3 min	12

Mass spectroscopic analysis revealed in all three cases that the isolated ester was only isotopomer [^{18}O$_1$]**8a**, thus the carbene was excluded as an intermediate for enantiomerization of chiral [D$_1$]**1**, which is undoubtedly significant at −30 °C beside chemical decomposition (entry 3, Table 4).

Mechanistic Studies toward the Decomposition of [1-D$_1$]1. Extensive experience with oxymethyllithium **1** proved it to be a chemically labile compound. It started to decompose around −50 °C and rapidly vanished at −30 °C. So far, we had no conclusive explanation for the mechanism, although we strongly suspected the formation of ethylene or insertion into the solvent (e.g., THF), common pathways for the decomposition of α-heteroatom-substituted organolithiums.[23] The analytical method of choice was ^{13}C NMR spectroscopy. To ease the tracing of the carbon atom in question, the starting stannane was ^{13}C-

(22) (a) Tanaka, N.; Araki, M. *J. Am. Chem. Soc.* **1985**, *107*, 7780–7781. (b) Schwab, J. M.; Ray, T.; Ho, C.-K. *J. Am. Chem. Soc.* **1989**, *111*, 1057–1063. (c) Wnuk, S. F.; Chowdhury, S. M.; Garcia, P. I., Jr.; Robins, M. J. *J. Org. Chem.* **2002**, *67*, 1816–1819.

SCHEME 13. Preparation of ^{13}C-Labeled 6[a]



[a] Ar = 2,4,6-(*i*-Pr)$_3$C$_6$H$_2$.

labeled. Thus, 2,4,6-triisopropylbenzoic acid (**22**) was converted to the potassium salt and alkylated with [$^{13}C_1$]methyl iodide. The ester formed was metalated and stannylated to give the required precursor [$^{13}C_1$]**5** (Scheme 13).

A sample of 30 mg of this compound was transmetalated at −78 °C in dry [D_8]THF in an NMR tube under argon. Afterward, NMR spectra (^{1}H, ^{13}C, HSQC, and HMBC) were recorded at −70, −50, −30, and +20 °C. As expected, the signal for O^{13}CH$_2$Li could be clearly seen at −70 °C (Figure 4) in the ^{13}C NMR spectrum (100 MHz), where it resonated as a broad singlet at δ = 83.6 ppm, shifted to lower field by $\Delta\delta$ = 31.5 ppm compared with the unlithiated compound. The signal at δ = 52.1 ppm resulted from the methyl group of methyl ester [1-$^{13}C_1$]**8** formed by protonation of [1-$^{13}C_1$]**1** due to traces of residual water. The ^{1}H spectrum showed a broad doublet at δ = 3.75 ppm with a rather small coupling constant $J \sim 109$ Hz, only 0.05 ppm downfield of [1-$^{13}C_1$]**8**. To the best of our knowledge, there are no comparable experimental values for an aroyloxy-substituted organolithium found in the literature. But there is an example from Boche et al., who reported that the CH$_2$O group of lithiated methyl *N*,*N*-diisopropyl carbamate in Et$_2$O resonated at 67.3 ppm, just shifted to a lower field by 7.0 ppm compared with the respective unlithiated species.[24] This rather small difference was attributed to the dipole-stabilized lithium-containing chelate ring, which was assumed to be the prevailing structure in Et$_2$O.[24] On the contrary, the shift difference of 31.5 ppm found by us for aroyloxymethyllithium **1** and methyl ester **8** in THF corresponds better to an alkoxy-substituted carbenoid than to a carbanion in a chelate ring. This is another argument for the increasing lithium-coordinating effect of THF to break down the chelate structure in favor of the carbenoid nature of **1**.

Following the course of the reaction in the NMR tube by ^{13}C NMR spectroscopy (Figure 4) revealed that the concentration of the lithiated species decreased by going from −70 to −50 °C but completely disappeared at −30 °C. The increasing signal at 123.5 ppm stemmed from ethylene,[25] although its low intensity spoke against this being the main decomposition pathway. Surprisingly, another signal around 9 ppm was detected that steadily increased in intensity at rising temperature. It was attributed to a ^{13}CH$_2$ group bound to tin, when taking the satellites with large coupling constants into account [$J(^{117/119}\mathrm{Sn})$ = 314.0, 300.1 Hz]. There were two possibilities for the formation of a stannane containing a Sn^{13}CH$_2$ group: First, direct insertion of [$^{13}C_1$]methylene into a Sn−C bond of tetrabutyltin, which seemed unlikely, and second, the reaction of excess *n*-BuLi with [$^{13}C_1$]**1** to give [1-$^{13}C_1$]pentyllithium, followed by an exchange of a butyl group of tetrabutyltin for the [1-$^{13}C_1$]pentyl group. The time difference between disappearance of [1-$^{13}C_1$]**1** and formation of tributyl-[1-$^{13}C_1$]pentyltin was an indication for the latter, as the exchange of substituents at tin seemed to need a higher temperature than the formation of [1-$^{13}C_1$]pentyllithium.

When we left the NMR tube at ambient temperature over 18 h, the signals of methyl ester [1-$^{13}C_1$]**8** disappeared. The contents of the NMR tube were worked up with dilute HCl and the crude product was investigated by ^{13}C NMR spectroscopy. Besides the already expected tributyl-[1-$^{13}C_1$]pentylstannane (10−30%, roughly estimated from the intensity of the peaks), also some tributyl-[1,2-$^{13}C_2$]hexylstannane (approximately one-third of the pentyl analogue) and traces of tributyl-[1,2,3-$^{13}C_3$]heptylstannane could be detected (Figure 5). This is another point in favor of the second pathway, as it would be easier for pentyllithium to attack another molecule of [$^{13}C_1$]**1** to form hexyllithium than exchange for a butyl group of tetrabutyltin. The products originating from the homologation of *n*-BuLi and insertion into tetrabutyltin only accounted for part of the ^{13}C, most of it went undetected. However, a mixture of stannanes and 2,4,6-triisopropylbenzoic acid could be recovered quantitatively.

To study the influence of the alkyllithium on the product distribution of the decomposition, two more test reactions with MeLi instead of *n*-BuLi were performed in a flask. Stannane [1-$^{13}C_1$]**1** was treated with 2.0 and 1.2 equiv of MeLi at −60 °C, and the reaction mixture was allowed to warm to −10 °C, before it was worked up under acidic conditions. Surprisingly, the amount of MeLi did not affect the outcome of the experiments. In analogy to the results with *n*-BuLi, a resonance at δ = 0.76 [$J(^{117/119}\mathrm{Sn})$ = 319.9, 305.2 Hz] was found in the ^{13}C NMR spectrum, revealing CH$_3$^{13}CH$_2$SnBu$_3$ (in about a 5% yield). Again, we were faced with the fact that most of the label was unaccounted for, about 10% of it was recovered as methyl ester [1-$^{13}C_1$]**8**.

Conclusions

In summary, we demonstrated that enantiopure aroyloxy-[D_1]methyllithium [1-D_1]**1** was macroscopically configurationally stable for minutes at −78 °C, as proven by trapping experiments performed with benzaldehyde. When the organolithium was aged for extended periods of time or at an elevated temperature, partial enantiomerization occurred, which was more pronounced in THF than in Et$_2$O/TMEDA as the solvent. Alkylation of [1-D_1]**1** with heptyl iodide afforded a partly racemized product of 29% ee, while benzyl bromide reacted too slowly to warrant further testing.

The usefulness of aroyloxymethyllithium [1-D_1]**1** as a general synthon for the preparation of stereospecifically deuterated compounds was demonstrated by the synthesis of chirally deuterated primary alcohols in an aldehyde-addition/deoxygenation sequence. It worked best for 2-phenyl-[1-D_1]ethanol (98% ee) but less well for [1-D_1]octanol (ee of <90%) starting from benzaldehyde and heptanal, respectively. Furthermore, the mechanism of racemization and decomposition of [1-D_1]**1** was investigated via isotope labeling and mass/NMR spectroscopic analysis. An intermediate carbene could be ruled out, as well as its insertion into THF. Experiments in the NMR tube followed by recording ^{13}C NMR spectra at increasing temperatures revealed that [1-$^{13}C_1$]**1** decomposed with formation of some ethylene and tetraalkylstannanes containing ^{13}CH$_2$Sn, (^{13}CH$_2$)$_2$Sn, and (^{13}CH$_2$)$_3$Sn fragments in decreasing quantity. The high downfield shift of the CH$_2$O signal of [1-$^{13}C_1$]**1**

(23) For a review see: (a) Boche, G.; Lohrenz, J. C. W. *Chem. Rev.* **2001**, *101*, 697–756. (b) Köbrich, G. *Bull. Soc. Chim. Fr.* **1969**, 2712–2720. (c) Köbrich, G.; Flory, K.; Fischer, H. R. *Chem. Ber.* **1966**, *99*, 1793–1804.

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

(25) Sadykov, R. A.; Shishlov, N. M. *J. Organomet. Chem.* **1989**, *369*, 1–7.

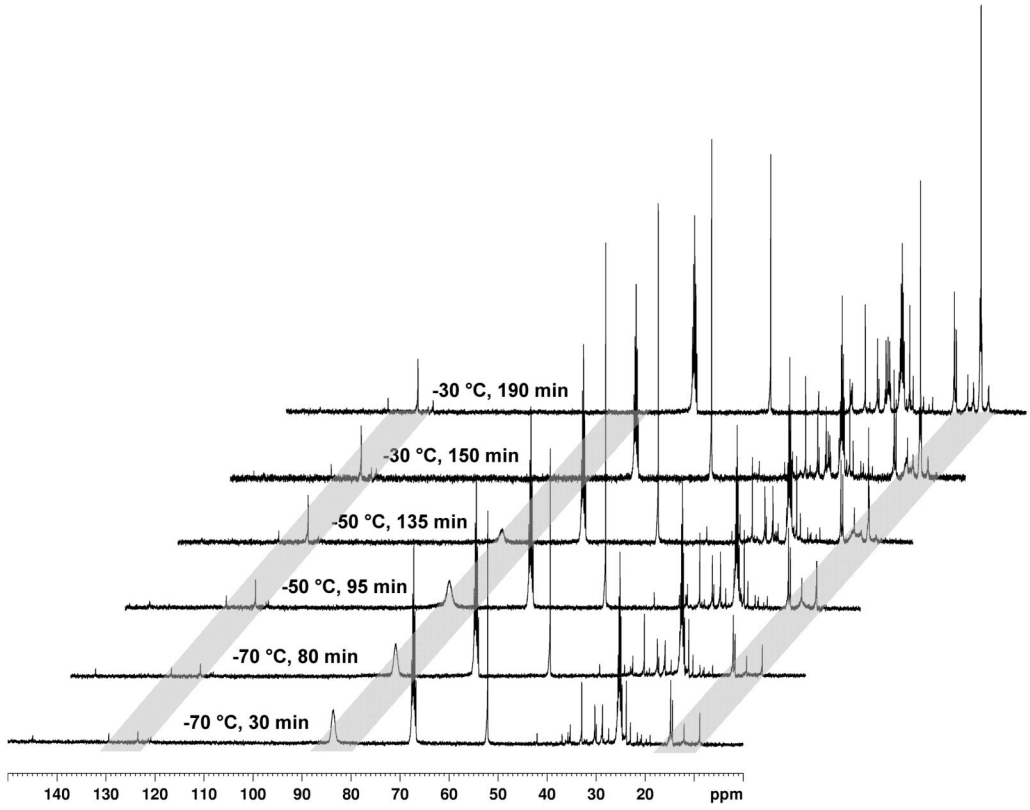


FIGURE 4. ^{13}C NMR spectra (100 MHz, THF-d_8) at various time (addition of *n*-BuLi, $t = 0$) and temperature intervals. The gray areas highlight (from left to right) the formation of ethylene, the disappearance of [^{13}C$_1$]**1**, and the formation of $^{13}CH_2Sn$.

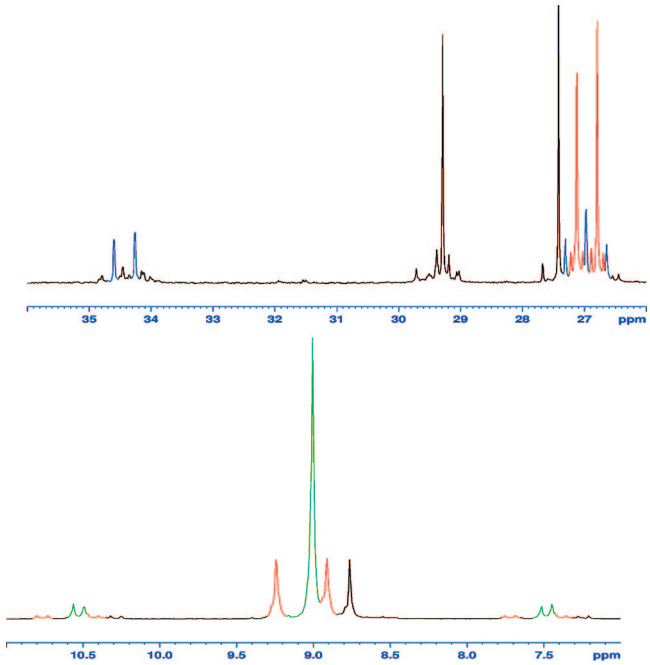


FIGURE 5. ^{13}C NMR spectrum (100.6 MHz, $CDCl_3$) of the crude product obtained from the reaction mixture in the NMR tube. Blue: ^{13}C signals of tributyl-[1,2,3-$^{13}C_3$]heptylstannane. Red: ^{13}C signals of tributyl-[1,2-$^{13}C_2$]hexylstannane. Green: ^{13}C signals of tributyl-[1-^{13}C$_1$]pentylstannane. Black: signals of tetrabutyltin.

compared with the CH_3O of its unlithiated analogue ($\Delta\delta = 31.5$ ppm in the ^{13}C NMR spectrum) underlines the high carbenoid character of this aroyloxyorganolithium species.

Experimental Section

Tributylstannylmethyl 2,4,6-Triisopropylbenzoate (6), (*S*)-[D$_1$]6, and (*R*)-[D$_1$]6. Tributylstannylmethanol (482 mg, 1.50 mmol), triphenylphosphine (472 mg, 1.80 mmol), and 2,4,6-triisopropylbenzoic acid (447 mg, 1.80 mmol) were dissolved in dry THF (6 mL) under argon. The solution was cooled to −20 °C, before addition of DIAD (346 mg, 350 μL, 1.80 mmol), and afterward stirred for 3 h (−20 °C → RT). Water (0.1 mL) was added, and the crude product was concentrated on a rotary evaporator and purified by flash chromatography (hexane/CH_2Cl_2 4:1, R_f 0.21) to yield benzoate **6**[5] as a colorless oil (811 mg, 98%): IR (Si) ν 2960, 2926, 1717, 1607, 1465, 1289, 1068 cm^{-1}; ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 6.97 (s, 2H$_{arom}$), 4.36 (s, $J(^{117/119}Sn) =$ 13.6 Hz, 2H), 2.86 (sept, $J = 6.8$ Hz, 1H), 2.77 (sept, $J = 6.8$ Hz, 2H), 1.55−1.46 (m, 6H), 1.29 (sext, $J = 7.3$ Hz, 6H), 1.22 (d, $J =$ 6.8 Hz, 6H), 1.21 (d, $J = 6.8$ Hz, 12H), 0.98−0.92 (m, 6H), 0.87 (t, $J = 7.3$ Hz, 9H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 172.2, 149.9, 144.8 (2C), 131.0, 120.7 (2C), 55.1 ($J(^{117/119}Sn) =$ 300.6, 286.0 Hz), 34.4, 31.6 (3C), 29.0 ($J(^{117/119}Sn) =$ 21.4 Hz, 3C), 27.3 ($J(^{117/119}Sn) =$ 54.3 Hz, 3C), 24.2 (2C), 23.9 (2C), 13.7 (3C), 9.5 ($J(^{117/119}Sn) =$ 333.5, 319.7 Hz, 3C).

(*S*)-[D$_1$]6: $[\alpha]^{20}_D$ +0.72 and $[\alpha]^{20}_{365}$ +2.76 (c 12.63, acetone). The spectroscopic data were identical to those of **6**, except for the following:^{1}H NMR (600.13 MHz, $CDCl_3$) δ 4.34 (s, $J(^{117/119}Sn) =$ 13.2 Hz, 1H) with a deuterium induced upfield shift of 12.8 Hz; ^{13}C NMR (150.90 MHz, $CDCl_3$) δ 54.87 (t, $J = 21.2$ Hz, 1C).

(*R*)-[D$_1$]6: $[\alpha]^{20}_D$ −0.70 and $[\alpha]^{20}_{365}$ −2.66 (*c* 14.94, acetone). The spectroscopic data were identical to those of (*S*)-[D$_1$]**6**.

(±)-2-Hydroxy-2-phenylethyl 2,4,6-Triisopropylbenzoate (7), (*S*)-[D$_1$]7, and (*R*)-[D$_1$]7. Macroscopic Conditions. Tributylstannylmethyl 2,4,6-triisopropylbenzoate (132 mg, 0.24 mmol) and TMEDA (55 mg, 72 μL, 0.48 mmol) were dissolved in dry solvent (2 mL) under argon and cooled to the respective temperature. *n*-BuLi (0.30 mL, 1.6 M solution in hexane, 0.48 mmol) was added,

and after the respective time span, the reaction was quenched with benzaldehyde (0.265 mL, 2 M solution in Et_2O, 0.53 mmol). After stirring for 30 min at bath temperature, a saturated aq solution of $NaHCO_3$ (3 mL) was added. The organic phase was separated and the aq one extracted with Et_2O (3 × 5 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude mixture was purified by flash chromatography (hexane/EtOAc 7:1; TLC, hexane/EtOAc 3:1, R_f 0.55) to yield an inseparable mixture of 1-phenyl-1-pentanol and the product **7** that was once separated by recrystallization from hexane (for results see Table 1 and 2).

Microscopic Conditions. Tributylstannylmethyl 2,4,6-triisopropylbenzoate (132 mg, 0.24 mmol), benzaldehyde (0.60 mL, 2 M solution in Et_2O, 1.2 mmol), and TMEDA (139 mg, 0.18 mL, 1.2 mmol) were dissolved in dry Et_2O (2 mL) under argon and cooled to 0 °C. *n*-BuLi (0.75 mL, 1.6 M solution in hexane, 1.2 mmol) was added, and the solution stirred for 30 min before workup, which was done according to the procedure for the macroscopic experiments.

7: mp 78−79 °C (hexane); IR (Si) ν 3470, 2962, 2930, 2871, 1728, 1462, 1252, 1139, 1077 cm^{-1}; ^1H NMR (400.13 MHz, $CDCl_3$) δ 7.45−7.41 (m, $2H_{arom}$), 7.39−7.28 (m, $3H_{arom}$), 7.00 (s, $2H_{arom}$), 5.04 (X-part of ABX-system, J = 8.1, 3.4 Hz, 1H), 4.47 (AB-part of ABX-system, J = 11.5, 8.1, 3.4 Hz, 2H), 2.88 (sept, J = 6.8 Hz, 1H), 2.81 (sept, J = 6.8 Hz, 2H), 2.51 (br s, 1H), 1.23 (d, J = 6.8 Hz, 1H), 1.21 (d, J = 6.8 Hz, 12H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 170.9, 150.4, 144.9 (2C), 139.6, 129.9, 128.6 (2C), 128.2, 126.2 (2C), 120.9 (2C), 72.3, 69.6, 34.4, 31.5 (2C), 24.1 (2C), 24.1 (2C), 23.9 (2C). Anal. Calcd for $C_{24}H_{32}O_3$: C, 78.22; H, 8.75. Found: C, 78.05; H, 8.66.

[D_1]7: ^1H NMR data were identical to that of **7**, except for the following: ^1H NMR (250.13 MHz, $CDCl_3$) δ 5.04 (d, J = 3.4 Hz, 1H, diastereomer A), 5.03 (d, J = 8.1 Hz, 1H, diastereomer B), 4.50 (d, J = 3.4 Hz, 1H, diastereomer A), 4.41 (d, J = 8.1 Hz, 1H, diastereomer B).

Tributylstannylmethyl [$^{18}O_2$]Benzoate ([$^{18}O_2$]21). To a mixture of [$^{18}O_2$]benzoic acid (330 mg, 2.50 mmol), tributylstannylmethanol[26] (883 mg, 2.75 mmol; prepared by addition of tributylstannyllithium[27] generated from hexabutylditin and *n*-BuLi at 0 °C to paraformaldehyde and stirred for 2 h at 0 °C), and triphenylphosphine (721 mg, 2.75 mmol) in dry THF (10 mL) under argon was added DIAD (0.54 mL, 2.75 mmol) at 0 °C. The reaction was stirred overnight at RT and quenched with a few drops of water. The solvent was then removed under reduced pressure, and the residue was purified by flash chromatography (hexane/CH_2Cl_2 2:1, R_f 0.44) to give ester [$^{18}O_2$]**21** as a colorless oil (1.02 g, 95%).

IR (Si): ν 2956, 2944, 2921, 1680, 1315, 1285, 1091 cm^{-1}. ^1H NMR (400.13 MHz, $CDCl_3$): δ 8.00−7.96 (m, $2H_{arom}$), 7.54−7.48 (m, $1H_{arom}$), 7.43−7.37 (m, $2H_{arom}$), 4.41 (s, $J(^{117/119}Sn)$ = 11.9 Hz, 2H), 1.56−1.46 (m, 6H), 1.27 (sext, J = 7.3 Hz, 6H), 0.97−0.91 (m, $J(^{117/119}Sn)$ = 51.8, 49.8 Hz, 6H), 0.85 (t, J = 7.3 Hz, 9H). ^{13}C NMR: (100.61 MHz, $CDCl_3$) δ 167.6, 132.5, 130.6, 129.3 (2C), 128.3 (2C), 56.4 ($J(^{117/119}Sn)$ = 305.9, 292.2 Hz), 29.0 ($J(^{117/119}Sn)$ = 20.6 Hz, 3C), 27.3 ($J(^{117/119}Sn)$ = 54.3 Hz, 3C), 13.7 (3C), 9.7 ($J(^{117/119}Sn)$ = 333.5, 318.2 Hz, 3C).

[$^{18}O_1$]Tributylstannylmethanol ([$^{18}O_1$]5). To a solution of tributylstannylmethyl [$^{18}O_2$]benzoate (1.00 g, 2.30 mmol) in dry Et_2O (23 mL) was added superhydride (5.06 mL, 1 M solution in THF, 5.06 mmol) at 0 °C under argon. The reaction was stirred for 1 h at RT and then quenched with acetone (2 mL). Furthermore, water was added (15 mL), the organic layer was separated, and the aq one extracted with Et_2O (3 × 15 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure, and the residue was purified by flash chromatography (hexane/EtOAc 10:1, R_f 0.36) to give stannylmethanol [$^{18}O_1$]**5** as a colorless oil (558 mg, 75%) that was spectroscopically identical to the unlabeled compound.[12]

Tributylstannylmethyl 2,4,6-Triisopropyl-[$^{18}O_1$]benzoate ([$^{18}O_1$]6). To a solution of [^{18}O]tributylstannylmethanol (680 mg, 2.11 mmol) in dry pyridine (12 mL) was added 2,4,6-triisopropylbenzoyl chloride (845 mg, 3.20 mmol) and DMAP (30 mg, 0.25 mmol) under argon. The reaction was stirred for 8 h at 50 °C, before adding another portion of the acid chloride (280 mg, 1.10 mmol). Two hours later pyridine was removed under reduced pressure, and the residue dissolved in a mixture of EtOAc (15 mL) and 1 M HCl (15 mL). The organic phase was separated and the aqueous one extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine and dried ($MgSO_4$), and the solvent was removed on a rotary evaporator. Afterward, the crude product was purified by flash chromatography (hexane/CH_2Cl_2 4:1, R_f 0.26) to give benzoate [$^{18}O_1$]**6** as a colorless oil (828 mg, 71%).

The spectroscopic data were identical to those of the unlabeled compound (see above), except for the following: ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 55.1 ($J(^{117/119}Sn)$ = 307.2, 293.5 Hz), with an oxygen-18 induced shift of 0.03 ppm to higher field.

[$^{13}C_1$]Methyl 2,4,6-Triisopropylbenzoate ([$^{13}C_1$]8). To a mixture of 2,4,6-triisopropylbenzoic acid (1.76 g, 7.10 mmol) and KO*t*-Bu (797 mg, 7.10 mmol) in dry THF (20 mL) under argon was added $^{13}CH_3I$ (1.00 g, 7.00 mmol, dissolved in 4 mL of dry THF). The resulting white slurry was stirred for 2 days at RT. Water (20 mL) and Et_2O (10 mL) were added, the organic phase was separated, and the aq one extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with a saturated aq solution of $NaHCO_3$ (25 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was purified by flash chromatography (hexane/CH_2Cl_2 2:1, R_f 0.30) to yield [$^{13}C_1$]**8** as colorless crystals (1.37 g, 75%, 99% ^{13}C).

The spectroscopic data were identical to those of the unlabeled compound, except for the following:^1H NMR (400.13 MHz, $CDCl_3$) δ 3.86 (d, J = 147.0 Hz, 3H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 51.7 of 100-fold intensity. MS (EI): m/z 263 (37.1, M^+), 248 (52.9, $M^+ - {}^{13}CH_2$), 230 (100.0, $M^+ - {}^{13}CH_3OH$).

Tributylstannyl-[$^{13}C_1$]methyl 2,4,6-Triisopropylbenzoate ([$^{13}C_1$]6). [^{13}C]Methyl 2,4,6-triisopropylbenzoate (790 mg, 3.0 mmol) and TMEDA (0.54 mL, 418 mg, 3.6 mmol) were dissolved in dry THF (9 mL) under argon. *s*-BuLi (2.8 mL, 1.3 M solution in cyclohexane, 3.6 mmol) was added at −78 °C, and the mixture was stirred for 2 h at that temperature. Afterward, the reaction was quenched with tributyltin chloride (1.22 g, 3.75 mmol in 2 mL of dry THF). Stirring was continued for another 45 min before the addition of a saturated aq solution of $NaHCO_3$ (2 mL) and water (10 mL). The organic phase was separated and the aq one extracted with Et_2O (3 × 15 mL). The combined organic layers were dried ($MgSO_4$), concentrated under reduced pressure, and purified by flash chromatography (hexane/CH_2Cl_2 4:1, R_f 0.42) to yield [$^{13}C_1$]**6** as a colorless liquid (1.23 g, 74%).

The spectroscopic data were identical to those of the unlabeled compound (see above), except for the following: ^1H NMR (400.13 MHz, $CDCl_3$) δ 4.36 (d, $J(^{117/119}Sn)$ = 13.7 Hz, J = 144.0 Hz, 2H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 55.2 ($J(^{117/119}Sn)$ = 306.7, 293.7 Hz) of 100-fold intensity.

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

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