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Preparation of Enantiopure Chiral Amino-[D_1]methyllithium Compounds and Determination of Their Micro- and Macroscopic Configurational Stabilities

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Abstract: Chiral amino-[D_1]methyllithiums have been tested with regard to their microscopic and macroscopic configurational stabilities. The *N*-Boc-*N*-diethoxyphosphinyl-substituted analogue immediately rearranged, showing complete retention of configuration at up to 0 °C. The *N*-Boc-*N*-PMB-protected analogue enantiomerized at −78 °C, but displayed an *ee* value of 65 % at −95 °C under macroscopic conditions when quenched with benzaldehyde seconds after its generation. Isocyanomethyllithium proved to be configurationally labile at this temperature and racemized completely, even on the microscopic timescale. Only the non-stabilized *N*,*N*-dibenzylaminomethyllithium was found to be virtually macroscopically configurationally stable below −95 °C.

Keywords: chirality · configuration analysis · tin–lithium exchange

Introduction

Chirality is of pivotal importance in chemistry and biology. The synthesis of enantiomerically pure compounds is still one of the main topics in organic chemistry. Combinations of the chiral methyl group (CHDT), chiral by virtue of the three isotopes of hydrogen, and a substituent such as CO_2H, NH_2, CN, or OH represent the smallest compounds that can exist as enantiomers. The first synthesis of such a compound in the form of chiral acetic acid by the groups of Cornforth and Arigoni and its use in the elucidation of reaction mechanisms in chemistry and enzymology were milestone achievements.[1,2] Recent years have witnessed an increased interest in chiral, nonracemic α-heteroatom-substituted alkylmetals, especially alkyllithiums, sparked by the research of Still and Sreekumar.[3] They found that α-oxy-substituted derivatives are configurationally stable up to −30 °C and react stereospecifically with electrophiles. Hoppe et al. prepared highly enantiomerically enriched α-oxyalkyllithiums by enantioselective metalation of carbamates derived from primary alcohols using *s*BuLi/(−)-sparteine.[4] Hoffmann et al. developed a method for the determination of the configurational stability of alkyllithiums.[5] Structural studies[6] and quantum chemical calculations[7] have underlined the importance of the heteroatom for the configurational stability of these compounds. In summary, it has been found that stability decreases in the following sequence: O > N > S.[8]

Many dipole-stabilized aminoorganolithiums can be prepared directly by metalation with alkyllithiums and are synthetically very useful reagents.[9–14] However, *N*,*N*-dialkylaminomethyllithiums can only be generated by tin–lithium exchange (Figure 1, **1**–**5**).[15–17] The enantioselective preparation, configurational stability, and reactivity of secondary α-aminoalkyllithiums have been extensively studied by the groups of Beak, Gawley, and others.[10,12,17–21] The configurationally most stable α-aminoorganolithiums are the 2-lithio-*N*-methyl-pyrrolidines and -piperidines, which retain their configurations at up to −40 °C.[18,22,23]

$R^1R^2N-CH_2Li$

1: $R^1 = R^2 = Me$
2: $R^1 = Ph$, $R^2 = Me$
3: $R^1 = R^2 = Ph$
4: $R^1 = Bn$, $R^2 = Me$
5: $R^1 = R^2 = Bn$

Figure 1. Survey of several aminomethyllithiums.

Until recently, no methyllithium of the general formula XCHDLi (X = heteroatom or heteroatom-containing functional group), which we refer to as chiral methyllithiums, has been accessible. These species are the smallest possible

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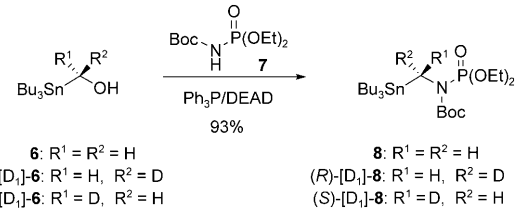
chiral organolithiums and represent the calculated species better than those in which deuterium is replaced by an alkyl group. We have found that carbamoyloxy-,[24a] (2,4,6-triisopropylbenzoyl)oxy-,[24b] and chloromethyllithium[25] are macroscopically configurationally stable at low temperature. Herein, we report our findings on the preparation and configurational stability of four chiral aminomethyllithiums. Microscopic configurational stability[5] refers to the configurational stability of a chiral, enantioenriched carbanion relative to the rate of an intramolecular reaction or its reaction with an electrophile already present upon the generation of the carbanion (in situ quenching). Macroscopic configurational stability, on the other hand, refers to prior formation of the enantioenriched carbanion, its aging for some time (here from 30 seconds to minutes), and finally its reaction with an added electrophile.

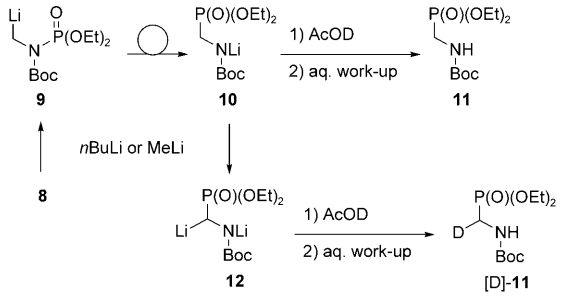
Results and Discussion

Microscopic configurational stability: To study the microscopic configurational stability of a dipole-stabilized aminomethyllithium (relative to its reaction), the phosphoramidate–aminophosphonate rearrangement was chosen.[26] It is an intramolecular isomerization with a short-lived aminomethyllithium as intermediate and therefore allows comparison with its oxygen analogue, the phosphate–hydroxyphosphonate rearrangement.[24a] We again chose the enantiopure tributylstannyldeuteromethanols (*ee* 99%) as precursors, which are easily prepared in five steps.[24a] However, before performing the reactions in the labeled series, unlabeled **6** was first transformed into **8** in 93% yield by a Mitsunobu reaction with phosphoramidate **7**[27] to optimize the reaction conditions (Scheme 1). The conversion was then repeated with (*R*)- and (*S*)-[D_1]-**6** (S_N2).



Scheme 1. Preparation of stannanes **8**.

It was then possible to start testing the conditions for the transmetalation/rearrangement sequence by treating unlabeled **8** with an alkyllithium (Scheme 2, Table 1). We feared that excess RLi might further metalate the intermediate product **10** α to the phosphorus atom to give dilithiated **12**, reminiscent of a similar observation concerning the rearrangement of *N*-benzyl-*N*-Boc phosphoramidate.[26] This would lead to a decrease in *ee* in the labeled series, assuming **12** to be configurationally labile. To test this, stannane **8** was transmetalated at −78 °C with 2.5 equiv of *n*BuLi or MeLi, respectively, and then quenched with AcOD after 15 min (entries 1 and 2 in Table 1). In the former case, over 100% deuterium incorporation was found by NMR spectroscopy, confirming that intermediate aminophosphonate **10** had been lithiated by excess *n*BuLi. With MeLi, the yield of aminophosphonate **11** was higher and only partial deuteration was observed ($D_1 = 57\%$). Reducing the amount of *n*BuLi from 2.5 to 1.1 equiv resulted in comparable yields at −78 and 0 °C (entries 3 and 4). However, in both cases about 20–30% of the starting material was recovered. In the case of MeLi (1.25 equiv, 0 °C) no starting material was present (entry 5).



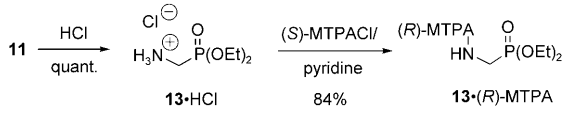
Scheme 2. Transmetalation and rearrangement of **8**; tests relating to dilithiation.

Table 1. Transmetalation/rearrangement in the unlabeled series: conditions and results.

Entry	RLi (equiv)	*T* [°C]	*t* [min]	Yield[a] [%]
1	*n*BuLi (2.5)	−78	15	57[b]
2	MeLi (2.5)	−78	15	79[c]
3	*n*BuLi (1.1)	−78	30	56[d]
4	*n*BuLi (1.1)	0	0.5	57[e]
5	MeLi (1.25)	0	1	69

[a] Determined by NMR spectroscopic analysis of the crude product. [b] Quenching with AcOD led to 115% deuterium incorporation. [c] Quenching with AcOD led to 57% deuterium incorporation. [d, e] Starting material was present: 23% and 31%, respectively.

It was decided to determine the *ee* values of the deuterated aminomethylphosphonates by ^{1}H NMR spectroscopic analysis of the (*R*)-Mosher amides formed upon removal of the Boc group (Scheme 3).



Scheme 3. Strategy for *ee* determination in the case of labeled **11**.

Accordingly, *N*-Boc-aminophosphonate **11** was smoothly deprotected with an ethereal solution of HCl to quantitatively afford **13**·HCl, which was transformed into the (*R*)-Mosher amide. Its ^{1}H NMR spectrum showed a nicely separated AB system ($\delta = 3.42$ ppm, $J_{AB} = 15.7$ Hz) with addition-

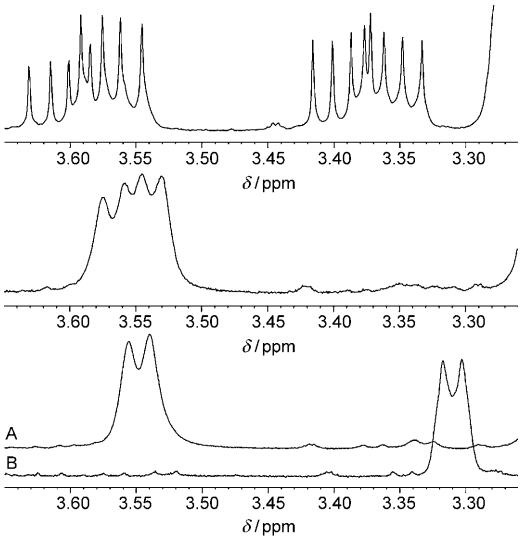


Figure 2. Relevant parts of ^{1}H NMR spectra (400 MHz, [D$_8$]toluene). Top: **13**·(*R*)-MTPA. Middle: (*R*)-[D$_1$]-**13**·(*R*)-MTPA of 94% *ee*. Bottom: A) (*R*)-[D$_1$]-**13**·(*R*)-MTPA of 94% *ee*, ^{31}P-decoupled; B) (*S*)-[D$_1$]-**13**·(*R*)-MTPA of 96% *ee*, ^{31}P-decoupled.

al NH ($J = 6.2$ Hz) and phosphorus ($J = 11.8$ Hz) couplings (Figure 2).

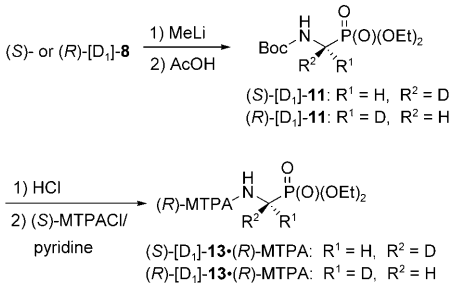
Finally, the rearrangement was performed with the labeled phosphoramidates under optimized conditions (Scheme 4). Initially, we used only a slight excess (1.3 equiv) of MeLi, hoping that it would not effect dilithiation, while still giving a good yield (85%) of the protected aminomethylphosphonate (*R*)-[D$_1$]-**11** (entry 1 in Table 2). The (*R*)-

Table 2. Transmetalation/rearrangement of [D$_1$]-**8**: conditions and results.

Entry	[D$_1$]-**8**	MeLi (equiv)	*T* [°C]	*t* [min]	Yield[a] [%]	*ee* [%]
1	(*S*)	1.3	−78	10	85	89
2	(*S*)	1.0	−78	5	89	99
3	(*R*)	1.0	−78	5	90	96
4	(*S*)	0.9	0	1	74[b]	94

[a] Determined by NMR spectroscopic analysis of the crude product; losses upon work-up. [b] Recovered starting material (25%).

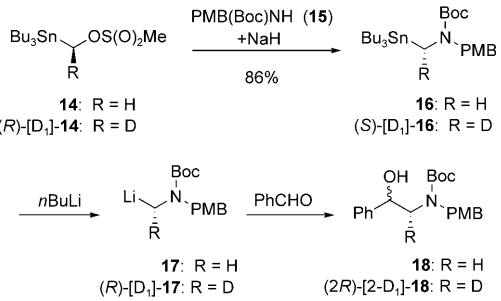
configuration was deduced by assuming that the migration followed a retentive course.[26] Unfortunately, the *ee* was only 89%. The ^{1}H NMR spectrum of the respective (*R*)-Mosher amide now exhibited a doublet of doublets, which collapsed to a doublet upon phosphorus decoupling (Figure 2). Evidently, excess MeLi preferentially removed hydrogen over deuterium from a small amount of supposedly enantiopure [D$_1$]-**10** to yield configurationally labile [D$_1$]-**12**. Aqueous work-up then furnished a small amount of racemic [D$_1$]-**11**, resulting in an erosion of the *ee*. Repeating this experiment with a stoichiometric amount of MeLi and quenching after 5 min to minimize dilithiation[26] delivered [D$_1$]-**11** with 99% *ee* in excellent yield (entry 2). This result unequivocally proved that aminomethyllithium [D$_1$]-**9** was microscopically configurationally stable and that [D$_1$]-**12** had interfered in the previous experiment. Similarly, phosphoramidate (*R*)-[D$_1$]-**8** furnished (*S*)-[D$_1$]-**11** with an *ee* of 96% (entry 3). When the rearrangement was performed at 0°C, still hardly any enantiomerization was detected, as evidenced by the high *ee* of 94% (entry 4). These results demonstrate that the *N*-Boc-protected (diethoxyphosphinyl)aminomethyllithium is microscopically configurationally stable and rearranges stereospecifically from −78°C up to 0°C, probably following a retentive course.



Scheme 4. Transmetalation/rearrangement of [D$_1$]-**8**.

Macroscopic configurational stability of Boc- and PMB-protected aminomethyllithium: The above findings cleared the way for further studying the configurational stability of an aminomethyllithium on the macroscopic timescale, that is, first its generation followed by its reaction with an electrophile after aging. We envisaged a dipole-stabilized system, because the required precursor would transmetalate more readily than any non-stabilized analogue, for which there is literature precedence.[18] Boc and PMB were chosen as protecting groups as each of these can be removed selectively.

The required precursors, **16** and (*S*)-[D$_1$]-**16**, were accessed from the respective stannylmethyl mesylates **14**[28] and (*R*)-[D$_1$]-**14** by treating them with the sodium salt of amide **15** derived from *p*-methoxybenzylamine and Boc anhydride (Scheme 5). The unlabeled stannane **16** was then



Scheme 5. Preparation of stannane **16**, its transmetalation, plus testing of the macroscopic configurational stability of [D$_1$]-**17**.

used to test the conditions of transmetalation/quenching with benzaldehyde as the electrophile (Scheme 5, Table 3). When the reaction was performed at −78°C with addition of the aldehyde 1 and 10 min after the addition of *n*BuLi,

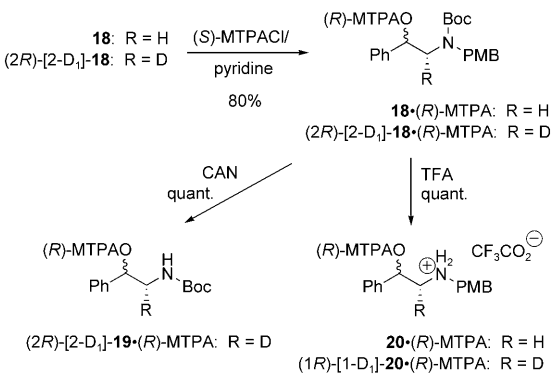
Table 3. Transmetalation/trapping of **16** in the unlabeled series: conditions and results.

Entry	T [°C]	t [min]	Yield [%]
1	−78	1	78
2	−78	10	75
3	−35	0.5	56

racemic amino alcohol **18** was isolated in yields of 78 and 75%, respectively (entries 1 and 2). Carrying out the transmetalation/quenching sequence at −35°C furnished amino alcohol **18** in 56% yield, demonstrating a higher chemical stability of the α-aminomethyllithium **17** compared to that of its oxygen analogue (entry 3).[24a]

Before repeating the sequence with the labeled compound, a method for the determination of the *ee* value of the amino alcohol [2-D_1]-**18** had to be elaborated (Scheme 5). For the sake of clarity, it is more convenient here to only give the enantiomeric excess of the deuterated center (*ee* at C-2), as C-1 is always racemic, resulting in a product with 0% *de* in the case of configurational stability.

In preliminary experiments, **18** was transformed into its (*R*)-Mosher ester (Scheme 6). However, ^{1}H NMR spectra



Scheme 6. Efforts towards the *ee* determination of [D_1]-**18**.

recorded in [D_8]toluene, $CDCl_3$, [D_6]DMSO, CD_3OD, and [D_6]acetone did not show adequate resolution of the ABX system of the $CHCH_2N$ group. The same result was found for [D_1]-**19**·(*R*)-MTPA after cleavage of the PMB group with CAN.[29] The second option, removal of the Boc group from [D_1]-**18**·(*R*)-MTPA, proceeded quantitatively on treatment with TFA. The resulting salt **20**·(*R*)-MTPA finally showed resolved signals for the AB parts of the ABX systems [at $\delta = 3.10$ and 3.07 ppm for the (*S*)- and (*R*)-configured alcohol, respectively, with $J = 13.5$, 8.7, and 3.8 Hz], which allowed integration of the signals of the individual diastereomers in the labeled series (Figure 3).

Having established a method for the determination of the *ee*, we transmetalated chiral (*S*)-[D_1]-**16**, which was expected to afford aminomethyllithium (*R*)-[D_1]-**17** assuming a retentive course for the tin–lithium exchange (Scheme 5). The first experiment was performed at −78°C, adding benzaldehyde 1 min after the addition of *n*BuLi used to effect tin–lithium exchange (entry 1 in Table 4).

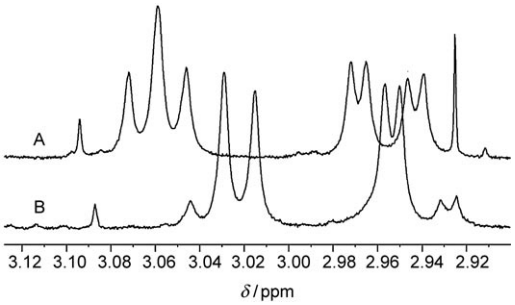


Figure 3. Relevant parts of ^{1}H NMR spectra (600 MHz, [D_8]toluene) with concentration/aggregation induced shifts. A) (1*R*)-[1-D_1]-**20**·(*R*)-MTPA of 6% *ee*; B) (1*R*)-[1-D_1]-**20**·(*R*)-MTPA of 65% *ee*.

The resulting amino alcohol [2-D_1]-**18** was found to be racemic at C-1, as expected, and almost racemic (6% *ee*) at

Table 4. Transmetalation/trapping of **16** in the labeled series: conditions and results.

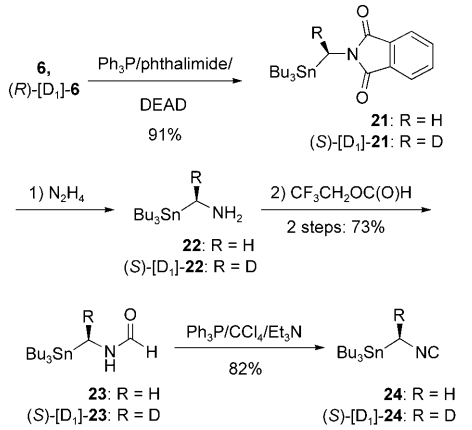
Entry	T [°C]	t [s]	Yield [%]	*ee* [%]
1	−78	60	66	6
2[a]	−78	30	48	17
3[a]	−95	30	68	65
4[a]	−95	10	75	64

[a] In the presence of a twofold excess of [12]crown-4.

the deuterated center C-2 (Figure 3A). Shortening the lifetime of (*R*)-[D_1]-**17** to 30 s did not greatly improve the result, as the *ee* was still only 17% (entry 2). At −95°C, the yields were comparable to those obtained at higher temperatures, but the *ee* was improved to 65%, irrespective of whether benzaldehyde was added after 10 or 30 s (entries 3 and 4, Figure 3B). In some cases (entries 2–4), [12]crown-4 was used, which we hoped would increase the stability of the intermediate aminomethyllithium by complexing the lithium cation, based on quantum chemical calculations[30] with water as a ligand for lithium. TLC analysis of the crude product from each of the experiments revealed the presence of some starting material, implying that transmetalation had yet to reach completion when the aldehyde was added. Therefore, some aminomethyllithium (*R*)-[D_1]-**17** was still formed after the addition of benzaldehyde, the amount depending on the relative rates of transmetalation and the addition of *n*BuLi to benzaldehyde. This would suggest that these experiments also involved partial microscopic stability. Consequently, the *ee* values for the macroscopic configurational stability would be slightly lower than those given in Table 4, especially considering the very short reaction time. To verify this, the experiment of entry 3 was repeated using methanol for trapping. The amount of **16** present in the crude product was calculated to be 15% by ^{1}H NMR spectroscopy, substantiating a small amount of interfering microscopic stability. In summary, [D_1]-**17** was found to be quite

configurationally labile, at least above −95 °C. However, comparably protected aminoalkyllithiums are configuratively more stable.[20]

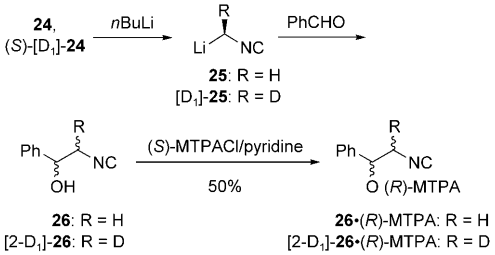
Configurational stability of isocyanomethyllithium: Isocyanomethyllithium, which was first prepared by Schoellkopf and Gerhart,[31a] is a well-known reagent in organic chemistry.[9,10] It may be considered as a specially protected aminomethyllithium, in which the carbanion is inductively stabilized by the dipole of the isocyano group. In contrast to the corresponding cyano analogue,[32] α-isocyano-2,2-diphenylcyclopropyllithium was found to be virtually macroscopically configurationally stable up to −52 °C, which can be largely attributed to the prevention of enantiomerization by the ring strain. To test this smallest protected aminomethyllithium, enantiomerically pure deuterated isocyanomethylstannane was prepared (Scheme 7).



Scheme 7. Preparation of isocyanomethylstannanes **24**.

Thus, first unlabeled and then labeled tributylstannylmethanol were converted into phthalimides **21** by a Mitsunobu reaction.[20] The unlabeled analogue was deprotected[33] to give the labile amine **22**, which was immediately converted to formamide **23**, employing 2,2,2-trifluoroethyl formate[34,35] as the reagent of choice. Dehydration under Appel conditions (Ph_3P/CCl_4)[36] finally delivered isonitrile **24** in an overall yield of 54 % based on tributylstannylmethanol.

Next, the feasibility of the transmetalation of isonitrile **24**, followed by reaction of the intermediate isocyanomethyllithium with benzaldehyde (macroscopic configurational stability), and determination of the *ee* were studied in the unlabeled series (Scheme 8). In all cases, THF was used as the solvent and *n*BuLi was used for transmetalation. Acidic work-up was necessary, as otherwise cyclization to 5-phenyl-2-oxazoline would have occurred.[31b,37] The first experiment was performed at −95 °C and involved the addition of benzaldehyde 1 min after initiating transmetalation with *n*BuLi (Table 5, entry 1). Isocyano alcohol **26** was isolated in 70 % yield and a ^{1}H NMR spectrum of the crude product revealed that it contained 30 % unreacted staring material. When the



Scheme 8. Transmetalation/trapping of **24** and [D$_1$]-**24** and subsequent *ee* determination.

Table 5. Transmetalation of **24**: conditions and results.

Entry	T [°C]	t [s]	Yield[a] [%]	SM[b] [%]
1	−95	60	70	30
2	−95	0	20	10
3	−78	30	84	traces

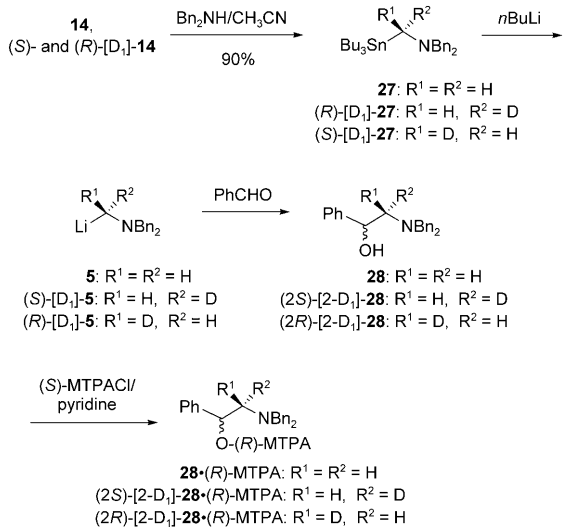
[a] Deduced from the ^{1}H NMR spectrum of the crude product; losses upon work-up. [b] SM = starting material.

temperature was increased to −78 °C, only a trace of the starting isonitrile remained after 30 s of tin–lithium exchange (entry 3). An experiment was also performed to study the possible microscopic configurational stability (with benzaldehyde being present upon tin–lithium exchange) of isocyanomethyllithium, in case it proved macroscopically configurationally labile. Unfortunately, the isolated yield of **26** was very low, as the addition of *n*BuLi to benzaldehyde was evidently faster than the transmetalation (entry 2).

Esterification of isocyano alcohol **26** with (*S*)-MTPACl furnished the (*R*)-Mosher ester, the ^{1}H NMR spectrum of which displayed two well-separated AB systems for the CH_2 groups of the diastereomers, suitable for the determination of the *ee* in the labeled series [$\delta = 2.78$ ppm, $J = 15.3$, 8.3, 4.0 Hz and $\delta = 2.71$ ppm, $J = 15.5$, 9.2, 3.4 Hz].

Next, an exploratory experiment with labeled isocyanomethylstannane (*S*)-[D$_1$]-**24** was performed (−95 °C/benzaldehyde added 90 s after the addition of *n*BuLi). The isocyano alcohol was obtained in 59 % yield (along with 15 % of the starting material) and ^{1}H NMR spectroscopic analysis of the corresponding (*R*)-Mosher ester showed it to be racemic at both chiral centers. To ascertain whether isocyanomethyllithium might be at least microscopically configurationally stable, transmetalation was performed in the presence of benzaldehyde at −95 °C. The labeled isocyano alcohol [2-D$_1$]-**26**, isolated in 25 % yield, was found to be racemic. Consequently, isocyanomethyllithium is neither macroscopically nor microscopically configurationally stable.

Macroscopic configurational stability of *N*,*N*-dibenzylaminomethyllithium: Having proven the (relative) configurational lability of dipole-stabilized aminomethyllithiums, we decided to test a non-stabilized one. Utilizing the experience of Pearson and Stevens, *N*,*N*-dibenzyl-tributylstannylmethylamine[38,39] was chosen as the precursor. It was prepared by S_N2 reaction of the mesylate **14**[28] with excess dibenzylamine in 90 % average yield (Scheme 9).



Scheme 9. Preparation of [D_1]-**27**, its transmetalation, and testing of the macroscopic configurational stability of [D_1]-**5**.

To ensure that no racemization occurred under these conditions, the ^{1}H NMR spectrum of **27** in an admixture with the chiral shift reagent (*R*)-(+)-*tert*-butyl(phenyl)monothiophosphinic acid[40] was recorded, which displayed an AB system for the diastereotopic protons ($\delta =$ 2.35 ppm, $J_{AB} = 13.4$ Hz). Its resonances collapsed to broadened singlets following deuterium labeling [(*S*)-[D_1]-**27**: $\delta =$ 2.36 ppm and (*R*)-[D_1]-**27**: $\delta = 2.27$ ppm] and showed that both enantiomers of [D_1]-**27** were enantiomerically pure. Having established this, we could then try subjecting the unlabeled stannane to transmetalation/quenching with benzaldehyde to optimize the reaction conditions for labeled [D_1]-**27** in order to probe the configurational stability of the intermediate *N*,*N*-dibenzylaminomethyllithium [D_1]-**5** (Scheme 9). All experiments were performed at −45 °C with 15 min between the addition of *n*BuLi and trapping with benzaldehyde. Initially, 2 equiv of *n*BuLi was used for tin–lithium exchange (entry 1 in Table 6). The yield of the *N*,*N*-dibenzylamino alcohol **28** was 70 %, but tin–lithium exchange was incomplete, as evidenced by 30 % recovery of the starting material being detected in the ^{1}H NMR spectrum of the crude product. Replacing *n*BuLi by MeLi or THF by Et_2O/TMEDA led to significant erosion of the yields and concomitant increases in the amounts of recovered starting material (entries 2 and 3).

Table 6. Transmetalation/trapping of **27** in the unlabeled series: conditions and results.

Entry[a]	Solvent	RLi	Yield[b] [%]	SM[c] [%]
1	THF	*n*BuLi	70	30
2	THF	MeLi	20	60
3	Et_2O/TMEDA	*n*BuLi	44	50

[a] Reaction temperature: −45 °C; reaction time for transmetalation: 15 min. [b] Deduced from the ^{1}H NMR spectrum of the crude product; losses upon work-up. [c] SM = starting material.

For the later determination of *ee* at the deuterated center, *N*,*N*-dibenzylamino alcohol **28** was converted to the (*R*)-Mosher ester. The ^{1}H NMR spectrum of this derivative featured a well-separated ABX system, suitable for the determination of *ee* in the labeled series [AB parts of ABX systems for (1*S*)-**28**·(*R*)-MTPA: $\delta = 2.90$ ppm, $J = 13.9$, 8.1, 4.8 Hz and (1*R*)-**28**·(*R*)-MTPA: $\delta = 2.86$ ppm, $J = 13.9$, 7.8, 5.3 Hz; Figure 4, top].

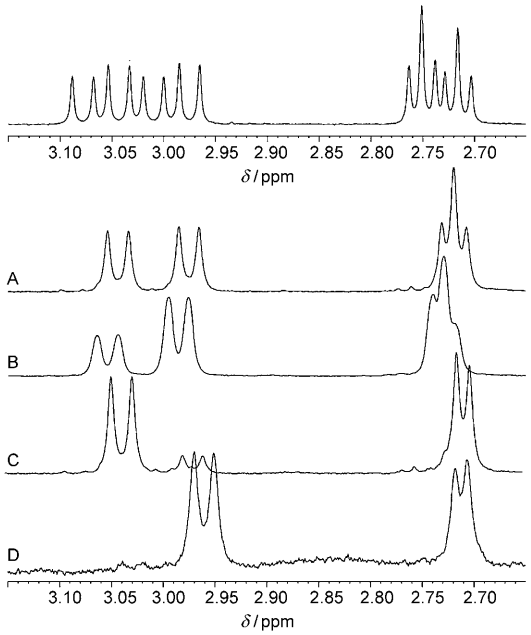


Figure 4. Relevant parts of ^{1}H NMR spectra (400 MHz, $CDCl_3$). Top: **28**·(*R*)-MTPA. Bottom: A) racemic [2-[D_1]-**28**·(*R*)-MTPA; B) (2*R*)-[2-[D_1]-**28**·(*R*)-MTPA of 30 % *ee*; C) (2*S*)-[2-[D_1]-**28**·(*R*)-MTPA of 70 % *ee*; D) (2*R*)-[2-[D_1]-**28**·(*R*)-MTPA of 90 % *ee*.

Repeating the transmetalation/quenching sequence with labeled [D_1]-**27** under our optimized conditions (*n*BuLi, THF, −45 °C, addition of benzaldehyde 15 min after addition of the alkyllithium) yielded a completely racemic product (entry 1 in Table 7). Reasoning that only a significant decrease of temperature could slow down enantiomerization, the reaction was performed at −78 °C and the time before quenching was doubled to compensate for the expected decrease in reaction rate (entry 2). Satisfyingly, the yield of alcohol [D_1]-**28** and its *ee* increased to 47 % and 30 %, respec-

Table 7. Transmetalation/trapping of [D_1]-**27**: conditions and results.

Entry	[D_1]-**27**	*T* [°C]	*t* [min]	Yield[a] [%]	*ee* [%]
1	(*R*)	−45	15	38	0
2	(*R*)	−78	30	47	30
3	(*S*)	−78	15	33	69
4	(*S*)	−95	15	10	90

[a] Isolated yield of [2-[D_1]-**28**.

tively. When the time allowed for the transmetalation was reduced from 30 to 15 min, the *ee* increased to 69%, but the yield decreased to 33% (entry 3). Finally, the reaction temperature was lowered to −95°C, which resulted in a further decrease in yield to 10% and a concomitant increase in *ee* to 90% (entry 4). Strictly speaking, the experiments summarized in Table 7 may not simply reflect the macroscopic configurational stability of chiral [D$_1$]-**5**, but a combination with the microscopic stability. As the starting material and *n*BuLi were present in the reaction mixture when benzaldehyde was added, tin–lithium exchange was still in progress during the addition of *N*,*N*-dibenzylamino-[D$_1$]methyllithium to the aldehyde. However, as tin–lithium exchange was obviously quite slow and addition of *n*BuLi to benzaldehyde usually proceeds very rapidly, the amount of product reflecting microscopic configurational stability is negligible. These data show that the temperature is of decisive importance for the enantiomerization of [D$_1$]-**5**. Below −95°C it is fairly slow, while at −45°C complete racemization is observed.

Conclusion

We have found that *N*-Boc-*N*-diethoxyphosphinyl-protected enantiopure amino-[D$_1$]methyllithium [D$_1$]-**9** rearranges to aminophosphonate [D$_1$]-**11** under complete stereocontrol up to 0°C, proving the microscopic configurational stability of the former. The *N*-Boc-*N*-PMB-protected, dipole-stabilized aminomethyllithium [D$_1$]-**17** was found to be configurationally labile at −78°C, but gave an amino alcohol of 65% *ee* at the deuterium-bearing center when the reaction temperature was lowered to −95°C (30 s). Isocyano-substituted methyllithium [D$_1$]-**25** was found to be completely configurationally labile, racemizing at −95°C, even under microscopic conditions. Enantiopure *N*,*N*-dibenzylaminomethyllithium [D$_1$]-**5** was by far the most configurationally stable of all of the studied aza-substituted methyllithiums, reacting with benzaldehyde after 15 min at −95°C to afford a product of 90% *ee*.

Experimental Section

General methods and materials: ^{1}H/^{13}C (*J*-modulated) NMR spectra were measured, unless otherwise specified, at 300 K on a Bruker Avance DPX 250, DRX 400, or DRX 600 spectrometer at 250.13/62.90 MHz, 400.13/100.61 MHz, or 600.13/150.92 MHz, respectively. 2D spectra were recorded on the DRX 400. All chemical shifts (δ) are given in ppm. They were referenced either to residual $CHCl_3$ (δ_H=7.24)/toluene (δ_H=2.09) or $CDCl_3$ (δ_C=77.00)/[D$_8$]toluene (CHD_2: δ_C=21.40). ^{31}P NMR spectra were measured on the Bruker Avance DRX 400 at 161.97 MHz. IR spectra were acquired on a silicon disc[41] on a Perkin-Elmer 1600 FT-IR spectrometer. Optical rotations were measured at 20°C on a Perkin-Elmer 351 polarimeter in a 1 dm cell. Flash column chromatography was performed on Merck silica gel 60 (230–400 mesh) and monitored by TLC, which was carried out on Merck plates coated with 0.25 mm thick silica gel 60 F_{254}. Spots were visualized by UV and/or by dipping the plate into a solution of $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ (23.0 g) and $Ce(SO_4)_2\cdot 4H_2O$ (1.0 g) in 10% aqueous H_2SO_4 (500 mL), followed by heating with a heat gun. TMEDA, DMF, and pyridine were refluxed over powdered CaH_2, toluene over sodium/benzophenone, then distilled and stored over 4 Å molecular sieves. CH_2Cl_2 was dried by passing it through aluminum oxide 90 active neutral (0.063–0.200 mm, activity grade I) and stored over 3 Å molecular sieves. Et_2O was refluxed over $LiAlH_4$, Et_3N over powdered CaH_2, and THF over potassium and each was distilled prior to use. All glassware for moisture-sensitive reactions was dried for several hours at 100°C. Reactions at −78°C were performed in an acetone/dry-ice bath, those at −95°C with additional liquid nitrogen. Small quantities of reagents (μL) were measured with appropriate syringes (Hamilton).

The experimental procedures, when identical for the non-deuterated and deuterated compounds, are generally given for the former. The deuterium content of all compounds, unless otherwise specified, lay between 97 and 98%.

General procedure for the preparation of (*R*)-Mosher esters/amides: A solution of alcohol/amine (0.10 mmol), dry pyridine (0.25 mL), and (*S*)-MTPACl (300 μL, 0.5 M solution in dry CH_2Cl_2, 0.15 mmol) in dry CH_2Cl_2 (2 mL) was stirred for 18 h at RT. Further CH_2Cl_2 (10 mL) and 1 M HCl (10 mL) were then added, and the organic layer was separated, washed with saturated aqueous $NaHCO_3$ solution, and dried ($MgSO_4$). The solvent was removed under reduced pressure. The residue was purified by flash column chromatography.

Diethyl *N*-tributylstannylmethyl-*N*-(*tert*-butoxycarbonyl)phosphoramidate {8, (*R*)- and (*S*)-[D$_1$]-8}: A solution of **6** (570 mg, 1.48 mmol), diethyl *N*-(*tert*-butoxycarbonyl)phosphoramidate[27] (**7**, 454 mg, 1.80 mmol), and Ph_3P (370 mg, 1.80 mmol) in dry THF (7 mL) was cooled to 0°C. After the addition of DEAD (314 mg, 290 μL, 1.80 mmol), the mixture was stirred for 30 min at the bath temperature and for 2 h at RT. Water (3 drops) was then added, the solvent was removed using a rotary evaporator, and the residue was purified by flash chromatography (hexane/EtOAc 5:1; R_f=0.22) to yield **8** as a colorless oil (762 mg, 93%).

Compound 8: ^{1}H NMR (400.13 MHz, $CDCl_3$): δ=4.16–4.00 (m, 4H), 3.18 (d, $J(^{117/119}Sn)$=23.7 Hz, $J(^{31}P)$=8.3 Hz, 2H), 1.51–1.41 (m, 6H), 1.45 (s, 9H), 1.31 (td, $J(^{31}P)$=1.0 Hz, J=7.1 Hz, 6H), 1.27 (sext, J=7.3 Hz, 6H), 0.89–0.83 (m, 6H), 0.86 ppm (t, J=7.3 Hz, 9H); ^{13}C NMR (100.61 MHz, $CDCl_3$): δ=154.4 (d, $J(^{31}P)$=6.1 Hz), 81.7, 63.1 (d, $J(^{31}P)$=5.4 Hz, 2C), 32.2 ($J(^{117/119}Sn)$=322.8, 308.2 Hz), 29.0 ($J(^{117/119}Sn)$=19.1 Hz, 3C), 28.1 (3C), 27.4 ($J(^{117/119}Sn)$=58.1, 55.1 Hz, 3C), 16.1 (d, $J(^{31}P)$=6.9 Hz, 2C), 13.7 (3C), 10.2 ppm ($J(^{117/119}Sn)$=330.4, 315.9 Hz, 3C); ^{31}P NMR (161.97 MHz, $CDCl_3$): δ=4.18 ppm ($J(^{117/119}Sn)$=25.8 Hz); IR (Si): $\tilde{\nu}$=2957, 2927, 1707, 1326, 1263, 1164, 1030 cm^{-1}; elemental analysis calcd (%) for $C_{22}H_{48}NO_5PSn$ (556.3): C 47.50, H 8.70, N 2.52; found: C 47.71, H 8.56, N 2.58.

(*R*)- and (*S*)-[D$_1$]-8: The spectroscopic data were identical to those of **8**, except for the following signals: ^{1}H NMR (400.13 MHz, $CDCl_3$): δ=3.16 ppm (br d, $J(^{117/119}Sn)$=23.2 Hz, $J(^{31}P)$=8.1 Hz, 1H) and ^{13}C NMR (100.61 MHz, $CDCl_3$): δ=32.0 ppm (t, J=21.4 Hz).

Diethyl *N*-(*tert*-butoxycarbonyl)aminomethylphosphonate {11, (*S*)- and (*R*)-[D$_1$]-11}: The alkyllithium reagent was added to a solution of **8** (215 mg, 0.40 mmol) and TMEDA (51 mg, 66 μL, 0.44 mmol) in dry Et_2O (2.5 mL) under argon at the requisite temperature. After stirring for the requisite time, the reaction was quenched with AcOH (AcOD) (0.56 mL, 1.4 M solution in THF, 0.78 mmol) and then water (3 mL) was added. The organic phase was separated, the aqueous phase was extracted with Et_2O, and the combined organic layers were dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography (EtOAc; R_f=0.29) to give **11**[42] as a colorless oil (for details, see Table 1).

Methyllithium (1.6 M solution in Et_2O) was added to a solution of [D$_1$]-**8** (221 mg, 0.40 mmol) and TMEDA (51 mg, 66 μL, 0.44 mmol) in dry Et_2O (2.5 mL) under argon at the desired temperature. After stirring for the requisite time, the reaction was quenched with 1 M aqueous acetic acid (1.0 mL, 1.0 mmol) and then water (3 mL) was added. The work-up was identical to that of the unlabeled compound (for details, see Table 2).

Compound 11: ^{1}H NMR (400.13 MHz, $CDCl_3$): δ=4.78 (br s, 1H), 4.18–4.06 (m, 4H), 3.53 (dd, $J(^{31}P)$=11.3 Hz, J=6.0 Hz, 2H), 1.42 (s, 9H), 1.30 ppm (t, J=7.1 Hz, 6H); ^{13}C NMR (100.61 MHz, $CDCl_3$): δ=80.1, 62.5 (d, $J(^{31}P)$=6.1 Hz, 2C), 36.1 (d, $J(^{31}P)$=136.7 Hz), 28.3 (3C),

16.4 ppm (d, $J(^{31}P)=6.1$ Hz, 2C); 1C not detected; ^{31}P NMR (161.97 MHz, $CDCl_3$): $\delta=24.38$ ppm; IR (Si): $\tilde{\nu}=3272$, 2981, 2930, 1714, 1527, 1367, 1255, 1173, 1028 cm^{-1}.

(*S*)- and (*R*)-[D_1]-11: The spectroscopic data were identical to those of **11**, except for the following signals: ^1H NMR (400.13 MHz, $CDCl_3$): $\delta=3.52$ ppm (br dd, $J(^{31}P)=11.3$ Hz, $J=6.0$ Hz, 1H) and ^{13}C NMR (100.61 MHz, $CDCl_3$): $\delta=155.4$ (d, $J(^{31}P)=6.1$ Hz), 35.8 ppm (dt, $J(^{31}P)=156.8$ Hz, $J=20.7$ Hz).

Diethoxyphosphinylmethylammonium chloride {13·HCl, (*R*)- and (*S*)-[D_1]-13·HCl}: A solution of **11** (76 mg, 0.28 mmol) in ethanol (1 mL) was cooled to 0 °C. HCl (1 mL, 5 M solution in Et_2O) was then added and the resulting mixture was stirred for 3 h at RT. Thereafter, the solvent was removed using a rotary evaporator and the residue was dried under high vacuum to give the salt **13**·HCl as colorless crystals (57 mg, 100 %).

Compound 13·HCl: ^1H NMR (250.13 MHz, $CDCl_3$): $\delta=8.60$ (br s, 3H), 4.30–4.12 (m, 4H), 3.50 (d, $J(^{31}P)=12.8$ Hz, 2H), 1.32 ppm (t, $J=7.0$ Hz, 6H).

(*R*)- and (*S*)-[D_1]-13·HCl: ^1H NMR (400.13 MHz, $CDCl_3$): $\delta=8.61$ (br s, 3H), 4.28–4.14 (m, 4H), 3.49 (br d, $J(^{31}P)=13.1$ Hz, 1H), 1.32 ppm (t, $J=7.1$ Hz, 6H); ^{13}C NMR (100.61 MHz, $CDCl_3$): $\delta=63.7$ (d, $J(^{31}P)=6.1$ Hz, 2C), 33.8 (td, $J(^{31}P)=154.5$, $J=19.9$ Hz), 16.3 ppm (d, $J(^{31}P)=6.1$ Hz, 2C); ^{31}P NMR (161.97 MHz, $CDCl_3$): $\delta=20.24$ ppm; IR (Si): $\tilde{\nu}=3402$, 2920, 2850, 1626, 1587, 1371, 1229, 1163, 1017 cm^{-1}.

(*R*)-Mosher amides of 13, (*S*)-, and (*R*)-[D_1]-13: These were prepared in 84 % yield starting from the hydrochloride according to the general procedure for Mosher esters/amides and were purified by flash chromatography (EtOAc, $R_f=0.51$). Chemical shifts and coupling constants varied slightly due to differences in concentration/aggregation.

Compound 13·(*R*)-MTPA: ^1H NMR (400.13 MHz, [D_8]toluene): $\delta=7.65$ (br d, $J=7.6$ Hz, 2H_{arom}), 7.12–7.00 (m, 3H_{arom}), 6.75 (br s, 1H), 3.88–3.76 (m, 4H), 3.42 (ddAB system, $J_{AB}\approx16$ Hz, $J(^{31}P)\approx12$ Hz, $J\approx6$ Hz, 2H), 3.22 (q, $J=1.5$ Hz, 3H), 1.00 (t, $J=7.1$ Hz, 3H), 0.97 ppm (t, $J=7.1$ Hz, 3H); ^{31}P NMR (161.97 MHz, [D_8]toluene): $\delta=22.77$ ppm.

(*R*)-[D_1]-13·(*R*)-MTPA: The spectroscopic data were identical to those of **13**·(*R*)-MTPA, except for the following signal: ^1H NMR (400.13 MHz, [D_8]toluene): $\delta=3.31$ ppm (br dd, $J(^{31}P)\approx11$ Hz, $J\approx6$ Hz, 1H), which collapsed to a br d after ^{31}P decoupling.

(*S*)-[D_1]-13·(*R*)-MTPA: The spectroscopic data were identical to those of **13**·(*R*)-MTPA, except for the following signal: ^1H NMR (400.13 MHz, [D_8]toluene): $\delta=3.55$ ppm (br dd, $J(^{31}P)\approx12$ Hz, $J\approx7$ Hz, 1H), which collapsed to a br d after ^{31}P decoupling.

***tert*-Butyl *N*-*p*-methoxybenzylcarbamate (15)**: *p*-Methoxybenzylamine (686 mg, 0.65 mL, 5.00 mmol) was added to a solution of Boc_2O (1.11 g, 5.10 mmol) and Et_3N (758 mg, 1.04 mL, 7.50 mmol) in dry CH_2Cl_2 (15 mL) at 0 °C. The solution was stirred for 2.5 h at RT and then 0.5 M HCl (10 mL) was added. The organic phase was separated and the aqueous phase was extracted with EtOAc (3×10 mL). The combined organic layers were washed with water, dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was purified by flash chromatography (hexane/EtOAc 5:1; $R_f=0.37$) to yield **15**[43] (1.19 g) as colorless crystals in quantitative yield. ^1H NMR (250.13 MHz, $CDCl_3$): $\delta=7.28$ (d, $J=8.5$ Hz, 2H_{arom}), 6.84 (d, $J=8.5$ Hz, 2H_{arom}), 4.73 (br s, 1H), 4.22 (d, $J=5.8$ Hz, 2H), 3.77 (s, 3H), 1.44 ppm (s, 9H); ^{13}C NMR (62.90 MHz, $CDCl_3$): $\delta=158.9$, 155.8, 131.0, 128.8 (2C), 114.0 (2C), 55.3, 44.2, 28.4 ppm (3C); 1C not detected.

***tert*-Butyl *N*-*p*-methoxybenzyl-*N*-tributylstannylmethylcarbamate {16 and (*S*)-[D_1]-16}**: NaH (34 mg, 0.64 mmol, 60 % in mineral oil) was washed three times with hexane and then suspended in dry DMF (1.5 mL) under argon at 0 °C. A solution of carbamate **15** (151 mg, 0.64 mmol) in dry DMF (0.5 mL) was added and the mixture stirred for 30 min, and then a solution of mesylate **14** (170 mg, 0.43 mmol) in dry DMF (0.5 mL) was added. After 1 h, the reaction was quenched with water (3 mL). The organic phase was separated and the aqueous phase was extracted with Et_2O (3×3 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure, and the residue was purified by flash chromatography (hexane/EtOAc 40:1; TLC: hexane/EtOAc 10:1; $R_f=0.75$) to yield **16** (199 mg, 86 %) as a colorless oil.

Compound 16: ^1H NMR (400.13 MHz, 80 °C, [D_8]toluene): $\delta=7.14$–7.09 (m, 2H_{arom}), 6.77–6.72 (m, 2H_{arom}), 4.33 (s, 2H), 3.40 (s, 3H), 2.81 (br s, $J(^{117/119}Sn)=26.8$ Hz, 2H), 1.65–1.56 (m, 6H), 1.43 (s, 9H), 1.37 (sext, $J=7.3$ Hz, 6H), 1.00–0.94 (m, $J(^{117/119}Sn)=50.8$ Hz, 6H), 0.93 ppm (t, $J=7.3$ Hz, 9H); ^{13}C NMR (100.61 MHz, 80 °C, [D_8]toluene): $\delta=161.0$ (from HMBC), 132.3, 130.3 (2C), 115.7 (2C), 80.5, 56.0, 34.9, 30.8 ($J(^{117/119}Sn)=20.6$ Hz, 3C), 29.8, 28.9 ($J(^{117/119}Sn)=55.1$ Hz, 3C), 14.9 (3C), 12.7 ppm; 2C not detected; IR (Si): $\tilde{\nu}=2956$, 2923, 1679, 1514, 1250, 1164 cm^{-1}; elemental analysis calcd (%) for $C_{26}H_{47}NO_3Sn$ (540.4): C 57.79, H 8.77, N, 2.59; found: C 57.86, H 8.77, N 2.66.

(*S*)-[D_1]-16: The spectroscopic data were identical to those of **16**, except for the following signals: ^1H NMR (400.13 MHz, 80 °C, [D_8]toluene): $\delta=2.78$ ppm (v br s, 1H) and ^{13}C NMR (100.61 MHz, 80 °C, [D_8]toluene): $\delta=34.5$ ppm (t, $J=21.8$ Hz).

2-(*N*-*tert*-Butoxycarbonyl-*N*-*p*-methoxybenzylamino)-1-phenylethanol {18 and (2*R*)-[2-D_1]-18}: The stannane **16** (190 mg, 0.35 mmol) was dissolved in dry THF (3.5 mL) under argon and the solution was cooled to the required temperature. *n*BuLi (275 μL, 1.6 M solution in hexane, 0.44 mmol) was added (yellow color) and the reaction was later quenched with benzaldehyde (0.70 mL, 1 M solution in dry THF, 0.70 mmol). After 15 min, water (3 mL) was added. The organic phase was separated and the aqueous phase was extracted with Et_2O (3×3 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure, and the residue was purified by flash chromatography (hexane/EtOAc 3:1; $R_f=0.30$) to yield **18** as a colorless oil (for details, see Tables 3 and 4).

Compound 18: ^1H NMR (400.13 MHz, 80 °C, [D_8]toluene): $\delta=7.28$–7.23 (m, 2H_{arom}), 7.15–7.09 (m, 2H_{arom}), 7.08–6.95 (m, 3H_{arom}), 6.71–6.67 (m, 2H_{arom}), 4.81 (X part of ABX system, $J=7.6$, 3.8 Hz, 1H), 4.27 (AB system, $J=15.2$ Hz, 2H), 3.37 (s, 3H), 3.37 (AB part of ABX system, $J=14.7$, 7.6, 3.8 Hz, 2H), 1.40 ppm (s, 9H); ^{13}C NMR (100.61 MHz, 80 °C, [D_8]toluene): $\delta=160.9$, 144.9, 132.2, 130.3, 129.6 (2C), 128.6 (2C), 127.4 (2C), 115.7 (2C), 81.2, 75.3, 56.9, 56.0, 53.1, 29.6 ppm (3C); 1C not detected; IR (Si): $\tilde{\nu}=3437$, 2975, 2930, 1692, 1464, 1412, 1367, 1248, 1165 cm^{-1}; elemental analysis calcd (%) for $C_{21}H_{27}NO_4$ (357.4): C 70.56, H 7.61, N 3.92; found: C 71.22, H 7.65, N 3.91.

(2*R*)-[2-D_1]-18: The spectroscopic data were identical to those of **18**, except for the following signals: ^1H NMR (400.13 MHz, 80 °C, [D_8]toluene): $\delta=4.80$ (br d, $J=6.8$ Hz, 1H), 3.40–3.31 ppm (m, 1H) and ^{13}C NMR (100.61 MHz, 80 °C, [D_8]toluene): $\delta=75.3$ and 75.2 (two diastereomers), 56.6 ppm (t, $J=19.1$ Hz).

(*R*)-Mosher esters of 18 and (2*R*)-[2-D_1]-18: These were prepared in 80 % yield according to the general procedure for Mosher esters/amides and were purified by flash chromatography (hexane/EtOAc 5:1; TLC: hexane/EtOAc 3:1; $R_f=0.53$).

Compound 18·(*R*)-MTPA: ^1H NMR (400.13 MHz, 80 °C, [D_8]toluene): $\delta=7.58$–7.50 (m, 2H_{arom}), 7.29–7.25 (m, 1H_{arom}), 7.19–7.16 (m, 1H_{arom}), 7.14–6.96 (m, 8H_{arom}), 6.69–6.65 (m, 2H_{arom}), 6.46 (X part of ABX system, $J=7.4$, 5.7 Hz, 1H) and 6.36 (X part of ABX system, $J=8.6$, 5.1 Hz, 1H), 4.36 and 4.17 (AB system, $J_{AB}=15.4$ Hz, 2H), 3.61–3.44 (m, 2H), 3.43 and 3.38 (q, $J=1.0$ Hz, 3H), 3.369 and 3.366 (s, 3H), 1.42 and 1.41 ppm (s, 9H); two diastereomers.

(2*R*)-[2-D_1]-18·(*R*)-MTPA: The spectroscopic data were identical to those of **18**·(*R*)-MTPA, except for the following signals: ^1H NMR (400.13 MHz, 80 °C, [D_8]toluene): $\delta=6.45$ (d, $J=7.6$ Hz, 1H) and 6.36 (d, $J=8.3$ Hz, 1H), 3.58–3.41 ppm (m, 1H). Resolution of the relevant signals was not adequate, even when other solvents ($CDCl_3$, [D_6]DMSO, CD_3OD, [D_6]acetone) were used.

(*R*)-Mosher ester of (2*R*)-2-(*N*-*tert*-butoxycarbonylamino)-1-phenyl-[2-D_1]ethanol {(2*R*)-[2-D_1]-19·(*R*)-MTPA} (PMB cleavage): A solution of the (*R*)-Mosher ester of [2-D_1]-**18** (11 mg, 0.02 mmol) and CAN (28 mg, 0.08 mmol) in MeCN (0.4 mL)/water (0.1 mL) was stirred for 1.5 h at 0 °C. Water (2 mL) and EtOAc (2 mL) were then added, the organic phase was separated, and the aqueous phase was extracted with EtOAc. The combined organic layers were dried ($MgSO_4$) and concentrated

under reduced pressure. The residue was purified by flash chromatography (hexane/EtOAc 10:1; R_f=0.15) to give (2*R*)-[2-D$_1$]-**19**·(*R*)-MTPA in quantitative yield (9 mg). ^{1}H NMR (400.13 MHz, 80 °C, [D$_8$]toluene): δ= 7.56–7.48 (m, 2H$_{arom}$), 7.17–6.94 (m, 8H$_{arom}$), 6.09 (d, J=4.3 Hz, 1H), 6.08 (d, J=8.3 Hz, 1H), 5.98 (d, J=8.1 Hz, 1H), 5.98 (d, J=4.7 Hz, 1H), 4.21–4.08 (br m, 1H), 3.41 and 3.34 (q, J=1.1 Hz, 3H), 3.42–3.29 (m, 1H), 3.23–3.16 (m, 0.5H), 3.12–3.06 (m, 0.5H), 1.38 and 1.37 ppm (s, 9H).

(*R*)-Mosher esters of *N*-(2-hydroxy-2-phenylethyl)-*N*-4-methoxybenzylammonium trifluoroacetate {20·(*R*)-MTPA and (1*R*)-[1-D$_1$]-20·(*R*)-MTPA} (Boc cleavage): A solution of **18**·(*R*)-MTPA (30 mg, 0.052 mmol) in TFA (1 mL) was stirred for 1.5 h at 0 °C. The solvent was then removed in vacuo to give **20**·(*R*)-MTPA as a colorless oil in quantitative yield. Chemical shifts and coupling constants varied slightly due to differences in concentration/aggregation.

Compound 20·(*R*)-MTPA: ^{1}H NMR (600.13 MHz, [D$_8$]toluene): δ=9.26 (v br s, 2H), 7.49 (d, J=7.7 Hz, 1H$_{arom}$), 7.41–7.37 (m, 1H$_{arom}$), 7.21 (d, J=6.8 Hz, 1H$_{arom}$), 7.12–6.96 (m, 9H$_{arom}$), 6.65 (dd, J=8.7, 2.9 Hz, 2H$_{arom}$), 6.36 (X part of ABX system, J=8.7, 3.8 Hz, 1H) and 6.31 (X part of ABX system, J=8.7, 3.8 Hz, 1H), 3.71 and 3.57 (AB system, J_{AB}=13.1 Hz, 2H), 3.43 and 3.30 (s, 3H), 3.20 (s, 3H), 3.15 (dd [AB part of ABX system], J=13.5, 8.7 Hz, 1H), 3.11 (dd [AB part of ABX system], J=13.5, 8.7 Hz, 1H), 3.05 (dd [AB part of ABX system], J= 13.5, 3.8 Hz, 1H), 3.02 ppm (dd [AB part of ABX system], J=13.5, 3.8 Hz, 1H); two diastereomers.

(1*R*)-[1-D$_1$]-20·(*R*)-MTPA: The spectroscopic data were identical to those of **20**·(*R*)-MTPA, except for the following signals: ^{1}H NMR (600.13 MHz, [D$_8$]toluene): δ=6.23 (d, J=4.0 Hz, 1H) and 6.15 (d, J= 8.4 Hz, 1H), 3.02 (d, J=8.4 Hz, 1H) and 2.95 ppm (d, J=4.0 Hz, 1H).

(1*S*)-[1-D$_1$]-20·(*R*)-MTPA: The spectroscopic data were identical to those of **20**·(*R*)-MTPA, except for the following signals: ^{1}H NMR (600.13 MHz, [D$_8$]toluene): δ=6.23 (d, J=7.5 Hz, 1H) and 6.14 (d, J= 4.4 Hz, 1H), 3.04 (d, J=7.5 Hz, 1H) and 2.93 ppm (d, J=4.4 Hz, 1H).

***N*-Tributylstannylmethylphthalimide {21 and (*S*)-[D$_1$]-21}**: Tributylstannylmethanol **6** (1.44 g, 4.50 mmol), Ph$_3$P (1.42 g, 5.4 mmol), and phthalimide (792 mg, 5.40 mmol) were dissolved in dry THF (22.5 mL) under argon. DEAD (940 mg, 850 μL, 5.40 mmol) was added at 0 °C, and then the mixture was stirred at ambient temperature for 1 h. The reaction was quenched by adding a few drops of water, the solvent was removed under reduced pressure, and the residue was purified by flash chromatography (hexane/EtOAc 15:1; R_f=0.33) to give 1.85 g (91 %) of **21** as a yellow oil. The spectroscopic data of the unlabeled compound were identical to those reported in the literature.[44]

(*S*)-[D$_1$]-21: ^{1}H NMR (400.13 MHz, CDCl$_3$): δ=7.80–7.75 (m, 2H$_{arom}$), 7.67–7.62 (m, 2H$_{arom}$), 3.20 (br s, J($^{117/119}$Sn)=26.0 Hz, 1H), 1.52–1.43 (m, 6H), 1.25 (sext, J=7.3 Hz, 6H), 0.95–0.89 (m, 6H), 0.83 ppm (t, J= 7.3 Hz, 9H); ^{13}C NMR (100.61 MHz, CDCl$_3$): δ=168.8 (2C), 133.6 (2C), 132.4 (2C), 122.8 (2C), 28.9 (J($^{117/119}$Sn)=20.7 Hz, 3C), 27.3 (J($^{117/119}$Sn)= 55.8 Hz, 3C), 21.0 (t, J=21.4 Hz), 13.6 (3C), 10.4 ppm (J($^{117/119}$Sn)= 335.0, 319.2 Hz, 3C); IR (Si): $\tilde{\nu}$=2955, 2922, 2870, 2853, 1768, 1708, 1465, 1396 cm^{-1}.

***N*-(Tributylstannylmethyl)formamide {23 and (*S*)-[D$_1$]-23}**: N_2H_4·H_2O (6.0 mL) was added dropwise to a refluxing solution of **21** (1.35 g, 3.0 mmol) in ethanol (9 mL). The mixture was stirred for 1 h, cooled, and diluted with freshly distilled Et$_2$O (20 mL). The organic phase was separated, washed with water (4×10 mL) and brine (2×10 mL), and concentrated under reduced pressure. The crude product (860 mg, 2.68 mmol) was dissolved in *tert*-butyl methyl ether (6 mL), treated with 2,2,2-trifluoroethyl formate (687 mg, 5.37 mmol, redistilled from P_2O_5),[33,34] and the resulting mixture was stirred for 1.5 h. The solvent was then removed under reduced pressure and the residue was purified by flash chromatography (hexane/EtOAc 3:1; R_f=0.26) to give formamide **22** (760 mg, 73 %) as a colorless oil. The spectroscopic data of **22** were identical to those reported in the literature.[44]

(*S*)-[D$_1$]-22: ^{1}H NMR (400.13 MHz, CDCl$_3$): δ=2.60 (br s, J($^{117/119}$Sn)= 29.3 Hz, 1H), 2.09 (v br s, 2H), 1.53–1.48 (m, 6H), 1.29 (sext, J=7.3 Hz, 6H), 0.93–0.86 (m, 6H), 0.88 ppm (t, J=7.3 Hz, 9H); ^{13}C NMR (100.61 MHz, CDCl$_3$): δ=29.2 (J($^{117/119}$Sn)=19.1 Hz, 3C), 27.4 (J($^{117/119}$Sn)=52.8 Hz, 3C), 25.3 (t, J=20.7 Hz), 13.7 (3C), 8.5 ppm (J($^{117/119}$Sn)=317.4, 303.6 Hz, 3C); IR (Si): $\tilde{\nu}$=2956, 2923, 2871, 1569, 1464 cm^{-1}.

Compound 23: ^{1}H NMR (400.13 MHz, [D$_8$]toluene): δ=7.56 (s, 1H), 4.47 (br s, 1H), 2.332 and 2.330 (d, J=4.3 Hz, J($^{117/119}$Sn)=31.6 Hz, 2H), 1.65–1.56 (m, 6H), 1.38 (sext, J=7.3 Hz, 6H), 1.02–0.97 (m, 6H), 0.97 ppm (t, J=7.3 Hz, 9H); ^{13}C NMR (100.61 MHz, [D$_8$]toluene): δ=161.7, 30.6 (J($^{117/119}$Sn)=20.7 Hz, 3C), 28.9 (J($^{117/119}$Sn)=54.3 Hz, 3C), 23.3, 15.0 (3C), 12.2 ppm (J($^{117/119}$Sn)=336.5, 321.1 Hz, 3C); IR (Si): $\tilde{\nu}$=3255, 3044, 2956, 2922, 2853, 1651, 1376 cm^{-1}; elemental analysis calcd (%) for $C_{14}H_{31}NOSn$ (348.1): C 48.30, H 8.98, N 4.02; found: C 49.15, H 9.00, N 4.07.

(*S*)-[D$_1$]-23: The spectroscopic data were identical to those of **23**, except for the following signals: ^{1}H NMR (400.13 MHz, [D$_8$]toluene): δ= 2.31 ppm (t, J=1.9 Hz, J($^{117/119}$Sn)=31.1 Hz, 1H); ^{13}C NMR (100.61 MHz, [D$_8$]toluene): δ=23.02 ppm (t, J=21.0 Hz, 1C).

Tributyl(isocyanomethyl)stannane {24 and (*S*)-[D$_1$]-24}: Et$_3$N (101 mg, 138 μL, 1.0 mmol) was added to a solution of **23** (290 mg, 0.83 mmol) and Ph$_3$P (262 mg, 1.0 mmol) in dry MeCN (1.3 mL) and CCl$_4$ (0.5 mL) under argon at 5 °C. The mixture was stirred for 2.5 h, during which it was allowed to warm to RT. A few drops of water were added and the solution was directly subjected to flash chromatography (hexane/EtOAc 40:1; R_f=0.28) to furnish 226 mg (82 %) of **24** as a colorless oil. The slightly reduced yield is due to the instability of the isonitrile and its decomposition on silica gel (probably through conversion to the formamide).

Compound 24: ^{1}H NMR (400.13 MHz, CDCl$_3$): δ=2.96 (s, J($^{117/119}$Sn)= 28.6 Hz, 2H), 1.57–1.47 (m, 6H), 1.31 (sext, J=7.3 Hz, 6H), 1.08–1.02 (m, 6H), 0.89 ppm (t, J=7.3 Hz, 9H); ^{13}C NMR (100.61 MHz, CDCl$_3$): δ=28.7 (J($^{117/119}$Sn)=22.2 Hz, 3C), 27.2 (J($^{117/119}$Sn)=57.4 Hz, 3C), 21.5, 13.6 (3C), 9.8 ppm (J($^{117/119}$Sn)=338.0, 323.5 Hz, 3C); 1C not detected; IR (Si): $\tilde{\nu}$=2958, 2929, 2872, 2131, 1464 cm^{-1}; elemental analysis calcd (%) for $C_{14}H_{29}NSn$ (330.1): C 50.94, H 8.86, N 4.24; found: C 51.79, H 9.17, N 4.16; HRMS: m/z: calcd for $C_{14}H_{29}NSn+H^+$: 331.1324 [M+H$^+$]; found: 331.1332.

(*S*)-[D$_1$]-24: The spectroscopic data were identical to those of **24**, except for the following signals: ^{1}H NMR (400.13 MHz, CDCl$_3$): δ=2.94 ppm (br s, J($^{117/119}$Sn)=28.3 Hz, 1H) and ^{13}C NMR (100.61 MHz, CDCl$_3$): δ= 21.2 ppm (t, J=22.2 Hz).

2-Isocyano-1-phenylethanol {26 and [2-D$_1$]-26}: **Macroscopic**: *n*BuLi (225 μL, 1.6 M solution in hexane, 0.36 mmol) was added to a solution of **24** (99 mg, 0.30 mmol) in dry THF (3 mL) under argon at the requisite temperature. The intermediate organolithium was trapped with benzaldehyde (390 μL, 1 M solution in dry THF, 0.39 mmol) after the required time. After a further 3 min, acetic acid (330 μL, 1 M solution in dry THF, 0.33 mmol) was added, followed by a saturated aqueous solution of NaHCO$_3$ (5 mL). The organic phase was separated, the aqueous phase was extracted with Et$_2$O (3×5 mL), and the combined organic layers were dried over MgSO$_4$. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (hexane/EtOAc 3:1; R_f=0.23) to give isocyano alcohol **26** as a colorless oil (for details, see Table 5).[31b,37]

Microscopic: *n*BuLi (0.75 mL, 1.6 M solution in hexane, 1.2 mmol) was slowly added to a solution of **24** (99 mg, 0.30 mmol) and benzaldehyde (1.2 mL, 1 M solution in dry THF, 1.2 mmol) in dry THF (2 mL) under argon at −95 °C. After 3 min, acetic acid (1.32 mL, 1 M solution in THF, 1.32 mmol) was added. The subsequent work-up was the same as described for the macroscopic conditions. Compound **26** proved to be quite unstable; if not stored as a dilute solution in toluene at −20 °C, it rapidly cyclized to 5-phenyl-2-oxazoline.

Compound 26: ^{1}H NMR (400.13 MHz, CDCl$_3$): δ=7.41–7.31 (m, 5H$_{arom}$), 4.95 (t, J=5.9 Hz, 1H), 3.61 (d, J=5.9 Hz, 2H), 2.56 ppm (s, 1H); ^{13}C NMR (100.61 MHz, CDCl$_3$): δ=157.9, 139.3, 128.9 (2C), 128.8, 125.9 (2C), 72.0, 49.2 ppm (t, J=6.9 Hz); IR (Si): $\tilde{\nu}$=3392, 3033, 2919, 2850, 2153, 1454, 1065 cm^{-1}; HRMS: m/z: calcd for C_9H_9NO: 147.0684; found: 147.0686 (also 147.1172).

[2-D$_1$]-26: The spectroscopic data were identical to those of **26**, except for the following signals: ^{1}H NMR (400.13 MHz, $CDCl_3$): $\delta = 4.95$ (d, $J =$ 5.3 Hz, 1H), 3.60 ppm (br s, 1H) and ^{13}C NMR (100.61 MHz, $CDCl_3$): $\delta =$ 48.95 ppm (tt, $J = 22.3$, 6.9 Hz).

(*R*)-Mosher esters of 26 and [2-D$_1$]-26: These were prepared according to the general procedure for Mosher esters/amides, except that 2 equiv of (*S*)-MTPACl was used and the reaction was terminated after 3 h, as otherwise the formation of an unidentified side product predominated. The crude product was purified by flash chromatography (hexane/EtOAc 7:1; $R_f = 0.24$) to give the esters in an average yield of 50%.

Compound 26·(*R*)-MTPA: ^{1}H NMR (400.13 MHz, [D$_8$]toluene): $\delta = 7.58$–7.53 (m, 1H$_{arom}$), 7.49–7.42 (m, 1H$_{arom}$), 7.11–6.88 (m, 7H$_{arom}$), 6.74–6.68 (m, 1H$_{arom}$), 5.78 (X part of ABX system, $J = 8.3$, 4.0 Hz, 1H) and 5.61 (X part of ABX system, $J = 9.2$, 3.4 Hz, 1H), 3.56 (q, $J = 1.5$ Hz, 3H) and 3.30 (q, $J = 1.0$ Hz, 3H), 2.78 (AB part of ABX system, $J = 15.3$, 8.3, 4.0 Hz, 2H) and 2.71 ppm (AB part of ABX system, $J = 15.5$, 9.2, 3.4 Hz, 2H); two diastereomers.

[2-D$_1$]-26·(*R*)-MTPA: The spectroscopic data were identical to those of **26**·(*R*)-MTPA, except for the following signals: ^{1}H NMR (400.13 MHz, [D$_8$]toluene): $\delta = 5.79$ (d, $J = 8.3$ Hz, 1H) and 5.79 (d, $J = 4.0$ Hz, 1H), 5.62 (d, $J = 9.2$ Hz, 1H) and 5.62 (d, $J = 3.4$ Hz, 1H), 2.87 (br d, $J = 8.3$ Hz, 1H) and 2.82 (br d, $J = 9.2$ Hz, 1H), 2.71–2.68 (m, 1H) and 2.63–2.59 ppm (m, 1H); four diastereomers in equal amounts.

***N*,*N*-Dibenzyl(tributylstannylmethyl)amine {27, (*R*)- and (*S*)-[D$_1$]-27}**: A solution of tributylstannylmethyl mesylate (**14**, 883 mg, 2.20 mmol) and Bn_2NH (1.74 g, 1.69 mL, 8.80 mmol) in MeCN (15 mL) was stirred for 1 day at 50 °C. Water (10 mL) was then added, the aqueous layer was extracted with EtOAc (3 × 10 mL), and the combined organic layers washed with brine and dried ($MgSO_4$). After removal of the solvent under reduced pressure, the residue was purified by flash chromatography (hexane/EtOAc 40:1; $R_f = 0.43$) to yield tertiary amine **27** as a colorless oil (992 mg, 90%). The spectroscopic data of **27** were identical to those reported in the literature.[38]

(*R*)- and (*S*)-[D$_1$]-27: ^{1}H NMR (400.13 MHz, $CDCl_3$): $\delta = 7.36$–7.18 (m, 10H$_{arom}$), 3.44 (AB system, $J_{AB} = 13.4$ Hz, 4H), 2.50 (s, $J(^{117/119}Sn) =$ 20.0 Hz, 1H), 1.48–1.39 (m, 6H), 1.26 (sext, $J = 7.3$ Hz, 6H), 0.90–0.84 (m, 6H), 0.85 ppm (t, $J = 7.3$ Hz, 9H); ^{13}C NMR (100.61 MHz, $CDCl_3$): $\delta = 140.0$ (2C), 128.7 (4C), 128.2 (4C), 126.8 (2C), 62.5 ($J(^{117/119}Sn) =$ 28.3 Hz, 2C), 42.5 (t, $J = 19.9$ Hz), 29.2 ($J(^{117/119}Sn) = 19.9$ Hz, 3C), 27.4 ($J(^{117/119}Sn) = 54.3$ Hz, 3C), 13.7 (3C), 10.0 ppm ($J(^{117/119}Sn) = 299.8$, 286.8 Hz, 3C); IR (Si): $\tilde{\nu} = 2956$, 2924, 2854, 1496, 1454 cm^{-1}.

To determine the *ee* of [D$_1$]-**27**, it was treated with 2 equiv of (*R*)-(+)-*tert*-butyl(phenyl)monothiophosphinic acid and a ^{1}H NMR spectrum was immediately recorded.[40]

Salt of 27: ^{1}H NMR (400.13 MHz, [D$_8$]toluene): $\delta = 8.18$–8.09 (m, 3H$_{arom}$), 7.42–7.35 (m, 2H$_{arom}$), 7.16–6.95 (m, 10H$_{arom}$), 4.31 (AB system, $J_{AB} = 13.9$ Hz, 4H), 2.35 (AB system, $J_{AB} = 13.4$ Hz, 2H), 1.45–1.20 (m, 12H), 1.25 (d, $J = 16.4$ Hz, 9H), 1.05–0.97 (m, 6H), 0.88 ppm (t, $J =$ 7.3 Hz, 9H).

Salt of (*S*)-[D$_1$]-27: The spectroscopic data were identical to those of the unlabeled compound, except for the following signal: ^{1}H NMR (400.13 MHz, [D$_8$]toluene): $\delta = 2.36$ ppm (s, $J(^{117/119}Sn) = 30.8$ Hz, 1H).

Salt of (*R*)-[D$_1$]-27: The spectroscopic data were identical to those of the unlabeled compound, except for the following signal: ^{1}H NMR (400.13 MHz, [D$_8$]toluene): $\delta = 2.27$ ppm (s, $J(^{117/119}Sn) = 25.5$ Hz, 1H).

2-(*N*,*N*-Dibenzylamino)-1-phenyl-1-ethanol {28, (2*S*)- and (2*R*)-[2-D$_1$]-28}: A solution of **27** (160 mg, 0.32 mmol) in dry THF (3 mL) was treated with *n*BuLi (400 μL, 1.6 M solution in hexane, 0.64 mmol) under argon at the requisite temperature. After the required time, the reaction was quenched with benzaldehyde (0.39 mL, 2 M in dry THF, 0.78 mmol), and then hexane (3 mL) and 10% H_2SO_4 (4 mL) were added. The organic layer was separated and extracted with 10% H_2SO_4 (3 × 4 mL). The combined aqueous phases were neutralized with solid NaOH and then extracted with Et_2O (4 × 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated, and the residue was purified by flash column chromatography (CH_2Cl_2; $R_f = 0.40$) to yield the amino alcohol **28** (for details, see Tables 6 and 7).[39]

Compound 28: ^{1}H NMR (400.13 MHz, $CDCl_3$): $\delta = 7.36$–7.19 (m, 15H$_{arom}$), 4.69 (t, $J = 6.8$ Hz, 1H), 3.69 (AB system, $J_{AB} = 13.4$ Hz), 2.63 (d, $J = 6.8$ Hz, 2H), 1.59 ppm (br s, 1H); ^{13}C NMR (100.61 MHz, $CDCl_3$): $\delta = 142.1$, 138.3 (2C), 129.1 (4C), 128.5 (4C), 128.3 (2C), 127.4, 127.4 (2C), 125.9 (2C), 69.6, 61.9, 58.4 ppm (2C); IR (Si): $\tilde{\nu} = 3452$, 3028, 2924, 1602, 1494, 1453 cm^{-1}.

(2*R*)-[2-D$_1$]-28: ^{1}H NMR (400.13 MHz, $CDCl_3$): $\delta = 7.37$–7.20 (m, 15H$_{arom}$), 4.69 (d, $J = 10.4$ Hz, 1H) and 4.69 (d, $J = 3.3$ Hz, 1H), 3.71 and 3.70 (AB system, $J_{AB} = 13.4$ Hz), 2.66–2.60 ppm (m, 1H); ^{13}C NMR (100.61 MHz, $CDCl_3$): $\delta = 142.13$ and 142.10 (2C), 138.29 and 138.28, 129.1 (4C), 128.5 (4C), 128.2 (2C), 127.39 (1C), 127.35 (2C), 125.9 (2C), 69.53 and 69.48, 61.51 and 61.47 (t, $J = 21.0$ Hz), 58.34 and 58.32 ppm (2C); two diastereomers.

(*R*)-Mosher esters of 28, (2*S*)-, and (2*R*)-[2-D$_1$]-28: These were prepared in 45% yield according to the general procedure for Mosher esters/amides, except that instead of 1 M HCl only water was added. The products were purified by flash column chromatography (hexane/CH_2Cl_2 1:1; $R_f = 0.57$).

Compound 28·(*R*)-MTPA: ^{1}H NMR (400.13 MHz, $CDCl_3$): $\delta = 7.48$–7.05 (m, 20H$_{arom}$), 6.08 (X part of ABX system, $J = 7.8$, 5.3 Hz, 1H) and 6.03 (X part of ABX system, $J = 8.1$, 4.8 Hz, 1H), 3.66 and 3.56 (AB system, $J_{AB} = 13.6$ Hz, 4H), 3.48 and 3.40 (q, $J = 1.0$ Hz, 3H), 3.06 (dd [AB part of ABX system], $J = 13.9$, 8.1 Hz, 1H) and 2.99 (dd [AB part of ABX system], $J = 13.9$, 7.8 Hz, 1H), 2.74 ppm (dd [AB part of ABX system], $J = 13.9$, 4.8 Hz, 1H) and 2.73 (dd [AB part of ABX system], $J = 13.9$, 5.3 Hz, 1H); two diastereomers.

(2*R*)-[2-D$_1$]-28·(*R*)-MTPA: The spectroscopic data were identical to those of **28**·(*R*)-MTPA, except for the following signals: ^{1}H NMR (400.13 MHz, $CDCl_3$): $\delta = 6.092$ (d, $J = 5.1$ Hz, 1H) and 6.033 (d, $J =$ 8.1 Hz, 1H), 3.04 (d, $J = 8.1$ Hz, 1H) and 2.71 ppm (d, $J = 5.1$ Hz, 1H).

(2*S*)-[2-D$_1$]-28·(*R*)-MTPA: The spectroscopic data were identical to those of **28**·(*R*)-MTPA, except for the following signals: ^{1}H NMR (400.13 MHz, $CDCl_3$): $\delta = 6.088$ (d, $J = 7.8$ Hz, 1H) and 6.038 (d, $J =$ 4.6 Hz, 1H), 2.98 (d, $J = 7.8$ Hz, 1H) and 2.73 ppm (d, $J = 4.6$ Hz, 1H).

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