

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

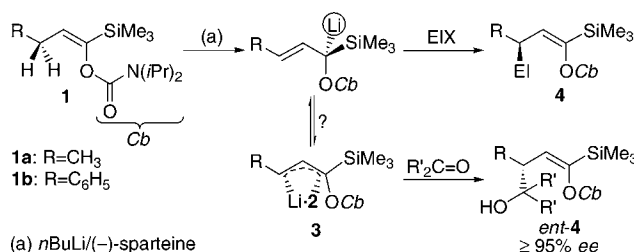
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ABSTRACT



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 homoenoate reagents are valuable synthetic building blocks.¹ In particular, 1-oxygen-² and 1-nitrogen-substituted³ 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 homoeno-

late reagents by (–)-sparteine-mediated γ -deprotonation of 1-aryl-1-alkenyl carbamates **1** (aryl for Me₃Si).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.

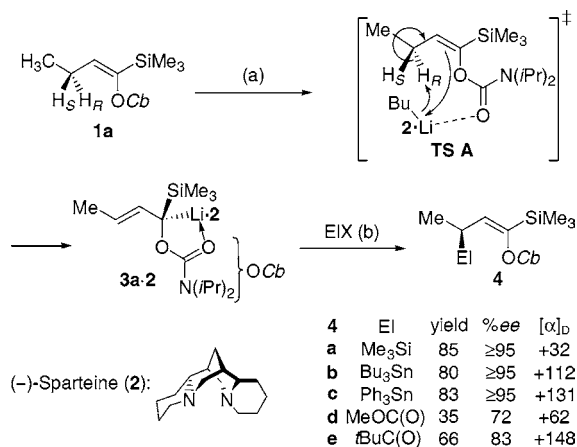
(2) (a) Hoppe, D.; Zschage, O. *Angew. Chem.* **1989**, *101*, 67; *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 69. (b) Zschage, O.; Hoppe, D. *Tetrahedron* **1992**, *48*, 5657. (c) Hoppe, D.; Krämer, T. *Angew. Chem.* **1986**, *98*, 171; *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 160.

(3) Beak, P.; Weisenburger, G. A. *J. Am. Chem. Soc.* **1996**, *118*, 12218.

(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).

Scheme 1. Lithiation of **1a** and Reaction with Electrophiles^a



^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 state¹⁰ in a strict *syn*- Se' 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	[α] _D ^c
CH ₃ (CH ₂) ₂ CH=O	<i>anti</i> - 6a	70	≥ 95	≥ 95:5	−25
(CH ₃) ₂ CHCH=O	<i>anti</i> - 6b	72	≥ 95	≥ 95:5	−27
(CH ₃) ₃ CCH=O	<i>anti</i> - 6c	80	≥ 95	≥ 95:5	−29
cC ₆ H ₁₁ CH=O	<i>anti</i> - 6d	69	≥ 95	≥ 95:5	−15
(C ₆ H ₅)CH=O	<i>anti</i> - 6e	71	89	≥ 95:5	−78

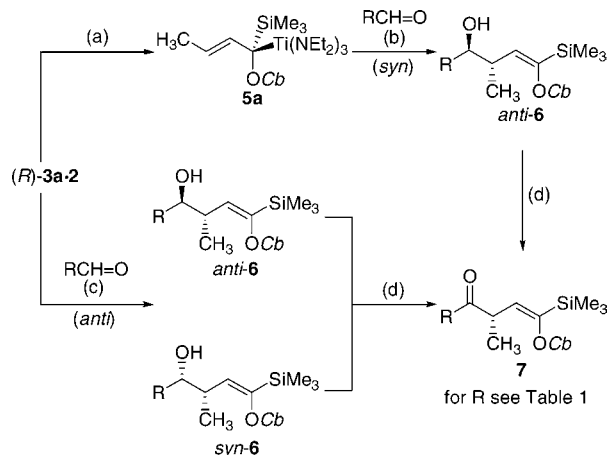
^a Determined by ¹H NMR shift experiments. ^b Determined by ¹H NMR and GC. ^c *c* = 0.8–2.8, CHCl₃.

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** ($[\alpha]_{\text{D}} = +112$) with *n*BuLi/Et₂O at -78°C and reaction of the formed (*S*)-**3a**·Et₂O with Ph₃SnCl afforded (*R*)-(-)-**4c** ($[\alpha]_{\text{D}} = -66$, 48% ee) with 87% yield. Since all known lithiodestannylation proceeds as suprafacial processes, the stereochemical course of the reverse reaction is (one time more) *anti*-S_E'.

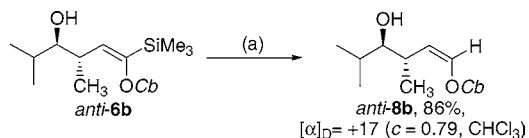
Scheme 2. Transmetalation and Homoaldol Reaction^a



^a Reagents and conditions: 3.5 equiv of ClTi(NEt₂)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, CH₂Cl₂, 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).

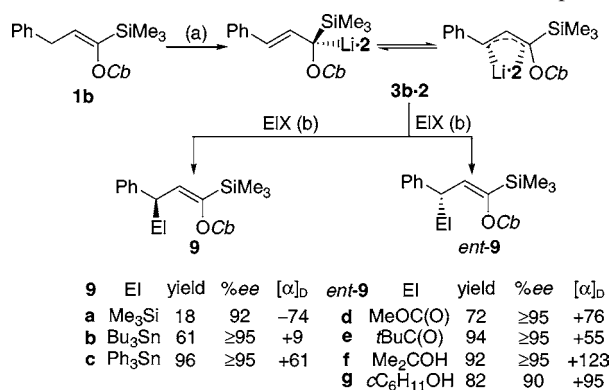
(7) Reviews: (a) Reetz, M. T. *Organotitanium Reagents in Organic Synthesis*, 1st ed.; Springer-Verlag: Berlin, 1986. (b) Weidmann, B.; Seebach, D. *Angew. Chem.* **1983**, 95, 12; *Angew. Chem., Int. Ed. Engl.* **1983**, 22, 32. (c) Reetz, M. T. *Organotitanium Chemistry*. In *Organometallics in Synthesis*, 2nd ed.; Schlosser, M., Ed.; Wiley: Chichester, 2002; p 817.

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

(9) When we used CITi(OiPr)₃ as exchange reagent, diminished yields (*anti*-**6b** 41%; *anti*-**6c** 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



^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

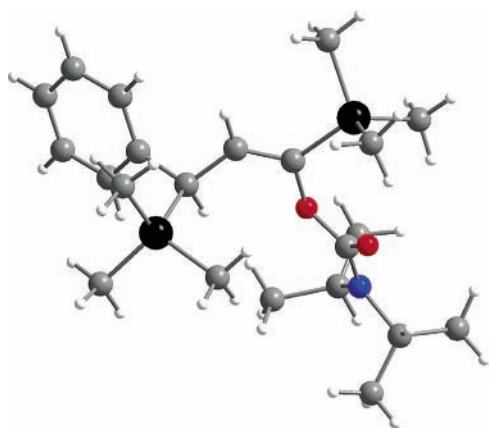


Figure 1. X-ray structure of **9a**.

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** ([α]_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).

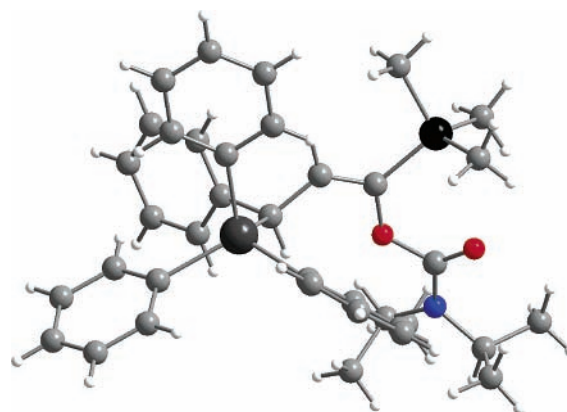


Figure 2. X-ray structure of **9c**.

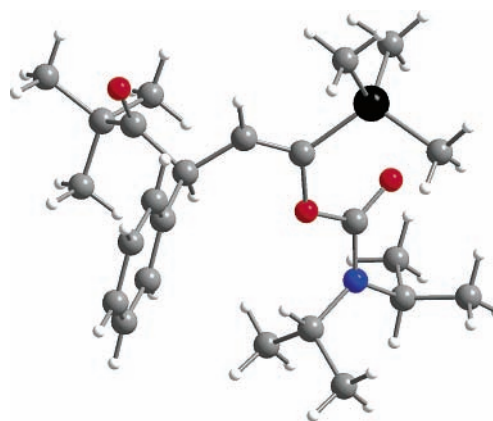
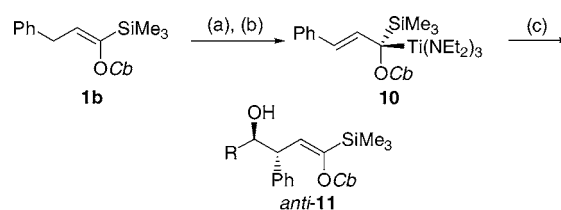


Figure 3. X-ray structure of *ent*-**9e**.

pure homoaldol products *anti*-**11** (Scheme 5, Table 2). A second diastereomer could not be detected by ¹H 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 CITi(NEt₂)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) ₂ CH=O	<i>anti</i> -11a	98	91 ^a	−144
(CH ₃) ₂ CHCH=O	<i>anti</i> -11b	95	94 ^a	−162
(CH ₃) ₃ CCH=O	<i>anti</i> -11c	98	95 ^a	−181
cC ₆ H ₁₁ CH=O	<i>anti</i> -11d	93	97 ^a	−113
4-Br(C ₆ H ₄)CH=O	<i>anti</i> -11e	99	≥95 ^b	−64

^a Determined by chiral HPLC. ^b Determined by ¹H NMR shift experiments. ^c $c = 0.78\text{--}1.8$, CHCl₃.

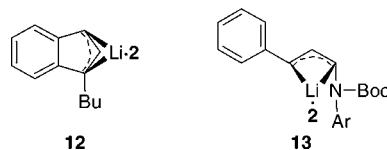
addition reactions toward carbonyl compounds, opposite to compound (*R*)-3a•2. What are the reasons? Compound (*R*)-3b•2 differs from (*R*)-3a•2 in the exchange of methyl for

(12) X-ray crystal structure analysis of 9a: formula C₂₂H₃₉NO₂Si₂, MW = 405.72, colorless crystal 0.40 × 0.25 × 0.20 mm³, $a = 21.838(1)$, $b = 9.844(2)$, $c = 12.235(1)$ Å, $V = 2630.2(6)$ Å³, $\rho_{\text{calc}} = 1.025$ g cm^{−3}, $\mu = 13.27$ cm^{−1}, empirical absorption correction via ψ scan data ($0.619 \leq T \leq 0.777$), $Z = 4$, orthorhombic, space group Pna2₁ (No. 33), $\lambda = 1.54178$ Å, $T = 223$ K, $\omega/2\theta$ scans, 2810 reflections collected ($-h, -k, -l$), $[(\sin \theta)/\lambda] = 0.62$ 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 C₃₇H₄₅NO₂SiSn, MW = 682.52, colorless crystal 0.30 × 0.20 × 0.15 mm³, $a = 9.245(1)$, $b = 11.945(1)$, $c = 32.509(1)$ Å, $V = 3590.0(5)$ Å³, $\rho_{\text{calc}} = 1.263$ g cm^{−3}, $\mu = 7.75$ cm^{−1}, empirical absorption correction ($0.801 \leq T \leq 0.893$), $Z = 4$, orthorhombic, space group P2₁2₁2₁ (No. 19), $\lambda = 0.71073$ Å, $T = 198$ K, ω and φ scans, 11789 reflections collected ($\pm h, \pm k, \pm l$), $[(\sin \theta)/\lambda] = 0.67$ Å^{−1}, 7633 independent ($R_{\text{int}} = 0.031$) 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 C₂₄H₃₉NO₃Si, MW = 417.65, colourless crystal 0.35 × 0.20 × 0.20 mm³, $a = 9.895(1)$, $b = 11.670(1)$, $c = 22.943(1)$ Å, $V = 2649.3(4)$ Å³, $\rho_{\text{calc}} = 1.047$ g cm^{−3}, $\mu = 1.10$ cm^{−1}, empirical absorption correction ($0.963 \leq T \leq 0.978$), $Z = 4$, orthorhombic, space group P2₁2₁2₁ (No. 19), $\lambda = 0.71073$ Å, $T = 198$ K, ω and φ scans, 20230 reflections collected ($\pm h, \pm k, \pm l$), $[(\sin \theta)/\lambda] = 0.66$ Å^{−1}, 6233 independent ($R_{\text{int}} = 0.067$) 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).

(13) Hoppe, D.; Hoppe, I.; Marsch, M.; Harms, K.; Boche, G. *Angew. Chem.* **1995**, 107, 2328; *Angew. Chem., Int. Ed. Engl.* **1995**, 34, 2158.

(14) Beak, P.; Pippel, D. J.; Weisenburger, G. A.; Wilson, S. R. *Angew. Chem.* **1998**, 110, 2600; *Angew. Chem., Int. Ed. Engl.* **1998**, 37, 2522.

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 equilibration. It has been demonstrated for the related lithium(−)-sparteine complexes 12¹³ and 13^{14,15} (Figure 4) that these have a η^3 -

**Figure 4.** Structures of complexes 12¹³ 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 Me₃Si in 9, *ent*-9 or *anti*-11), highly enantioenriched products that derive from the homo-enolate of 3-phenyl-2-propenal are accessible;¹⁵ the direct carbamate-type homo-enolate 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 ¹H and ¹³C 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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(15) (a) Beak, P.; Weisenburger, G. A.; Faibish, N. C.; Pippel, D. J. *J. Am. Chem. Soc.* **1999**, 121, 9522. (b) Beak, P.; Whisler, M. C.; Vaillancourt, L. *Org. Lett.* **2000**, 2, 2655.

(16) Hoppe, D.; Behrens, K.; Fröhlich, R.; Meyer, O. *Eur. J. Org. Chem.* **1998**, 2397, 7.

(17) O’Brien, P.; Dearden, M. J.; Firkin, C. R.; Nermat, J.-P. R.; *J. Am. Chem. Soc.* **2002**, 124, 11870.