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Highly Enantioenriched Homoenolate Reagents by Asymmetric γ-Deprotonation of Achiral 1-Silyl-Substituted 1-Alkenyl Carbamates

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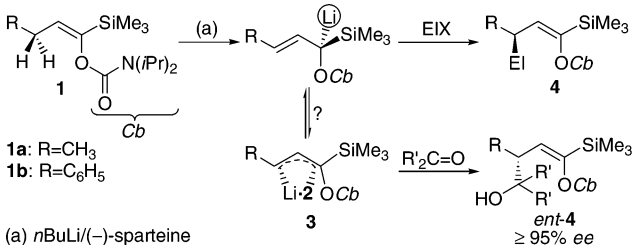
ABSTRACT



1-Trimethylsilyl-1-alkenyl carbamates 1 are deprotonated by *n*-butyllithium/(−)-sparteine (2) with a high degree of enantiotopic differentiation in the γ-position to form the enantiomerically enriched allyllithium derivatives 3. Trapping these with several electrophiles proceeds stereospecifically in an *anti*-S_E' or *syn*-S_E' substitution to form products 4 or *ent*-4, respectively. Compounds 3a (R = Me) and 3b (R = Ph) exhibit toward carbonyl electrophiles opposite senses of almost complete stereospecificity, thus for 3b·2 the involvement of a η^3-complex is suggested.

Enantioenriched homoenolate reagents are valuable synthetic building blocks.[1] In particular, 1-oxygen-[2] and 1-nitrogen-substituted[3] 1-metalallyl derivatives proved to be ideal reagents for enantio- and diastereoselective homoaldol reactions. Quite recently, we found a surprisingly simple approach to configurationally stable, enantioenriched homoenolate reagents by (−)-sparteine-mediated γ-deprotonation of 1-aryl-1-alkenyl carbamates **1** (aryl for Me_3Si).[4] Here, the 3-*pro*-*R*-proton, which is localized in a position remote from the complexing group, is removed with high selectivity by the chiral base. Taking into account that an anion-stabilizing group in position 1 may be required, we now investigated the 1-trimethylsilyl-1-butenyl carbamate **1a** (Scheme 1).[5] For efficient deprotonation in toluene, 3 equiv of *n*-butyllithium/(−)-sparteine (**2**) and a reaction time of 12 h at −78 °C were required. Under these conditions, the lithium compound **3a** proved to be perfectly configurationally stable, and trapping it provided the γ-substitution products **4a**−**c** in high yield and with ≥95% ee. Acylations of **3a** to

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(1) Reviews: (a) Hoppe, D.; Hense, T. *Angew. Chem.* **1997**, *109*, 2376; *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2282. (b) Hoppe, D.; Marr, F.; Brüggemann, M. In *Organolithium in Enantioselective Synthesis*; Hodgson, D. M., Ed.; Topics in Organometallic Chemistry; Springer-Verlag: Berlin, 2003; Vol. 5, p 61. (c) Beak, P.; Johnson, T. A.; Kim, D. D.; Lim, S. H. In *Organolithium in Enantioselective Synthesis*; Hodgson, D. M., Ed.; Topics in Organometallic Chemistry; Springer-Verlag: Berlin, 2003; Vol. 5, p 134. (d) Ahlbrecht, H.; Beyer, U. *Synthesis* **1999**, 365.

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(4) Hoppe, D.; Seppi, M.; Kalkofen, R.; Reupohl, J.; Fröhlich, R. *Angew. Chem.* **2004**, *116*, in press.

(5) (*E*)-1-Trimethylsilyl-1-butenyl *N*,*N*-diisopropylcarbamate was produced from the 2-buten-1-ol in a three-step sequence (see Supporting Information).

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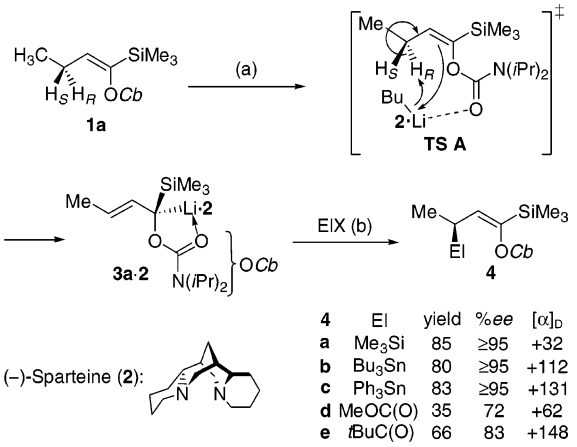
Scheme 1. Lithiation of **1a** and Reaction with Electrophiles[a]



4	El	yield	%*ee*	$[\alpha]_D$
a	Me_3Si	85	≥95	+32
b	Bu_3Sn	80	≥95	+112
c	Ph_3Sn	83	≥95	+131
d	MeOC(O)	35	72	+62
e	*t*BuC(O)	66	83	+148

[a] Reagents and conditions: (a) 3.0 equiv of *n*BuLi/(−)-sparteine, toluene, −78 °C, 12 h; (b) (i) 6.0 equiv of EIX, −78 °C, 2 h, (ii) MeOH, HOAc , (iii) rt.

form alkenyl ester **4d** and ketone **4e** were less efficient (Scheme 1). We assume that enolate formation by excess of base is the origin of partial racemization and decomposition. As will be shown below,[6] products **4a**−**e** have (*S*)-configuration, resulting from *anti*-S_E' attack of the electrophile onto (*R*)-**3a·2**.

The exchange of lithium for tris(diethylamino)titanium[7−9] in (*R*)-**3a·2** generally proceeds with inversion of configuration to form the intermediate (*R*)-**5a**, which adds to aldehydes via a Zimmerman-Traxler transition state[10] in a strict *syn*-S_E' fashion, leading with complete 1,3-transfer of chirality to essentially enantiopure homoaldol products *anti*-**6** (Scheme 2 and Table 1). Direct addition of the aldehydes to the

Table 1. Prepared Homoaldol Products **6**

RCH=O	product	yield	% ee[a]	dr[b]	$[\alpha]_D$[c]
$CH_3(CH_2)_2CH$=O	*anti*-**6a**	70	≥95	≥95:5	−25
$(CH_3)_2CHCH$=O	*anti*-**6b**	72	≥95	≥95:5	−27
$(CH_3)_3CCH$=O	*anti*-**6c**	80	≥95	≥95:5	−29
c$C_6H_{11}CH$=O	*anti*-**6d**	69	≥95	≥95:5	−15
$(C_6H_5)CH$=O	*anti*-**6e**	71	89	≥95:5	−78

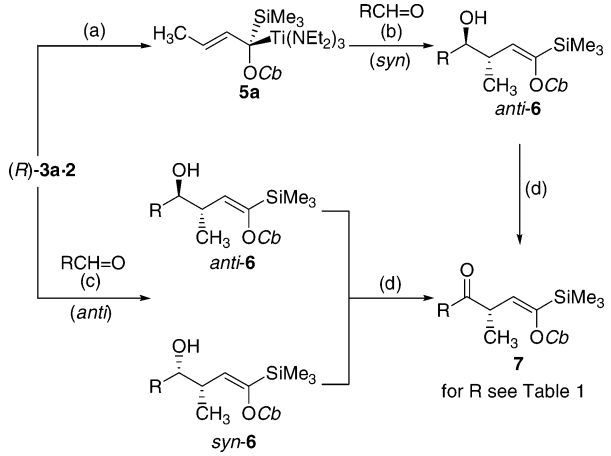
[a] Determined by ^{1}H NMR shift experiments. [b] Determined by ^{1}H NMR and GC. [c] c = 0.8−2.8, $CHCl_3$.

lithiated compound (*R*)-**3a·2** furnishes mixtures of *anti*- and *syn*-**6** (approximately 1:1) (Scheme 2).

Samples of the homoallylic alcohols **6d** and **6e** were oxidized to ketones (+)-**7d** ($[\alpha]_D$ = +169 and +168) and (+)-**7e** ($[\alpha]_D$ = +158 and +160), respectively, giving evidence for the identical absolute configuration at C-3 in

(6) Lithiodestannylation of (*S*)-(+)-**4b** ($[\alpha]_D$ = +112) with *n*BuLi/Et_2O at −78 °C and reaction of the formed (*S*)-**3a**·Et_2O with Ph_3SnCl afforded (*R*)-(−)-**4c** ($[\alpha]_D$ = −66, 48% ee) with 87% yield. Since all known lithiodestannylations proceed as suprafacial processes, the stereochemical course of the reverse reaction is (one time more) *anti*-S_E'.

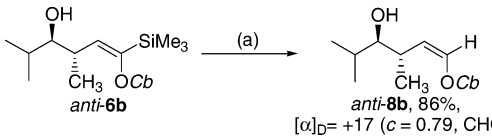
Scheme 2. Transmetalation and Homoaldol Reaction[a]



[a] Reagents and conditions: 3.5 equiv of $ClTi(NEt_2)_3$, toluene, −78 °C, 6 h; (b) (i) 7.0 equiv of EIX, −25 °C, 2 h, (ii) MeOH, HOAc, −78 °C, (iii) rt; (c) (i) 7.0 equiv of EIX, −78 °C, 2 h, (ii) MeOH, HOAc, −89 °C, (iii) rt; (d) 1.5 equiv of PDC, CH_2Cl_2, rt.

the addition products arising from both pathways. Desilylation of (−)-*anti*-**6b** led to the known homoaldol product **8b**,[2] which has the configuration (3*S*,4*R*) (Scheme 3). It has to be assumed that, unlike with the titanium intermediate **5a**, the lithium compound (*R*)-**3a·2** undergoes addition in an open-chain *anti*-S_E' process.

Scheme 3. Desilylation of (−)-anti-**6b**[a]



[a] Reagents and conditions: (a) 1.5 equiv of TBAF, THF, 22 h.

In conclusion, the lithium compound (*R*)-**3a·2** has a very pronounced tendency for *anti*-S_E' processes with most electrophiles exceeding those of the recently investigated 1-aryl derivative.[4]

When we investigated the analogous (*E*)-3-phenyl-1-trimethylsilyl-1-propenyl carbamate **1b**[11] we encountered some surprises (Scheme 4).

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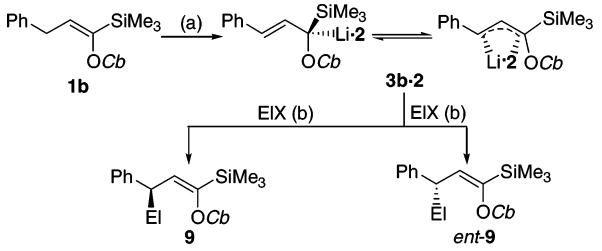
(8) Hoppe, D.; Hanko, R. *Angew. Chem.* **1982**, *94*, 378; *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 372.

(9) When we used $ClTi(OiPr)_3$ as exchange reagent, diminished yields (*anti*-**6b** 41%; *anti*-**6e** 42%) were obtained. This is due to the formation of radicals, since we isolated an oxidative dimer of **3a** ((1*E*,5*E*)-[3,4-dimethyl-1,6-bis(trimethylsilyl)-1,5-hexadien-1,6-diyl] bis[*N*,*N*-diisopropylcarbamate]).

(10) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920.

Scheme 4. Lithiation of **1b** and Reaction with Electrophiles



9	El	yield	%*ee*	$[\alpha]_D$	*ent*-9	El	yield	%*ee*	$[\alpha]_D$
a	Me_3Si	18	92	−74	**d**	MeOC(O)	72	≥95	+76
b	Bu_3Sn	61	≥95	+9	**e**	*t*BuC(O)	94	≥95	+55
c	Ph_3Sn	96	≥95	+61	**f**	Me_2COH	92	≥95	+123
					g	$cC_6H_{11}OH$	82	90	+95

[a] Reagents and conditions: (a) 1.2 equiv of *n*BuLi/(−)-sparteine, toluene, −78 °C, 1 h; (b) (i) 3.0 equiv of EIX, −78 °C, 2 h, (ii) MeOH, HOAc, −78 °C, (iii) rt.

As expected, as a result of the attached phenyl residue, the deprotonation proceeded very smoothly. On trapping the reaction mixture with silyl and tin chlorides, almost enantiopure products **9a**, **9b**, or **9c** were produced. From **9a** and **9c**[12] X-ray analysis with anomalous diffraction were obtained (Figures 1 and 2) to reveal the (3*R*)-configuration arising

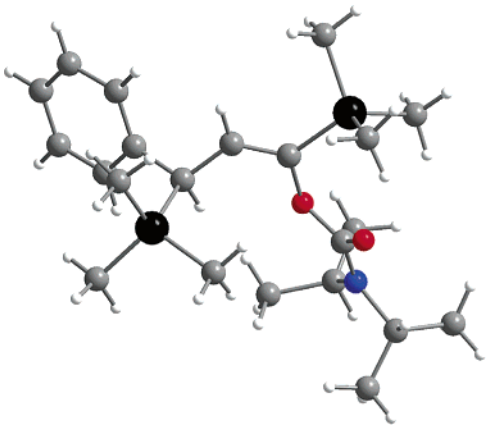


Figure 1. X-ray structure of **9a**.

from a clean *anti*-S_E'-attack. On the other hand, from carbonyl electrophiles, without exception, the enantiomers *ent*-**9d**−**g** were formed. The absolute configuration of *ent*-**9e**[12] (Figure 3) could be explored by X-ray analysis; the other ones were subjected to chemical correlations.

After lithium−titanium exchange in (*R*)-**3b·2**, acetone furnished the enantiomer **9f** ($[\alpha]_D$ = −123, 93%, ≥95%). Addition of aldehydes to the intermediate titanium compound **10** provides the highly enantioenriched diastereomerically

(11) *E*)-3-Phenyl-1-trimethylsilyl-1-propenyl *N*,*N*-diisopropylcarbamate was produced from cinnamyl alcohol in a three-step sequence (see Supporting Information).

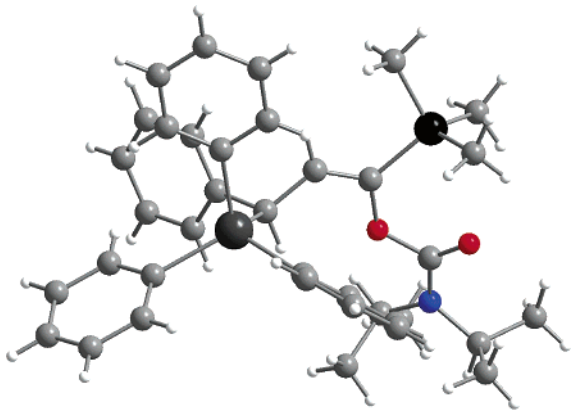


Figure 2. X-ray structure of **9c**.

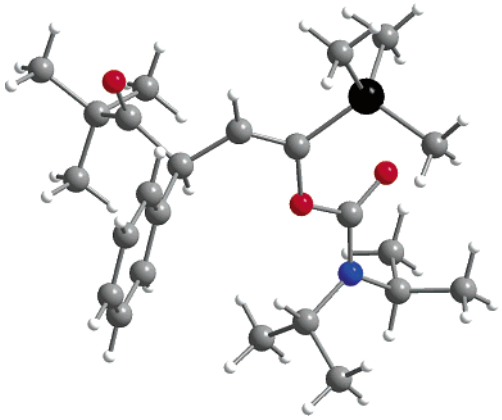
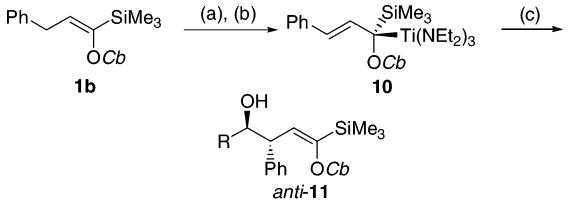


Figure 3. X-ray structure of *ent*-**9e**.

pure homoaldol products *anti*-**11** (Scheme 5, Table 2). A second diastereomer could not be detected by ^{1}H NMR and GC in the crude mixture, and thus the dr is concluded to be ≥95:5.

Scheme 5. Transmetalation and Homoaldol Reaction[a]



[a] Reagents and conditions: (a) 1.2 equiv of *n*BuLi/(−)-sparteine, toluene, −78 °C, 1 h; (b) 1.5 equiv of $ClTi(NEt_2)_3$, −78 °C, 30 min; (c) (i) 3.0 equiv of RCH═O, −78 °C, 2 h, (ii) MeOH, HOAc, −78 °C, (iii) rt.

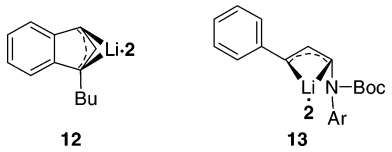
It is evident from these results that the lithium-(−)-sparteine compound (*R*)-**3b·2** has a high tendency for *syn*-

Table 2. Prepared Homoaldol Products *anti*-**11**

RCH=O	product	yield	% ee	$[\alpha]_D$[c]
$CH_3(CH_2)_2CH$=O	*anti*-**11a**	98	91[a]	−144
$(CH_3)_2CHCH$=O	*anti*-**11b**	95	94[a]	−162
$(CH_3)_3CCH$=O	*anti*-**11c**	98	95[a]	−181
$cC_6H_{11}CH$=O	*anti*-**11d**	93	97[a]	−113
4-Br(C_6H_4)CH=O	*anti*-**11e**	99	≥95[b]	−64

[a] Determined by chiral HPLC. [b] Determined by ^{1}H NMR shift experiments. [c] c = 0.78−1.8, $CHCl_3$.

addition reactions toward carbonyl compounds, opposite to compound (*R*)-**3a·2**. What are the reasons? Compound (*R*)-**3b·2** differs from (*R*)-**3a·2** in the exchange of methyl for phenyl at C-3, which causes a stabilization of the negative charge in the anion in position 3. Therefore, we assume that (*R*)-**3b·2** has a η^3-structure (see Scheme 4) either in the ground state or its involvement in a rapid equilibrium. It has been demonstrated for the related lithium-(−)-sparteine complexes **12**[13] and **13**[14,15] (Figure 4) that these have a η^3-



12 **13**

Figure 4. Structures of complexes **12** [13] and **13**,[14,15] elucidated by X-ray analysis.

structure (at least in solid state) and that they react with aldehydes, ketones, and acid chlorides in a strict suprafacial manner.[13,15] Obviously, the lithium cation here has a higher Lewis acidity toward carbonyl groups than in the appropriate η^1-complexes and, thus, "lures" the carbonyl compound to enter from the same face of the allylic system.

After desilylation (H for Me_3Si in **9**, *ent*-**9** or *anti*-**11**), highly enantioenriched products that derive from the homoenolate of 3-phenyl-2-propenal are accessible;[15] the direct carbamate-type homoenolate reagent had turned out not to be configurationally stable.[16] Furthermore, in many cases, both enantiomers can be selectively approached via the same intermediate **3b·2** or by utilization of a surrogate, recently introduced by O'Brien and co-workers.[17]

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Supporting Information Available: Experimental procedures, spectroscopic data, and ^{1}H and ^{13}C NMR spectra for **1a**, **1b**, **4a**, *anti*-**6a**, *ent*-**9e**, *anti*-**11b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) X-ray crystal structure analysis of **9a**: formula $C_{22}H_{39}NO_2Si_2$, MW = 405.72, colorless crystal 0.40 × 0.25 × 0.20 mm^3, a = 21.838(1), b = 9.844(2), c = 12.235(1) Å, V = 2630.2(6) Å^3, ρ_{calc} = 1.025 g cm^{-3}, μ = 13.27 cm^{-1}, empirical absorption correction via ψ scan data (0.619 ≤ T ≤ 0.777), Z = 4, orthorhombic, space group $Pna2_1$ (No. 33), λ = 1.54178 Å, T = 223 K, $\omega/2\theta$ scans, 2810 reflections collected (-h, -k, -l), [(sin θ)/λ] = 0.62 Å^{-1}, 2810 independent and 2370 observed reflections [$I \geq 2\sigma(I)$], 254 refined parameters, R = 0.052, wR^2 = 0.140, Flack parameter 0.01(5), max residual electron density 0.27 (−0.27) e Å^{-3}, hydrogens calculated and refined as riding atoms. X-ray crystal structure analysis of **9c**: formula $C_{37}H_{45}NO_2SiSn$, MW = 682.52, colorless crystal 0.30 × 0.20 × 0.15 mm^3, a = 9.245(1), b = 11.945(1), c = 32.509(1) Å, V = 3590.0(5) Å^3, ρ_{calc} = 1.263 g cm^{-3}, μ = 7.75 cm^{-1}, empirical absorption correction (0.801 ≤ T ≤ 0.893), Z = 4, orthorhombic, space group $P2_12_12_1$ (No. 19), λ = 0.71073 Å, T = 198 K, ω and φ scans, 11789 reflections collected (±h, ±k, ±l), [(sin θ)/λ] = 0.67 Å^{-1}, 7633 independent (R_{int} = 0.031) and 5703 observed reflections [$I \geq 2\sigma(I)$], 386 refined parameters, R = 0.040, wR^2 = 0.061, Flack parameter −0.05(2), max. residual electron density 0.48 (−0.46) e Å^{-3}, hydrogens calculated and refined as riding atoms. X-ray crystal structure analysis of *ent*-**9e**: formula $C_{24}H_{39}NO_3Si$, MW = 417.65, colourless crystal 0.35 × 0.20 × 0.20 mm^3, a = 9.895(1), b = 11.670(1), c = 22.943(1) Å, V = 2649.3(4) Å^3, ρ_{calc} = 1.047 g cm^{-3}, μ = 1.10 cm^{-1}, empirical absorption correction (0.963 ≤ T ≤ 0.978), Z = 4, orthorhombic, space group $P2_12_12_1$ (No. 19), λ = 0.71073 Å, T = 198 K, ω and φ scans, 20230 reflections collected (±h, ±k, ±l), [(sin θ)/λ] = 0.66 Å^{-1}, 6233 independent (R_{int} = 0.067) and 4461 observed reflections [$I \geq 2\sigma(I)$], 274 refined parameters, R = 0.047, wR^2 = 0.105, Flack parameter −0.08(12), max. residual electron density 0.22 (−0.18) e Å^{-3}, hydrogens calculated and refined as riding atoms. Data sets were collected with Enraf-Nonius CAD4 and Nonius KappaCCD diffractometers, the later equipped with a rotating anode generator Nonius FR591. Programs used: data collection EXPRESS (Nonius B.V., 1994) and COLLECT (Nonius B. V., 1998), data reduction MolEN (Fair, K. Enraf-Nonius B.V., 1990) and Denzo-SMN (Otwinowski, Z.; Minor, W. *Methods in Enzymology*, **1997**, *276*, 307−326), absorption correction for CCD data SORTAV (Blessing, R. H. *Acta Crystallogr.* **1995**, *A51*, 33−37; *J. Appl. Crystallogr.* **1997**, *30*, 421−426), structure solution SHELXS-97 (Sheldrick, G. M. *Acta Crystallogr.* **1990**, *A46*, 467−473), structure refinement SHELXL-97 (Sheldrick, G. M. Universität Göttingen, 1997), graphics Diamond (Brandenburg, K. Universität Bonn, 1997).

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