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Generation of a Configurationally Stable, Enantioenriched α-Oxy-α-methylbenzyllithium: Stereodivergence of Its Electrophilic Substitution[1]

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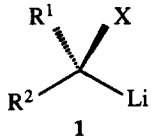
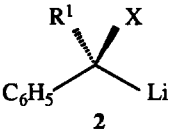
Abstract: The deprotonation of (*R*)- or (*S*)-1-phenylethyl *N,N*-diisopropylcarbamate with *s*-butyllithium/TMEDA in unpolar solvents (e.g. ether or hexane) at -78°C produces configurationally stable ion pairs which are substituted stereospecifically by different electrophiles. In several examples, complete stereoretention or inversion, respectively, was achieved. Electrophiles, which have an energetically low LUMO, such as acid chlorides, heterocumulenes and trialkyltin chlorides prefer antarafacial attack. If the leaving group has a high tendency to interact with the lithium cation, such as in esters, suprafacial substitution with retention takes place.

Chiral, heterosubstituted carbanions and the factors, influencing their rate of racemization, are of current interest in enantioselective synthesis[1]. Enantiomerically enriched α-lithiated alkyl ethers[2] **1a**,

Scheme 1



1



2

	R^1= alkyl or H, R^2= alkyl
a	X= -OCH_2O-R
b	X= -O-(C=O)-NR_2
c	X= -N-(alkyl)-(C=O)-OR
d	X= -(S=O)-Ph
e	X= -SO_2CF_3

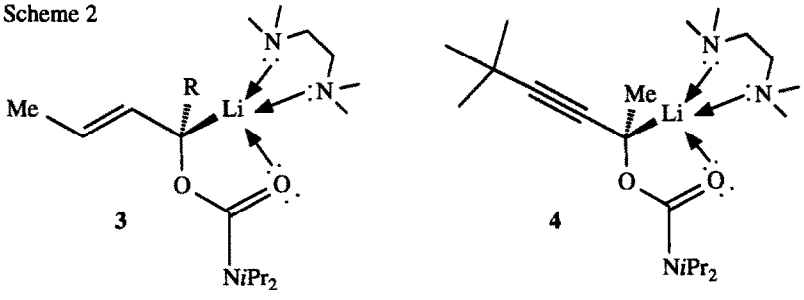
	R^1	X
a	H	-CH_3
b	H	-SPh
c	H	-SePh
d	H	-$SiMe_3$

O-alkyl carbamates[3] **1b**, *N*-alkyl carbamates[4] **1c** and related compounds[5] , alkyl aryl sulfoxides[6,7] **1d**, and alkyl trifluoromethyl sulfones[7,8] **1e** were shown to exhibit a synthetically useful extent of configurational stability in ethereal solvents at low temperatures.

The introduction of a phenyl group for R^2 into **1** enhances the stability of the carbanion by resonance leading to increasing planarization of the carbanionic center[9,10,11] and to a higher tendency for the formation of solvent-separated ion pairs. Both factors are suspected to facilitate the migration of the lithium cation from one enantiotopic face to the other one by intra- and intermolecular processes and thus, promoting racemization. As a consequence, enantiomerically enriched benzyllithium derivatives, bearing solely a center of chirality at the carbanion moiety, were unknown before 1990. Short-lived chiral α,α-dialkylbenzyl[12] or α-oxybenzyl carbanions[13], formed as transient intermediates, could be trapped by very reactive electrophiles. An activation barrier of enantiomerization of 16 kcal/mol was determinated in the lithium salt of racemic (1,2-diphenylethyl) trifluoromethyl sulfone[8a], this implicates that the enantiomerically enriched compound should racemize only slowly. It was demonstrated by the Hoffmann racemization test[14], which can be carried out with racemic samples, that α-methyl-[15], α-phenylthio-[16], α-phenylselenyl-[16], and α-trimethylsilyl-benzyllithium[16] enantiomerize in THF at -78°C at a rate, which is higher than that of the addition to aldehydes. Cyclic α-amino-benzyllithium derivatives epimerize rapidly at the benzylic center[10].

Lithiation. We expected that clamping the lithium cation in a tight chelate complex would hamper its migration from one enantiotopic face of the carbanion to the other one and, in addition, would slow down intermoleculare exchange processes. *N,N*-Dialkylcarbamoyloxy groups, introduced by us[14b,17] in order to enhance the kinetic acidity in lithiation reactions and to direct the regioselectivity in electrophilic substitution of allyllithium derivatives[18], turned out to be ideally suited for this purpose. The application of the "carbamate trick" led to the hitherto only known type of configurationally stable allyllithium derivatives[19] **3**, and as well, to enantioenriched 1-oxy-alkynyl derivatives[20] **4**, which are formed by deprotonation of the non-racemic precursors in unpolar solvents below -70°C in the presence of 1 equiv. of *N,N,N',N'*-tetramethylethylenediamine.

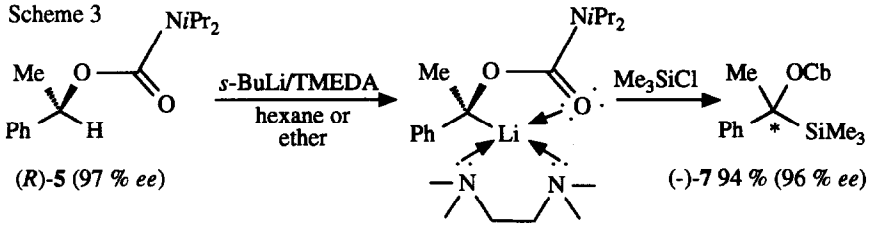
Scheme 2



Now we investigated the lithiation of (*R*)- and (*S*)-1-phenylethyl *N,N*-diisopropyl-carbamate[1] [(*R*)-and (*S*)-**5**]. These were prepared by the usual method[21] from the enantiomerically enriched alcohols (≥ 97% *ee*) obtained by enzymatic hydrolysis according to Schneider[22].

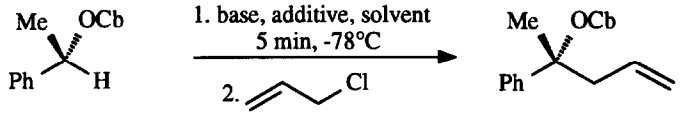
The deprotonation of (*R*)- or (*S*)-**5** by means of 1.1 equiv. *s*-butyllithium/TMEDA at -78°C in hexane or pentane was complete within 5 min. Addition of Me_3SiCl, after stirring at -78°C, afforded the optically active silane (-)-**7** of unknown configuration[23] with 94 % yield and 96 % *ee*. The identical result was obtained, when the reaction was performed in diethyl ether as solvent. Virtually no racemization had occured under the reaction conditions and the subsequent silylation had proceeded stereospecifically.

Scheme 3



The influence of the solvent, the additive, and the counter ion was studied in a series of allylation experiments. The results underline the importance of a tight ion pair for the configurative stability[41]. In THF, as also recently reported by Gawley[24], or by using a Schlosser-mixture[25] in ether, the formation of a racemic product **8** resulted. Interestingly, the high degree of ion separation in these experiments could be visually recognized by the deep red colour of the reaction mixture, which under usual conditions appears yellow to orange.

Scheme 4



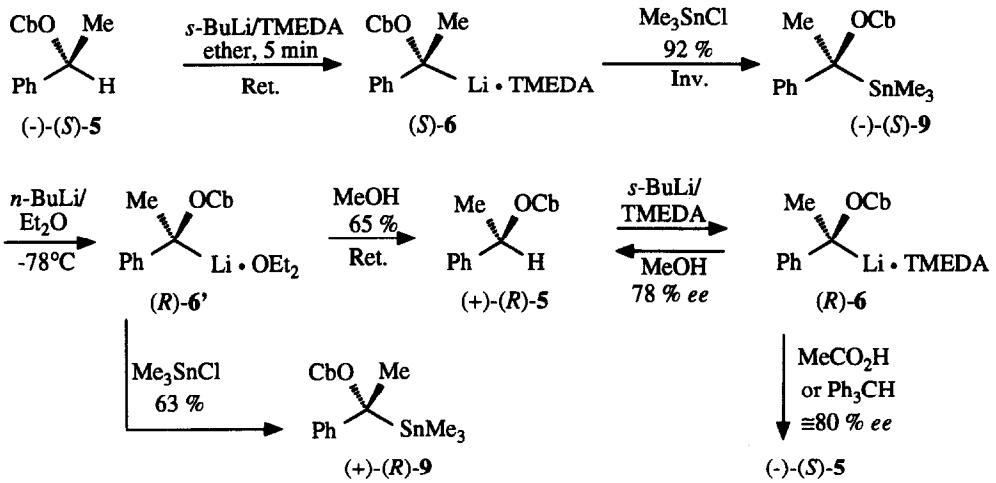
s-BuLi, TMEDA, pentane	88 % (83 % *ee*)
s-BuLi, TMEDA, ether	96 % (83 % *ee*)
s-BuLi, TMEDA, THF	44 % (5 % *ee*)
n-BuLi, K-*t*-pentoxide	61 % (0 % *ee*)

Closer investigations on the structure of the ion pair have not been accomplished yet. Theoretical calculations on the deprotonation by lithium bases predict stereoretention[26] and this is supported by the sum of experimental evidence shown below. The monomeric structure of the chelate complex **6** is deduced from the X-ray structures of related lithiated allyl carbamates[27] and of a benzyllithium • TMEDA • THF complex[28].

Stereochemistry of the protonation, stannylation, and acylation. Cram et al.[29] studied already in the late fifties short-lived, chiral α,α-dialkylbenzyl anions, generated by deprotonation or by several anionic fragmentation reactions in the presence of proton donors. Sense and direction of the chirality transfer largely depended on the conditions and the proton source. Transient tertiary benzyl anions, produced by Haller-Bauer cleavage[30], usually were protonated with stereoretention, whereas α-oxy-substituted benzyl anions, being involved in the Brook[13a] and reverse Brook[13b,31] rearrangement, usually reacted with inversion. Due to the non-availability of configurationally stable benzyllithium compounds, no systematic studies on the stereochemistry of electrophilic attack by various electrophiles had been undertaken. Anions, which bear a further stereogenic center, are problematic in this respect, since it is impossible to separate the effects of stereospecificity and of chiral induction[10].

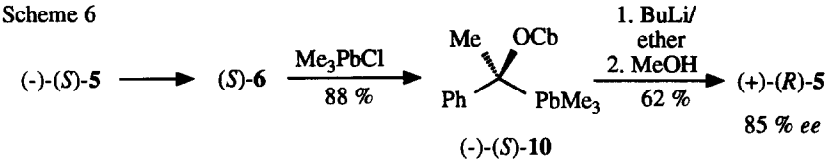
The lithium carbanions **6**, for the first time, permitted an investigation of chiral benzylic carbanions, untouched by the problems mentioned above[1]. The stereochemistry of stannylation and protonation was uncovered by the following reaction sequence: (-)-(*S*)-**5** (≥ 99 % *ee*) was deprotonated and reacted with Me_3SnCl to afford the stannane (-)-**9** with 92 % yield. The *ee*-value could not be determined on this stage. (-)-**9** was cleaved with *n*-BuLi in ether and the ether complex **6'** quenched with methanol to afford the enantiomer (+)-(*R*)-**5** of the starting material with 65 % yield and ≥ 95 % *ee*. The deprotonation of the carbamate (+)-(*R*)-**5**, followed by methanolysis, proceeds with overall retention, however the protonation by means of acetic acid or triphenylmethane caused inversion. Since all lithiodestannylation reactions, known in their stereochemical course, take place with stereoretention[32], the described stannylation of **5** must have occured with inversion. So the reaction outlined above permits the stereospecific inversion of a chiral benzyllithium, which might be of synthetic interest.

Scheme 5



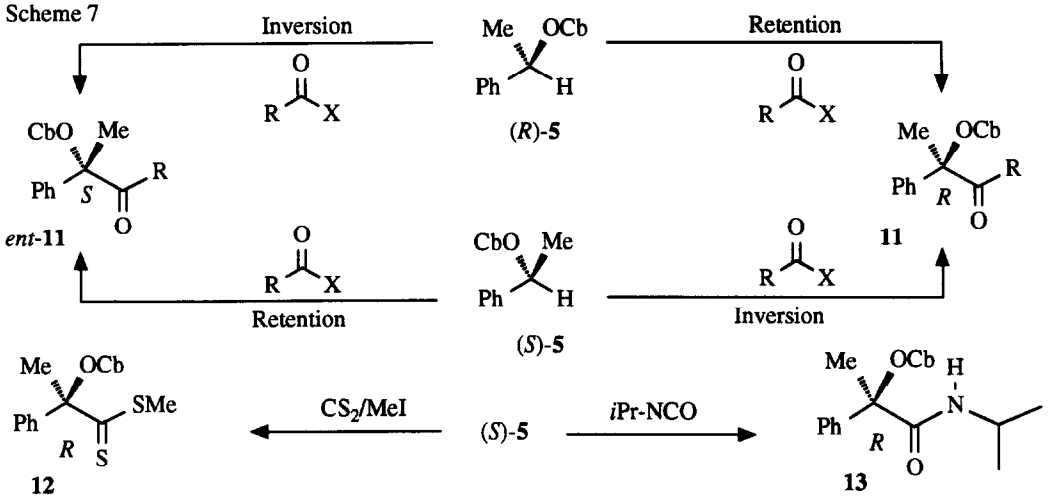
The trimethylplumbylation[33,34] of (*S*)-**6**, via (-)-(*S*)-**10** followed by lithio-deplumbylation and methanolysis took, a little less efficiently, the same stereochemical course.

Scheme 6



Several carbonyl and heterocarbonyl compounds were allowed to react with the lithium carbanion, derived either from (*R*)-**5** (97 % *ee*) or (*S*)-**5** (≥ 99 % *ee*), and the sense and degree of stereospecificity were determined (Scheme 7, Table 1). Methyl carboxylates (entries 6, 7, 11, 12) yielded the appropriate ketones **11** or *ent*-**11** with almost complete stereoretention, similarly to dimethyl carbonate (entry 1). Acid chlorides (entries 10 and 13), on the other hand, exhibit complete stereoinversion, which is slightly diminished for methyl chlorocarbonate (entry 2). Interestingly, also methyl cyanoformate (entry 5) causes inversion, but acid anhydrides (entries 3, 8, 9) react with retention, though to a reduced extent. Heterocumulenes, such as carbon dioxide and disulfide (entries 4 and 14) or isopropyl isocyanate (entry 15) again prefer the attack from the rear face.

Scheme 7



How can the stereodivergence of electrophilic substitution, which is determined by the type of electrophile, and as well, by the nucleofugic leaving group be explained? We propose as a working hypothesis the following: Non-mesomerically stabilized α-oxyalkyllithium derivatives, being sp^3-hybridized, react with all investigated electrophiles under clean stereoretention[2,3]. Benzyllithium derivatives have a flattened - but not completely planar - carbanionic moiety[9] and, thus, have a consider-

able electron density at the rear face. The attacking electrophile, figuratively speaking, has the choice of approaching antarafacially, avoiding hindrance by the complexed cation (path A, inversion), or, alternatively, taking advantage from an interaction with the lithium cation in a suprafacial attack (path B, retention). Those electrophiles, which prefer antarafacial attack (e. g. acid chlorides, cyanides, heterocumulenes, and stannyl chlorides), possess an energetically low LUMO, but do not have particularly good complexing groups for the lithium cation. The pre-complexation however dictates the reaction path, if a good electron-donating ability to lithium and a less favourable LUMO is involved (for esters, alcohols, or aliphatic aldehydes and ketones[35], or alkyl halides[1]). Obviously, acyl anhydrides constitute a borderline case with an energetic difference of less than 1.5 kcal/mol between both competing reaction paths. The protonation experiment with acetic acid, causing inversion, seems to contradict the hypothesis. Presumably, here an intermediate ammonium salt is the actual proton source.

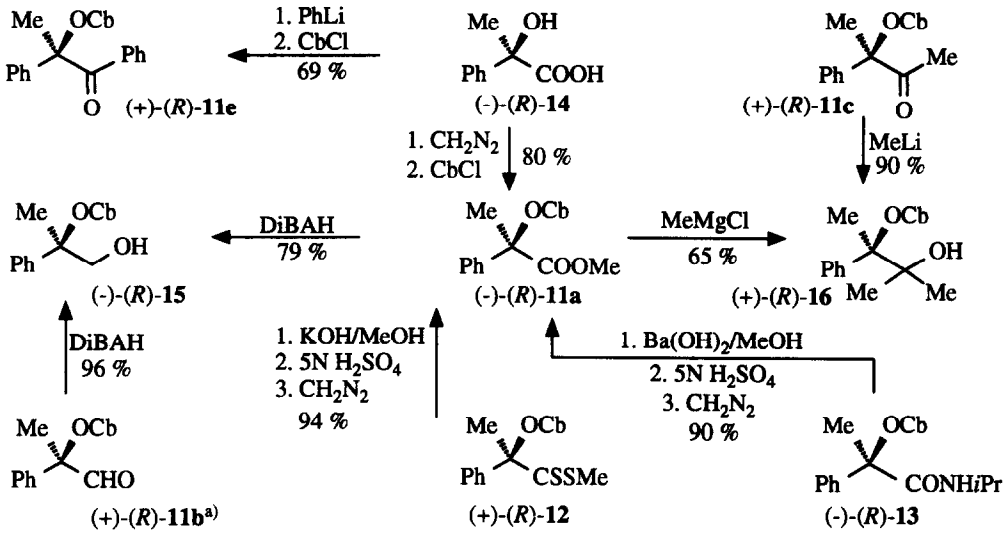
Table 1 Acylation of lithium compounds **6**

Entry	Educt	Electrophile /Conditions[a)]	Product	R	Yield (%)	*ee* (%)	Conf.	Course
1	(*R*)-**5** [c)]	MeOC(=O)OMe /C	**11a**	OMe	85	94	(-)-(*R*)	Ret.
2	(*R*)-**5** [c)]	MeOC(=O)Cl /C	*ent*-**11a**	OMe	90	85	(+)-(*S*)	Inv.
3	(*R*)-**5** [c)]	MeOC(=O)-OCO_2Me /C	**11a**	OMe	40	62	(-)-(*R*)	Ret.
4	(*R*)-**5** [c)]	CO_2 /C	*ent*-**11a** [d)]	OMe	84	84	(+)-(*S*)	Inv.
5	(*S*)-**5** [e)]	MeC(=O)CN /A	**11a**	OMe	43	92	(-)-(*R*)	Inv.
6	(*S*)-**5** [e)]	H-C(=O)OMe /A	*ent*-**11b**	H	60	≥ 95	(-)-(*S*)	Ret.
7	(*S*)-**5** [e)]	MeC(=O)OMe /A	*ent*-**11c**	Me	60	≥ 95	(-)-(*S*)	Ret.
8	(*S*)-**5** [e)]	MeC(=O)OAc /A	*ent*-**11c**	Me	53	76	(-)-(*S*)	Ret.
9	(*S*)-**5** [e)]	MeC(=O)OAc /B	*ent*-**11c**	Me	35	60	(-)-(*S*)	Ret.
10	(*S*)-**5** [e)]	MeC(=O)Cl /A	**11c**	Me	35	≥ 95	(+)-(*R*)	Inv.
11	(*S*)-**5** [e)]	*i*PrC(=O)OMe /A	*ent*-**11d**	*i*Pr	94	≥ 95	(-)-(*S*)	Ret.
12	(*S*)-**5** [e)]	PhC(=O)OMe /A	*ent*-**11e**	Ph	95	≥ 95	(-)-(*S*)	Ret.
13	(*S*)-**5** [e)]	PhC(=O)Cl /A	**11e**	Ph	95	≥ 95	(+)-(*R*)	Inv.
14	(*S*)-**5** [e)]	S=C=S /A	**12** [f)]	-	67	≥ 95	(+)-(*R*)	Inv.
15	(*S*)-**5** [e)]	*i*Pr-N=C=O /A	**13**	-	90	85	(-)-(*R*)	Inv.

a) Conditions for deprotonation; A: 5 min in ether; B: 5 min in pentane; C: 30 min hexane.
b) Determinated by ^{1}H-NMR, see experimental part. c) 97 % *ee*. d) After methylation of the crude acid with CH_2N_2. e) ≥ 95 % *ee*. f) After methylation of the dithiocarboxylate with MeI.

Stereochemical correlations. All new enantioenriched compounds (except for (-)-**7**, (+)-**8**, and *ent*-**11d**) were correlated by chemical transformations via relais compounds with (+)-(*S*)-atrolactic acid[36] (**14**) and (+)-(*S*)-2-methyl-3-phenyl-2,3-butanediol[37] or, respectively, with the corresponding enantiomers. Scheme 8 summarizes the results without further comment. The allylation product (+)-(*R*)-**8**[35] was shown to have the same configuration as (+)-(*R*)-2-phenyl-2-butanol[38].

Scheme 8



a) The reaction was performed with the enantiomeric compound.

EXPERIMENTAL

Diethyl ether, hexane, and pentane were dried by distillation in Ar atmosphere over $LiAlH_4$; TMEDA and pyridine were distilled over CaH_2. The content of approx. 1.4M *s*-BuLi soln. in cyclohexane/isopentane was determined by titration with diphenylacetic acid[38] before use. Separation on scales below 2 mmol were carried out by flash LC on silica gel 32-63 μm. NMR spectra were recorded on spectrometers EM 360 and EM 390 (Varian) or AM 300 and AC 200 (Bruker). ^1H NMR spectroscopic determinations of *ee*-values were carried out with the chiral shift reagent $Eu(hfc)_3$ in $CDCl_3$ solution and the racemates were used for standards. Optical rotations were recorded with the polarimeter 241 (Perkin-Elmer) in 1 dm cuvettes.

*(R)- or (S)-1-Phenylethyl N,N-diisopropylcarbamate [(R)- or (S)-**5**].* (*R*)- or (*S*)-1-phenylethanol[22] (≥ 97 % *ee*, 38.0 g, 0.31 mol), dry pyridine (34.8 g, 0.44 mol), *N,N*-diisopropylcarbamoyl chloride (49.1 g, 0.30 mol) were stirred at 90°C for 10 h. Then, the reaction mixture was chilled to room temp. and poured to a slurry of ice (150 g), 35 proc. aqu. HCl (60 mL), and ether (150 mL). The aqu. soln. was extracted with ether (3 x 60 mL), the combined etheral solns. washed with sat. aqu. $NaHCO_3$ (60 mL) followed by sat. aqu. KCl (60 mL). After drying ($MgSO_4$) and evaporation of the solvent under reduced pressure, the residue was purified by LC (silica gel, ether/pentane 1:10) to yield 71.4 g (92 %) **5** as colourless oil.
^1H NMR (300 MHz, $CDCl_3$): δ= 1.20 [d, $^3J_{iPr}$= 6.7 Hz, $NCH(CH_3)_2$], 1.55 (d, $^3J_{1,2}$= 6.6 Hz, 2-H_3, 3.94 (qq, NCH), 5.85 (q, 1-H), 7.21-7.39 (m, Ar-H). IR (neat): 1690 cm^{-1} (C=O). (*R*)-**5**, 97 % *ee*, $[\alpha]_D^{20}$= +5.1 (c = 1.2, CH_2Cl_2). (*S*)-**5**, ≥ 99 % *ee*, $[\alpha]_D^{20}$= -5.5 (c= 1.2, CH_2Cl_2).
$C_{15}H_{23}NO_2$ (249.36) calc. C 72.25 H 9.30 found C 72.41 H 9.29.

*Lithiation and electrophilic substitution of (R)- or (S)-**5**.* To a solution of (*R*)- or (*S*)-**5** (97 or ≥ 99 % *ee*, resp.; 249 mg, 1.00 mmol) and *N,N,N',N'*-tetramethylethylenediamine (128 mg, 1.10 mmol) in dry ether (2 mL, conditions A), pentane (2 mL, conditions B), hexane (2 mL, conditions C) was added dropwise with a syringe within 2 min below -70°C approx. 1.4M *s*-butyllithium in cyclohexane/isopentane

(1.10 mmol). Stirring of the solution of the lithium compound **6** was continued for 5 min (for A and B) or for 30 min (for C) before the electrophile (1.10 mmol) in ether (1 mL) was added. Stirring was continued for 30 min at -78°C. The reaction mixture was allowed to warm to 20°C within 30 min, 2N aqu. HCl (2 mL) was added, the aqu. soln. extracted with ether (3 x 20 mL), the etheral soln. washed with sat. aqu. $NaHCO_3$ (20 mL). After drying ($MgSO_4$), evaporation of the solvent i. vak., the residue was purified by LC (silica gel, ether/pentane 1:2-20). The *ee*-values were determined by ^1H NMR spectroscopy (if not stated otherwise).

Protonation of (R)-**6**. The solution of (*R*)-**6**, prepared from (*R*)-**5** (97 % *ee*), conditions C, was reacted with 1.1 equiv. of "acid" as the electrophile.

With methanol: 194 mg (78 %) (*R*)-**5**, 78 % *ee*, $[\alpha]_D^{20}$= +4.0 (c= 1, CH_2Cl_2). - *With acetic acid*: 186 mg (74 %) (*S*)-**5**, 79 % *ee*, $[\alpha]_D^{20}$= -3.3 (c= 0.76, CH_2Cl_2). - *With triphenylmethane*: 114 mg (46 %) (*S*)-**5**, 80 % *ee*, $[\alpha]_D^{20}$= -4.2 (c = 1, CH_2Cl_2).

*(-)-1-Phenyl-1-(trimethylsilyl)ethyl N,N-diisopropylcarbamate [(-)-***7***].* From (*R*)-**5** and Me_3SiCl, conditions C, 302 mg (94 %), oil; 96 % *ee*, $[\alpha]_D^{20}$= -17.3 (c= 2.3, CH_2Cl_2). NMR and microanalytical data see table 2.

*(+)-(R)-1-Methyl-1-phenylbut-3-enyl N,N-diisopropylcarbamate [(R)-***8***].* From (*S*)-**5** and 1-chloro-2-propene; A: 278 mg (96 %), oil; 84 % *ee*; B: 253 mg (88 %), 83 % *ee*, $[\alpha]_D^{20}$= +15.6 (c = 1, CH_2Cl_2).

Following the procedure in THF as solvent afforded 127 mg (44 %) (*R*)-**8**, 5 % *ee*, $[\alpha]_D^{20}$= +1.1 (c = 1.1, CH_2Cl_2).

Deprotonation with potassium t-pentoxide/butyllithium: To a soln. of (*S*)-**5** (249 mg, 1.00 mmol) in ether (2 mL) were sequentially added below -70°C 1.7M potassium *t*-pentylate in toluene (0.65 mL, 1.10 mmol) and 1.73M butyllithium in hexane (0.63 mL, 1.10 mmol). After 2 min stirring, 1-chloro-2-propene (84 mg, 1.1 mmol) was added. The red colour of the reaction mixture disappeared immediately and workup was accomplished as described above. Yield: 176 mg (61 %) *rac*-**8**.

*(-)-(S)-1-Phenyl-1-(trimethylstannyl)ethyl N,N-diisopropylcarbamate [(S)-***9***].* From (*S*)-**5** (3.24 g, 13 mmol), A, and trimethyltin chloride (2.69 g, 13.5 mmol), LC with ether/pentane (1:20), 4.93 g (92 %) (*S*)-**9**; m.p. 62°C (without solvent), were obtained. $[\alpha]_D^{20}$= -77.0 (c = 1.2, CH_2Cl_2), ≥ 95 % *ee* (see below).

*Lithio-destannylation of (S)-***9** *and methanolysis.* To a soln. of (*S*)-**9** (206 mg, 0.50 mmol) in ether (2 mL) was added 1.73M butyllithium in hexane (0.32 mL, 0.55 mmol) below -70°C. After stirring for 5 min, the reaction mixture was quenched with methanol (20 mg, 0.60 mmol). The subsequent workup was accomplished as described above and yielded 81 mg (65 %) (*R*)-**5**, ≥ 95 % *ee*, $[\alpha]_D^{20}$= +6.1 (c = 0.7, CH_2Cl_2).

*(-)-(S)-1-Phenyl-1-(trimethylplumbyl)ethyl N,N-diisopropylcarbamate [(S)-***10***].* From (*S*)-**5** and trimethyllead bromide[33] (dissolved in 1 mL THF), yield 443 mg (88 %) (*S*)-**10**, m.p. 54°C (without solvent), $[\alpha]_D^{20}$= -61.1 (c = 1, CH_2Cl_2), ≥ 85 % *ee* (see below).

*Lithio-deplumbylation of (S)-***10** *and methanolysis:* The procedure, described for **9**, afforded 77 mg (62 %) (*R*)-**5** with 85 % *ee*.

*(-)-(R)- and (+)-(S)-Methyl 2-(N,N-diisopropylcarbamoyloxy)-2-phenylpropanoate (***11a** *and ent-***11a***).* From (*R*)-**5** and dimethyl carbonate, C, 261 mg (85 %) **11a**, m.p. 80°C (ether/pentane), 94 % *ee*, $[\alpha]_D^{20}$= -7.5 (c= 1.2, CH_2Cl_2). - With methyl chloroformate, C, 277 mg (90 %) *ent*-**11a**, 85 % *ee*, $[\alpha]_D^{20}$= +6.9 (c= 1.1, CH_2Cl_2). - With dimethyl dicarbonate, C, 123 mg (40 %) **11a**, 62 % *ee*, $[\alpha]_D^{20}$= -5.2 (c = 1.0, CH_2Cl_2). - With carbon dioxide, C (no $NaHCO_3$ extraction, esterification of the crude acid with diazomethane), 258 mg (84 %) *ent*-**11a**, 84 % *ee*, $[\alpha]_D^{20}$= +6.8 (c = 1.4, CH_2Cl_2). - With (*S*)-**5** and methyl cyanoformate, A, 133 mg (43 %) **11a**, 92 % *ee*, $[\alpha]_D^{20}$= -6.2 (c = 1.2, CH_2Cl_2).

*(-)-(S)-2-(N,N-Diisopropylcarbamoyloxy)-2-phenylpropanal (ent-***11b***).* From (*S*)-**5** and methyl formate, A, crystallization from pentane, 167 mg (60 %), m.p. 105°C, ≥ 95 % *ee*, $[\alpha]_D^{20}$= -116.1 (c = 0.7, CH_2Cl_2).

*(+)-(R)- and (-)-(S)-3-(N,N-Diisopropylcarbamoyloxy)-3-phenyl-2-butanone (**11c** and ent-**11c**).* From (*S*)-**5** and methyl acetate, A, 173 mg (60 %), m.p. 62°C (no solvent), *ent*-**11c**, ≥ 95 % *ee*, $[\alpha]_D^{20}$= -124.1 (c = 1.1, CH_2Cl_2). - With acetic acid anhydride, A, 154 mg (53 %) *ent*-**11c**, 76 % *ee*, $[\alpha]_D^{20}$= -94.3 (c = 1.3, CH_2Cl_2). - With acetic acid anhydride, B, 101 mg (35 %), *ent*-**11c**, 60 % *ee*, $[\alpha]_D^{20}$= -74.2 (c = 1.3, CH_2Cl_2). - With acetyl chloride, A, 100 mg (35 %), **11c**, ≥ 95 % *ee*, $[\alpha]_D^{20}$= +111.7 (c = 1.1, CH_2Cl_2).

Table 2. Selected IR, ^1H NMR, ^{13}C NMR data (ppm, $CDCl_3$) and microanalytical data of the compounds **7** - **16**

	IR (cm^{-1})	CH_3 (CH_3)	El, ^1H (El, ^{13}C)	Mol. Formula (Mol. Weight)	C,H (calc.) C,H (found)
7	1690, 840	1.90 (s) (22.45)	0.01 (s) (-2.98)	$C_{18}H_{31}NO_2Si$ (321.54)	C 67.24 H 9.72 C 67.26 H 9.86
8	1690	1.82 (s) (25.38)	2.81 (ddt),5.01-5.12 (m), 5.58-5.79 (m) (47.09, 118.37, 133.48)	$C_{18}H_{27}NO_2$ (289.42)	C 74.70 H 9.40 C 74.84 H 9.50
9	1670, 760	1.83 (s) (25.49)	-0.03 (s) (-6.83)	$C_{18}H_{31}NO_2Sn$ (412.16)	C 52.45 H 7.58 C 52.28 H 7.63
10	1675, 760	2.03 (s) (26.74)	0.60 (s) (-2.98)	$C_{18}H_{31}NO_2Pb$ (500.65)	a)
11a	1735, 1700	1.98 (s) (25.20)	3.69 (s) (52.24, 172.13)	$C_{17}H_{25}NO_4$ (307.39)	C 66.43 H 8.76 C 66.27 H 8.71
11b	1720, 1690	1.84 (s) (21.33)	9.47 (s) (194.34)	$C_{16}H_{23}NO_3$ (277.36)	C 69.29 H 8.36 C 69.24 H 8.54
11c	1710, 1680	1.85 (s) (23.61)	1.96 (s) (23.88, 204.19)	$C_{17}H_{25}NO_3$ (291.39)	C 70.07 H 8.65 C 70.28 H 8.72
11d	1710, 1700	1.87 (s) (24.20)	0.44 (d), 1.06 (d), 2.86 (qq) (19.47, 22.27, 34.06, 211.78)	$C_{19}H_{29}NO_3$ (319.44)	C 71.44 H 9.15 C 71.39 H 9.36
11e	1700, 1685	1.98 (s) (27.84)	7.18-7.71 (m) (127.57, 128.88, 131.23, 136.71, 197.30)	$C_{22}H_{27}NO_3$ (353.46)	C 74.76 H 7.70 C 74.92 H 7.75
12	1705, 1315	2.37 (s) (28.34)	2.54 (s) (19.79, 237.62)	$C_{17}H_{25}NO_2S_2$ (339.52)	C 60.14 H 7.42 C 60.25 H 7.65
13	3335 1705,, 1655	1.96 (s) (25.19)	1.06 (d), 1.12 (d), 4.08 (qq), 5.84 (d) (22.51, 22.58, 41.43, 170.84)	$C_{19}H_{30}N_2O_3$ (334.46)	C 68.23 H 9.04 C 68.42 H 9.17
15	3450, 1670	1.73 (s) (24.50)	3.95 (dd), 4.90 (t) (70.63)	$C_{16}H_{25}NO_3$ (279.38)	C 68.79 H 9.02 C 68.92 H 8.89
16	3400, 1670	1.96 (s) (21.07)	1.09-1.26 (m), 3.47(s) (25.05, 26.43, 74.71)	$C_{18}H_{29}NO_3$ (307.43)	C 70.32 H 9.51 C 70.10 H 9.38

a) No correct microanalysis could be obtained due to partial decomposition.

*(-)-(S)-2-(N,N-Diisopropylcarbamoyloxy)-4-methyl-2-phenyl-3-pentanone (ent-***11d***).* From (*S*)-**5** and methyl 2-methylpropanoate, A, 300 mg (94 %) *ent*-**11d**, m.p. 58°C (no solvent), ≥ 95 % *ee*, $[\alpha]_D^{20}$= -134.2 (c = 1.0, CH_2Cl_2).

*(+)-(R)- and (-)-(S)-2-(N,N-Diisopropylcarbamoyloxy)-1,2-diphenyl-1-propanone (***11e** *and ent-***11e***).* From (*S*)-**5** and methyl benzoate, A, 336 mg (95 %) *ent*-**11e**, m.p. 105°C (no solvent), ≥ 95 % *ee*; $[\alpha]_D^{20}$= -104.7 (c = 1.1, CH_2Cl_2). - With benzoyl chloride, A, 304 mg (86 %) **11e**, ≥ 95 % *ee*, $[\alpha]_D^{20}$= +113.0 (c = 1.1, CH_2Cl_2).

*(+)-(R)-S-Methyl 2-(N,N-Diisopropylcarbamoyloxy)-2-methylpropanedithioate (***12***).* From (*S*)-**5** and carbon disulfide, A, followed by addition of 1 equiv. of methyl iodide, 229 mg (67 %) **12**, m.p. 82°C (no solvent), ≥ 95 % *ee*; $[\alpha]_D^{20}$= +242.0 (c = 0.6, CH_2Cl_2).

*(-)-(R)-2-(N,N-Diisopropylcarbamoyloxy)-N-isopropyl-2-phenyl-propanamide (***13***).* From (*S*)-**5** and isopropyl isocyanate, A, 246 mg (74 %) **13**, m.p. 69°C (no solvent), ≥ 85 % *ee* (see below), $[\alpha]_D^{20}$= -0.8 (c = 1.1, CH_2Cl_2).

Conversion into **11a**. 334 mg (1.00 mmol) **13** and $Ba(OH)_2 \cdot 8\ H_2O$ (950 mg, 3.0 mmol) in methanol (5 mL) were refluxed for 4h. Acidic workup, followed by diazomethane afforded 276 mg (90 %) **11a** with 85 % *ee* and $[\alpha]_D^{20}$= -6.8 (c = 1.1, CH_2Cl_2).

Stereochemical correlations

*Conversion of (+)-(S)-atrolactic acid (ent-***14***) into ent-***11a**. To a soln. of (*S*)-atrolactic acid[37] *(ent-***14***)* (341 mg, 2.0 mmol), $[\alpha]_D^{20}$= +35.9 (c = 3.5, EtOH), in ether (4 mL) was added etheral diazomethane soln. until it remained yellow. Excess reagent was destroyed by addition of few silica gel and workup accomplished as usual. The crude methyl ester and (*N,N*)-diisopropylcarbamoyl chloride (655 mg, 4.0 mmol) yielded 490 mg (80 %) (-)-(*S*)-**11a**, ≥ 95 % *ee*, $[\alpha]_D^{20}$= -8.9 (c = 1.2, CH_2Cl_2).

Methyl carboxylate **11a** *from dithiocarboxylate* **12**. A soln. of (+)-(*R*)-**12** (340 mg, 1.00 mmol) and of KOH (168 mg, 3.0 mmol) in methanol (5 mL) was refluxed for 30 min. 5N H_2SO_4 (1 mL) was added and the crude acid converted into the ester to yield 289 mg (94 %) (-)-(*R*)-**11a**, ≥ 95 % *ee*, $[\alpha]_D^{20}$= -8.2 (c = 1.0, CH_2Cl_2).

*(-)-(R)- and (+)-(S)-(2-Hydroxy-1-methyl-1-phenylethyl) N,N-diisopropylcarbamate [***15** *and ent-***15***] from* **11b** *and ent-***11a**. To a soln. of (-)-(*S*)-**11b** (277 mg, 1.00 mmol) in ether (2 mL) was added at 0°C 1M diisobutylaluminium hydride (DIBAH) in hexane (1.0 mmol) and stirring was continued for 2h. Usual workup and LC [silica gel, ether/pentane (1:1)] yielded 267 mg (96 %) (*S*)-**15**, m.p. 82°C (no solvent), $[\alpha]_D^{20}$= +51.8 (c = 1.1, CH_2Cl_2). Similarly, with 2.2 equiv. of DIBAH, were obtained from *ent*-**11a** 220 mg (*R*)-**15** (79 %), ≥ 95 % *ee*, $[\alpha]_D^{20}$= -52.2 (c = 1.1, CH_2Cl_2). Further data see table 2.

*(+)-(R)-(1,2-Dimethyl-2-hydroxy-1-phenylpropyl) N,N-diisopropylcarbamate (***16***) from* **11a**. To a soln. of (*R*)-**11a** (307 mg, 1.00 mmol) in ether (5 mL) was added 3M methylmagnesium chloride in THF (0.73 mL, 2.2 mmol) and stirring was continued for 12h at 20°C. Usual workup and LC [silica gel, ether/pentane (1:4)] afforded 200 mg (65 %) (*R*)-**16**, m.p. 84°C (no solvent), $[\alpha]_D^{20}$= +32.4 (c = 1.1, CH_2Cl_2); ≥ 95 % *ee*. Further data see table 2.

*Alcohol ent-***16** *from ketone ent-***11c**. To a soln. of ketone (-)-(*S*)-**11c** (178 mg, 0.61 mmol) in ether (2 mL) was added at 0°C 1.6M methyllithium in ether (0.42 mL, 0.67 mmol) and stirring continued for 30 min. Usual workup yielded 169 mg (90 %) *ent*-**16**, $[\alpha]_D^{20}$= -30.2 (c = 1.0, CH_2Cl_2).

Ketone **11e** *from (R)-atrolactic acid (***14***).* (+)-(*R*)-2-hydroxy-1,2-diphenylpropan-1-one[40] (469 mg, 2.07 mmol), prepared from (-)-(*R*)-**14**, was converted (as described for **5**) into (+)-(*R*)-**11e**, $[\alpha]_D^{20}$= +98.2 (c = 1.1, CH_2Cl_2); yield 488 mg (67 %).

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