# Asymmetric γ-Deprotonation and Substitution Reactions of (*Z*)-1,3-Diphenyl-1-propenyl *N*,*N*-Diisopropylcarbamate

**Jenny Reuber,[a] Roland Fröhlich,[a][‡] and Dieter Hoppe*[a]**

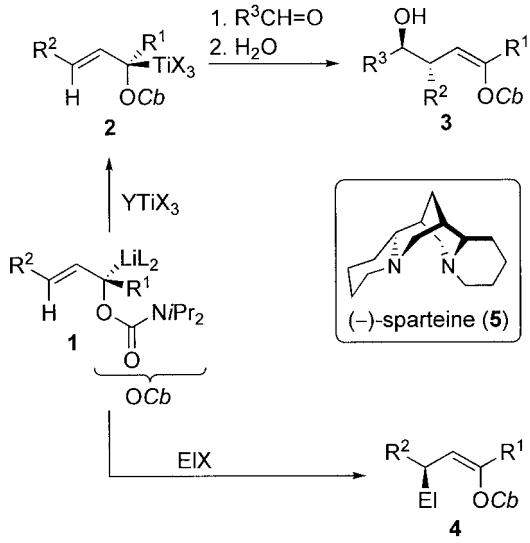
**Keywords:** Asymmetric synthesis / Carbanions / Allylic compounds / Homoaldol addition / (–)-Sparteine

(Z)-1,3-Diphenyl-1-propenyl *N*,*N*-diisopropylcarbamate (**6d**) is deprotonated by *n*-butyllithium/(–)-sparteine (**5**) with a high degree of enantiotopic differentiation in the γ-position to form the enantiomerically enriched allyllithium derivative **7d**. Despite of its high mesomeric stabilization it shows a high degree of configurational stability. Trapping with carbonyl electrophiles proceeds exclusively in a *syn*-$S_E'$ substitution as shown by direct assignments and stereochemical correlations. Thus, the involvement of a $\eta^3$ complex is suggested. After transfer to the analogous allyltitanates **16** enantiomerically and diastereomerically pure homoaldol products **17** are furnished. Evidence for a competing retro-homoaldol reaction is reported.



## Introduction

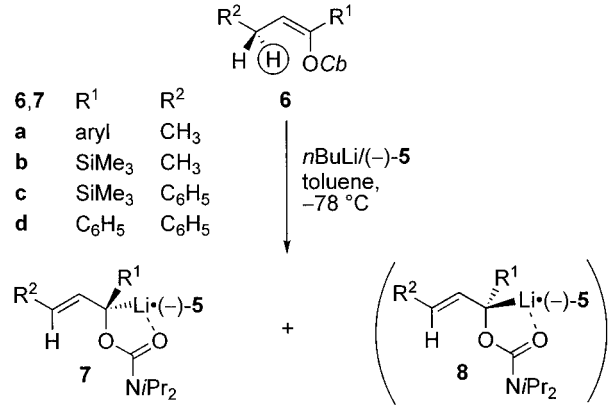
Nonracemic, chiral lithio-2-alkenyl *N*,*N*-diisopropylcarbamates **1** proved to be valuable intermediates in enantioselective homoaldol reactions (Scheme 1).[1]




Scheme 1.

Their synthetic utility largely depends on the configurational stability of the lithium intermediates **1**. After transmetallation to titanium compounds **2**, these add to aldehydes with a high degree of chirality transfer to give *anti*-configured 4-hydroxy-1-alkenyl carbamates **3** which are enol esters of γ-hydroxy carbonyl compounds.[2] The enantiomeric ratio of **3** usually reflects the enantiomeric purity of intermediates **2**. Other electrophiles such as trialkylsilyl- and trialkyltin halides prefer *anti*-$S_E'$ substitution to form preferentially products **4**. Lithium compound **1** ($R^1$, $R^2$ = alkyl, $L_2$ = TMEDA) could be produced by deprotonation of the enantioenriched precursors and are configurationally stable in diethyl ether or pentane below –70 °C.[3] Configurational stability was also found for appropriate α,γ-disubstituted (–)-sparteine complexes ($L_2$ = **5**) furnished from racemic precursors through kinetic resolution during deprotonation.[4]

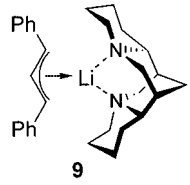
Previously, a surprising and efficient approach to highly enantioenriched 1,3-disubstituted (–)-sparteine complexes was found through γ-deprotonation of achiral 1-alkenyl carbamates **6a**–**c** (Scheme 2).[5,6]




Scheme 2.

[a] Organisch-Chemisches Institut, Westfälische Wilhelms-Universität Münster,
Corrensstrasse 40, 48149 Münster, Germany
Fax: +49-251-8336531
E-mail: dhoppe@uni-muenster.de
[‡] To whom correspondence regarding X-ray analysis should be addressed.

In most cases, diastereomeric ratios of the carbanionic intermediates **7a**–**c**:**8a**–**c** of greater than 95:5 were produced, as determined by trapping experiments.[5,6] The question if the 1,3-diphenyl-substituted **7d** has considerable configurational stability, due to its high mesomeric stabilization, is now addressed. This issue was questionable since the (–)-α-isosparteine complex **9** (Figure 1) and the appropriate (–)-sparteine complex, of which an X-ray structure analysis could be obtained, is configurationally labile even at –78 °C.[7]

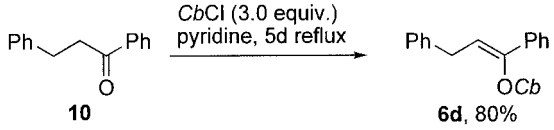



**9**

Figure 1.

## Results and Discussion

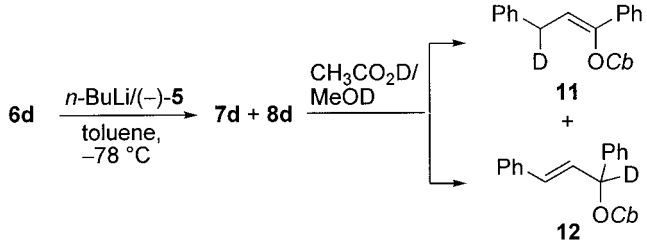
1,3-Diphenylallyl carbamate was obtained by heating 1,3-diphenyl-1-propanone (**10**) with *N*,*N*-diisopropylcarbamoyl chloride (*Cb*Cl) in pyridine (Scheme 3).[8]




**10** **6d**, 80%

Scheme 3.

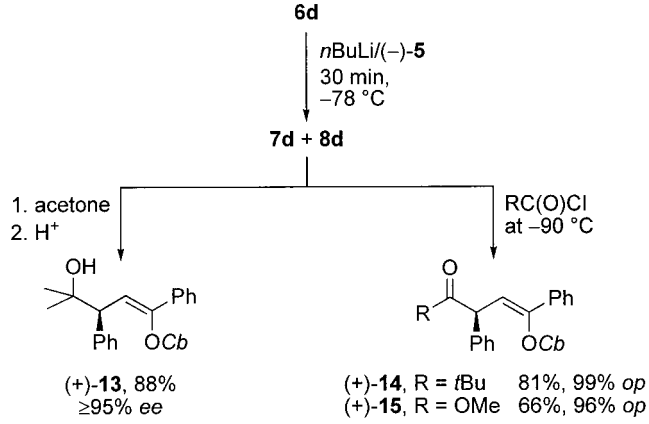
Deprotonation with *n*-butyllithium/(–)-sparteine (**5**) in toluene at –78 °C furnished immediately a deeply red solution of the carbanion, which was quenched below –70 °C after 30 min with $CH_3CO_2D$/MeOD to give a mixture of the γ- and α-deuterated precursors **11** and **12** with 97% yield in a ratio 1:2, indicating complete and rapid deprotonation (Scheme 4).[9]




Scheme 4.

No substantial reaction of **7d** and **8d** occurred with chloro(trimethyl)silane or chloro(tributyl)tin, indicating a low reactivity of the intermediate carbanionic species.

Trapping the lithium species by acetone yielded the homoaldol product (+)-**13** with high yield and ≥ 95% *ee* (Scheme 5). Acylations with excess 2,2-dimethylpropanoyl chloride to form the ketone (+)–**14** (99% *op*) and with methyl chloroformate with formation of ester (+)-**15** (96% *op*) also produced highly enantioenriched products when the reaction was carried out at –90 °C (Scheme 5). Lower enantiomeric excesses (89% *ee* and 69% *ee*, respectively) were recorded at the usual reaction temperature of –78 °C, presumably due to subsequent partial enolization at the stage of the carbonyl compounds. For assignment of the absolute configurations see below.




Scheme 5.

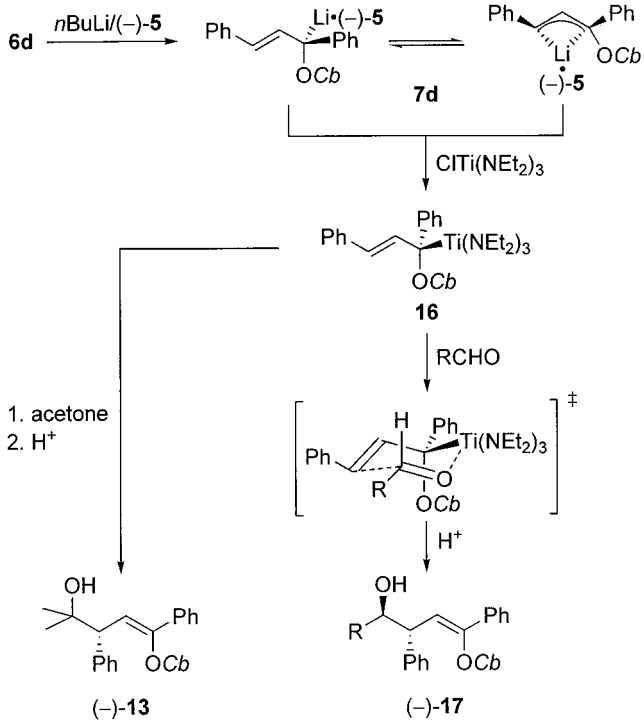
### Homoaldol Reactions

The exchange of the lithium cation in compound **7** with $ClTi(NEt_2)_3$[10] to covalently bound intermediate **16** proceeds with inversion of the configuration (Scheme 6). Remarkably, acetone now forms the opposite enantiomer (–)-**13**. Since in the titanation method one inversion step is involved, it is concluded that both intermediates **7d** and **16** undergo a *syn*-$S_E'$-reaction with acetone. An X-ray structure analysis of the *p*-bromobenzaldehyde adduct **17e** reveals (Figure 2), besides the 3,4-*anti*- and the (1*Z*)-configuration, the absolute configuration (*R*) at C-3; this is in accordance with (*S*)-**7** as the lithium precursor (Scheme 6).

The enantiomeric excesses of compounds (–)-**13** and (–)-**17**, obtained after lithium-titanium exchange (Method A, Table 1), vary between 73 and 92% *ee*. This is surprising, since usually the enantiomeric purity of the titanium intermediate determines the enantiomeric excesses of the products and leads therefore to equally high enantiomeric excesses with different carbonyl electrophiles. In a second set of experiments, $Ti(OiPr)_4$ (3.0 equiv.) was added (Method B) together with the carbonyl compound and the optical purities rose up to 99%. We assumed that a retro-homoaldol reaction, which might not be completely stereospecific, comes into operation,[11] due to the high stabilization of the carbanionic part. The involvement of a partial retro-cleavage was confirmed for the lithium alcoholate, derived from the acetone adduct (–)-**13** by the following experiments:

Compound (–)-**13** was converted by *n*-butyllithium/(–)-sparteine (**5**) into its alcoholate and stirred with excess 2,2-dimethylpropanal for 1 h at –90 °C affording **17d** with




Scheme 6.

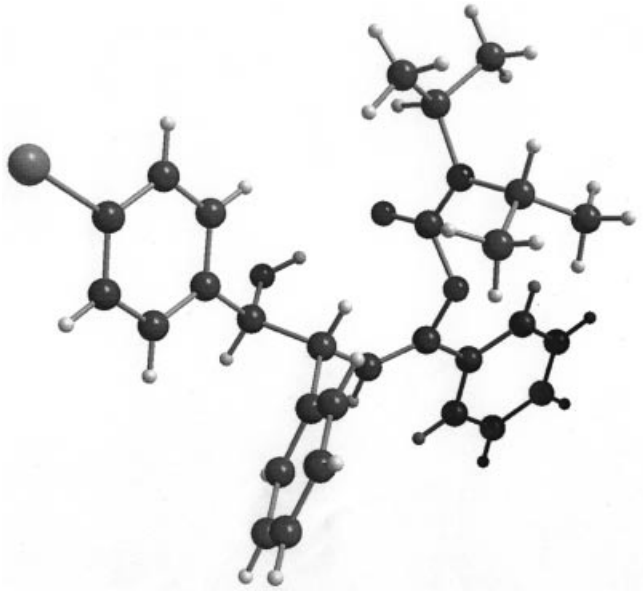


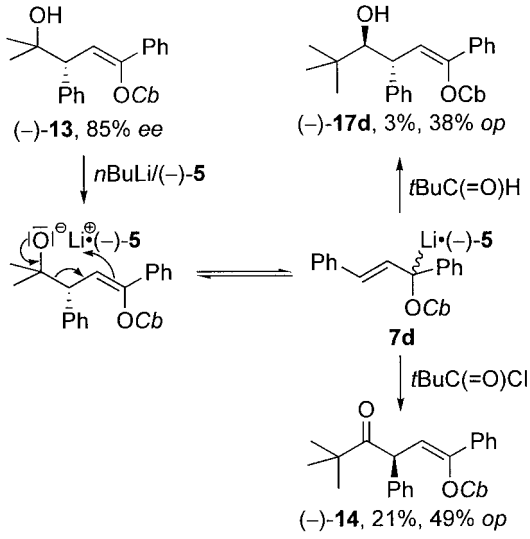
Figure 2. X-ray structure of **17e**.

3% yield and 38% *op* (Scheme 7). A similar experiment in the presence of 5 equiv. of 2,2-dimethylpropanoyl chloride, which was carried out at –78 °C, furnished the ketone (–)-**14** with 21% yield and 49% *op*. Although the reasons are unknown, the addition of $Ti(OiPr)_4$ (3.0 equiv.) suppresses the formation of **17d** under these conditions. Excess $Ti(OiPr)_4$ might retard the retro-homoaldol reaction by formation of the less reactive titanium alkoxide of **13**.

Table 1. Yields and enantiomeric purities of homoaldol products (–)-**17** and (–)-**13**.

| $R^1$ | $R^2$ | **17** | Method A[a] | | Method B[b] | |
|---|---|---|---|---|---|---|
| | | | Yield (%) | *ee*/*op* | Yield (%) | *ee* |
| $(CH_3)_2CHCH_2$ | H | **a** | – | – | 68 | 91% |
| $(CH_3)_2CH$ | H | **b** | 83 | 89% *ee* | 81 | 99% |
| *c*-propyl | H | **c** | – | – | 64 | ≥ 95% |
| $(CH_3)_3C$ | H | **d** | 75 | 92% *ee* | 92 | 91% |
| *p*-Br-$C_6H_4$ | H | **e** | 59 | 89% *op* | 77 | ≥ 95% |
| $CH_3$ | $CH_3$ | **13** | 88 | 73% *op* | 48 | ≥ 95% |

[a] Method A: i. *n*-butyllithium/(–)-**5**, toluene, –78 °C, 30 min; ii. $ClTi(NEt_2)_3$, –78 °C, 30 min; iii. RCHO; iv. $H^+$. [b] Method B: i. *n*-butyllithium/(–)-**5**, toluene, –90 °C, 20 min; ii. $ClTi(NEt_2)_3$, –90 °C, 15 min; iii. RCHO/$Ti(OiPr)_4$; iv. $H^+$.



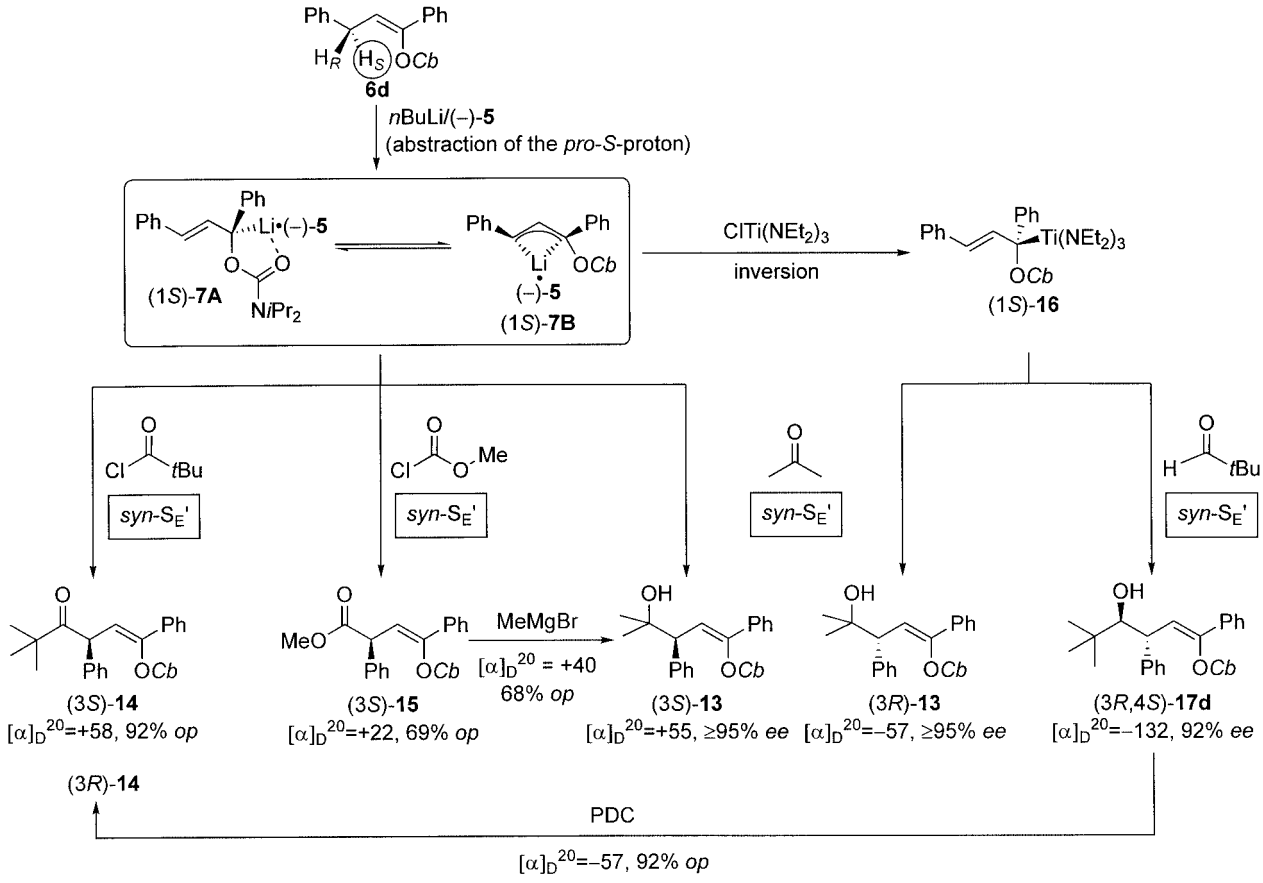

Scheme 7.

## Stereochemical Correlations

Scheme 8 summarizes the stereochemical relationships which could be established by either direct assignments or chemical correlations.

All carbonyl additions of aldehydes, ketones and acid chlorides onto lithium intermediate (*S*)-**7** proceed as highly γ-selective *syn*-$S_E'$ processes. This fact implies the involvement of a $\eta^3$-ion pair **7B**, since in all reactions, where an allylic $\eta^3$-intermediate is likely to contribute, similar stereochemical characteristics had been recorded by Hoppe et al.[6,12] and Beak et al.[13,14] It seems that $\eta^3$-allyllithium compounds (e.g. **7B**) have a higher Lewis acidity than the $\eta^1$-isomers (e.g. **7A**) and thus, the lithium cation "lures" all incoming carbonyl electrophiles by complexation to enter from the face accommodating it. It is concluded on the base of the experimental results, that the lithium carbanion pair **7** is highly diastereomerically enriched and possesses a considerable configurational stability at and below –78 °C. We here exclude a mobile equilibrium between diastereomeric carbanion pairs and a kinetic resolution[15] in the substitution step as the origin of high enantioenrichment, since all




Scheme 8.

applied electrophiles lead to substitution products of nearly identical enantiomeric excesses.

After lithium–titanium exchange under stereoinversion, the addition of aldehydes and ketones leads, via a Zimmerman–Traxler transition state, to the opposite enantiomers *ent*-**17** or *ent*-**13** (Scheme 8).

## Conclusions

In summary, the methodology outlined above permits the simple generation of enantiomerically pure (1,3-diphenylallyl)lithium carbanion pairs. The absolute configuration of intermediate **7** as well as the substitution mechanism to carbonyl electrophiles was determined. After transfer to the analogous allyl titanate **16**, enantiomerically and diastereomerically pure homoaldol products are accessible in the reaction with aldehydes.

## Experimental Section

**General Remarks:** All organometallic reactions were performed under anhydrous conditions under argon in dried glassware. Solutions were transferred by means of syringes. Toluene was dried with Na before use. Electrophiles were distilled prior to use. (–)-Sparteine was kept under argon in a refrigerator after the original bottles had been opened. Analytical thin-layer chromatography was performed on Merck silica gel plates (Silica gel 60 $F_{254}$). Visualization was accomplished with UV light and $KMnO_4$ or vanilline solution. Column chromatography was carried out at 1.5 bar on silica gel 40–63 μm (Merck, Darmstadt). Only distilled solvents were used as eluents. $^1H$ NMR and $^{13}C$ NMR spectra were recorded at room temp. with a Bruker AM 300 (300 MHz and 75.5 MHz for $^1H$ and $^{13}C$ NMR, respectively) or with a Bruker AM 400 (400 MHz and 100 MHz for $^1H$ and $^{13}C$ NMR, respectively). $CDCl_3$ or $C_6D_6$ were used as solvents; chemical shifts are reported in ppm ($\delta$); $^1H$ shifts are related to TMS and $^{13}C$ shifts to $\delta_C$ = 77.0 ppm; multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), $m_c$ (centric multiplet) and bs (broad singlet); $\psi$ refers to pseudo signals; * refers to signals which are interchangeable; brackets refer to signals which arise from frozen rotations of the amide bond. The numbering of the compounds can differ from the IUPAC name. Mass spectroscopy and elemental analysis were performed at the Institute of Organic Chemistry, University of Münster. IR absorption spectra were recorded using a Perkin–Elmer 298. The optical rotations were measured using a Perkin–Elmer polarimeter 241. Melting points are not corrected.

**(*Z*)-1,3-Diphenyl-1-propenyl *N*,*N*-Diisopropylcarbamate (6d):** *N*,*N*-Diisopropylcarbamoyl chloride (*Cb*Cl) (3.0 equiv., 60.00 mmol, 9.880 g) was dissolved in anhydrous, refluxing pyridine (5.0 mL). Afterwards, 1,3-diphenyl-1-propanone (**10**) (20.00 mmol, 4.260 g), dissolved in pyridine (1.0 mL), was added over a period of 10 min. The solution was refluxed for 5 days. The cooled solution was poured to a mixture of 2 N HCl (100 mL) and 30 g ice. The two-phase mixture was filtered through Celite. After warming to room temp. and separation of the phases, the aqueous solution was extracted with diethyl ether (3 × 50 mL). The organic layers were com-

bined and dried with $MgSO_4$. After evaporation of the solvent in vacuo, the residue was purified by flash chromatography on silica gel (pentane/$Et_2O$, 12:1) to afford 5.400 g (16.00 mmol, 80%) **6d** as a colourless solid. $R_f$ = 0.27 (pentane/$Et_2O$, 4:1). M.p. 75 °C (pentane/$Et_2O$). $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 1.31 ($m_c$, 12 H, O*Cb*-$CH_3$), 3.50 [d, $^3J_{H,H}$ = 7.2 Hz, 2 H, $CH_2$], 4.05 ($m_c$, 2 H, O*Cb*-CH), 5.90 (t, $^3J_{H,H}$ = 7.2 Hz, 1 H, CH), 7.15–7.55 (m, 5 H, aryl-H) ppm. $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 20.5 [21.7] (O*Cb*-$CH_3$), 32.5 ($CH_2$), 46.3 [46.6] (O*Cb*-CH), 116.5 (CH), 124.6/126.2/127.8/128.2/128.4/128.6 (CH-aryl), 136.1/140.2 (Cq-aryl), 146.9 (Cq), 152.8 (O*C*ON) ppm. IR (KBr): $\tilde{\nu}$ = 1708 $cm^{-1}$. ESI-MS: (*m*/*z*) = 338.2 $[M + H]^+$, 360.1 $[M + Na]^+$. $C_{22}H_{27}NO_2$ (337.46): calcd. C 78.30, H 8.06, N 4.15; found C 78.21, H 7.97, N 4.05.

**General Procedure for the Deprotonation and Substitution of Enol Carbamate 6d at –78 °C (GP1):** A solution of (–)-sparteine (**5**) (1.2 equiv.) in toluene (1.5 mL) was cooled to –78 °C and *n*-butyllithium (1.2 equiv., 1.6 M in hexane) was added. After the mixture was stirred for 10 min, a solution of (*Z*)-1,3-diphenyl-1-propenyl *N*,*N*-diisopropylcarbamate (**6d**) (1.0 equiv., 0.30–0.50 mmol) in toluene (1.1 mL) was slowly added over 10 min. After a deprotonation time of 10–30 min, the electrophile (3.0 equiv.) was added over 10 min and the resulting mixture was stirred at –78 °C for 2.0–2.5 hours. The pale yellow reaction mixture was quenched by addition of acetic acid (0.05 mL) and methanol (0.3 mL) at –78 °C. After warming to room temp., the organic phase was diluted with diethyl ether and dried with $MgSO_4$. The solvent was removed with a rotary evaporator. The resultant crude mixture was applied to silica gel purification and eluted with solvent mixtures of pentane and diethyl ether.

**General Procedure for the Deprotonation and Substitution of Enol Carbamate 6d at –90 °C (GP2):** To a stirred solution of (–)-sparteine (**5**) (1.01 equiv., 0.51 mmol, 120 mg) in toluene (1.5 mL) was added *n*-butyllithium (1.6 M in hexane, 1.01 equiv., 0.51 mmol, 0.32 mL) at –90 °C. After 10 min, a solution of **6d** (1.0 equiv., 0.50 mmol, 169 mg) in toluene (1.1 mL) was added dropwise over 10 min, and the clear deep red solution was stirred for additional 10 min. A solution of the electrophile (3.0 equiv.) in toluene (0.5 mL) was added dropwise over 10 min. Then the reaction mixture was stirred for 1 hour at –90 °C and was quenched with acetic acid (0.05 mL) and methanol (0.3 mL). After warming to room temp. and dilution of the organic phase with diethyl ether, it was dried with $MgSO_4$, and the solvent was removed in vacuo. The crude product was purified by column chromatography with solvent mixtures of pentane and diethyl ether.

**(1*Z*,3*S*)-4-Hydroxy-4-methyl-1,3-diphenyl-1-pentenyl *N*,*N*-Diisopropylcarbamate (13):** To a solution of (–)-sparteine (**5**) (1.2 equiv., 0.36 mmol, 84 mg) in toluene (1.5 mL) at –78 °C was added dropwise *n*-butyllithium (1.2 equiv., 0.36 mmol, 0.23 mL, 1.6 M in hexane) ) whilst stirring according to GP1. The reaction mixture was stirred for 10 min and then **6d** (1.0 equiv., 0.30 mmol, 101 mg) in toluene (1.1 mL) was added slowly over 10 min. The reaction mixture was stirred for 30 min at –78 °C and then, acetone (3.0 equiv., 0.90 mmol, 55 mg), dissolved in toluene (0.5 mL), was added. Finally, the reaction mixture was stirred for 2 hours at –78 °C and quenched as described by GP1. The residue was purified by silica gel flash column chromatography (pentane/$Et_2O$, 2:1 → 1:1) to afford 105 mg (0.27 mmol, 88%) (3*S*)-**13** as a colourless resinous oil. $R_F$ = 0.22 (pentane/$Et_2O$, 1:1). $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 1.22–1.29 (m, 12 H, O*Cb*-$CH_3$), 1.33/1.35 [s, 6 H, C(OH)($CH_3$)$_2$], 2.35 (s, 1 H, OH), 3.72 [d, $^3J_{H,H}$ = 10.5 Hz, 1 H, CHC*H*C(OH)], 3.92 [4.07] (sept, $^3J_{H,H}$ = 6.4 Hz, 2 H, O*Cb*-CH), 6.31 [d, $^3J_{H,H}$ = 10.5 Hz, 1 H, C*H*CHC(OH)], 7.18–7.45 (m, 10 H, aryl-H) ppm. $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 20.5 [21.6] (O*Cb*-$CH_3$), 27.4/28.6 [C(OH)($CH_3$)$_2$], 46.6 (O*Cb*-CH), 53.9 [CH*C*HC(OH)], 72.8 (Cq-OH), 117.2 [*C*HCHC(OH)], 124.9/126.7/128.1/128.2/128.3/129.1 (aryl-CH), 136.1/140.9 (aryl-Cq), 147.7 (Cq), 152.9 (O*C*ON) ppm. IR (KBr): $\tilde{\nu}$ = 3441, 1697 $cm^{-1}$. ESI-MS: (*m*/*z*) = 396.2 $[M + H]^+$, 418.4 $[M + Na]^+$, 434.3 $[M + K]^+$. $C_{25}H_{33}NO_3$ (395.53): calcd. C 75.91, H 8.41, N 3.54; found C 75.70, H 8.38, N 3.53. $[\alpha]_D^{20}$ = +55 (*c* = 0.59 in $CHCl_3$, ≥ 95% *ee*). Shift experiment (300 MHz): 10 mol-% Eu(hfc)$_3$ in $CDCl_3$, $\delta$ (CH) = 6.79 ppm (major enantiomer appears at lower field). Compound *rac*-**13** [yield 80%, m.p. 84 °C (pentane/$Et_2O$)] was obtained as a colourless powder in the same way by using 1.4 equiv. *rac*-*trans*-*N*,*N*,*N*′,*N*′-tetramethylcyclohexane-1,2-diamine/*n*-butyllithium for the deprotonation.

**(1*Z*,3*S*)-5,5-Dimethyl-4-oxo-1,3-diphenyl-1-hexenyl *N*,*N*-Diisopropylcarbamate (14). GP1:** According to GP1 (–)-sparteine (**5**) (1.2 equiv., 0.36 mmol, 84 mg) was dissolved in toluene (1.5 mL) and cooled to –78 °C before 1.6 M *n*-butyllithium (1.2 equiv., 0.36 mmol, 0.23 mL) was added, followed by a solution of **6d** (1.0 equiv., 0.30 mmol, 101 mg) in toluene (1.1 mL) after 10 min. The reaction mixture was stirred for 30 min and then pivaloyl chloride (3.0 equiv., 0.90 mmol, 153 mg) was added and stirring was continued for 2.5 hours. After quenching at –78 °C and work up, the residue was purified by flash chromatography (pentane/$Et_2O$, 6:1 → 4:1) to give 103 mg (0.24 mmol, 81%) (3*S*)-**14** as colourless oil. $R_F$ = 0.47 (pentane/$Et_2O$, 2:1). $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 1.15 (s, 9 H, *t*Bu), 1.30 [1.41] ($m_c$, 12 H, O*Cb*-$CH_3$), 3.86 [4.27] (sept, $^3J_{H,H}$ = 6.7 Hz, 2 H, O*Cb*-CH), 5.28 (d, $^3J_{H,H}$ = 10.0 Hz, 1 H, CHC*H*C=O), 6.24 (d, $^3J_{H,H}$ = 10.0 Hz, 1 H, C*H*CHC=O), 7.20–7.40 (m, 10 H, aryl-H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 20.5 [21.6] (O*Cb*-$CH_3$), 26.5 (*t*Bu-$CH_3$), 45.3 (*t*Bu-Cq), 46.3 [46.9] (O*Cb*-CH), 49.4 (CH*C*HC=O), 117.4 (*C*HCHC=O), 124.6/126.7/127.8/127.9/128.5 (aryl-CH), 128.8/135.7 (aryl-Cq), 146.1 (Cq), 151.8 (O*C*ON), 213.2 (*C*O*t*Bu) ppm. IR (KBr): $\tilde{\nu}$ = 1709 $cm^{-1}$. ESI-MS (*m*/*z*) = 422.1 $[M + H]^+$, 439.2 $[M + NH_4]^+$, 444.2 $[M + Na]^+$, 860.5 $[2M + NH_4]^+$. $C_{27}H_{35}NO_3$ (421.57): calcd. C 76.92, H 8.37, N 3.32; found C 76.91, H 8.46, N 3.27. $[\alpha]_D^{20}$ = +56 (*c* = 0.75 in $CHCl_3$; 89% *op*, determined by conversion of **17d** to **14**, see below). Compound *rac*-**14** (yield 93%) was obtained in the same way by using 1.4 equiv. *rac*-*trans*-*N*,*N*,*N*′,*N*′-tetramethylcyclohexane-1,2-diamine/*n*-butyllithium for the deprotonation.

**(3*S*)-14 (GP2):** According to GP2 (–)-sparteine (**5**) (1.01 equiv., 0.51 mmol, 120 mg) and 1.6 M *n*-butyllithium (1.01 equiv., 0.51 mmol, 0.32 mL) was used for the deprotonation of **6d** (1.0 equiv., 0.50 mmol, 169 mg) at –90 °C. After a deprotonation time of 10 min, a solution of pivaloyl chloride (3.0 equiv., 1.50 mmol, 182 mg) in toluene (0.5 mL) was added dropwise over 10 min. Then the reaction mixture was stirred for 1 hour at –90 °C and was quenched and worked up as described. Purification by column chromatography (pentane/$Et_2O$, 8:1 → 6:1) furnished 171 mg (3*S*)-**14** (0.41 mmol, 81%). $[\alpha]_D^{20}$ = +63 (*c* = 0.79 in $CHCl_3$; 99% *op*, determined by conversion of **17d** to **14**, see below).

**(1*Z*,3*S*)-3-Methoxycarbonyl-1,3-diphenyl-1-propenyl *N*,*N*-Diisopropylcarbamate (15). GP1:** According to GP1 (–)-sparteine (**5**) (1.2 equiv., 0.60 mmol, 141 mg) was dissolved in toluene (2.0 mL) and cooled to –78 °C before 1.6 M *n*-butyllithium (1.2 equiv., 0.60 mmol, 0.38 mL) was added, followed by a solution of **6d** (1.0 equiv., 0.50 mmol, 169 mg) in toluene (1.1 mL) after 10 min. The reaction mixture was stirred for 30 min and then methyl chloroformate (3.0 equiv, 1.50 mmol, 142 mg) was added. Stirring was continued for 2.0 hours. After quenching at –78 °C and work up, the residue was purified by flash chromatography (pentane/$Et_2O$, 4:1) to give 60 mg (0.15 mmol, 30%) (3*S*)-**15** as a colourless oil. $R_F$

= 0.28 (pentane/$Et_2O$, 2:1). $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 1.18–1.33 (m, 12 H, O*Cb*-$CH_3$), 3.70 (s, 3 H, $OCH_3$), 3.86 [4.09] ($m_c$, 2 H, O*Cb*-CH), 4.68 (d, $^3J_{H,H}$ = 9.3 Hz, 1 H, CH*CH*C=O), 6.25 (d, $^3J_{H,H}$ = 9.3 Hz, 1 H, *CH*CHC=O), 7.21–7.46 (m, 10 H, aryl-H) ppm. $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 20.4 [21.5] (O*Cb*-$CH_3$), 46.5 (O*Cb*-CH), 48.8 (CH*CH*C=O), 52.3 ($OCH_3$), 114.9 (*CH*CHC=O), 124.9/127.2/127.7/127.8/128.3/128.8 (aryl-CH), 135.6/138.3 (aryl-Cq), 148. (Cq), 152.0 (O*C*ON), 172.4 (*C*OOMe). IR (film): $\tilde{\nu}$ = 1735 $cm^{-1}$. ESI-MS: (*m*/*z*) = 396.2 $[M + H]^+$, 413.2 $[M + NH_4]^+$, 808.3 $[2M + NH_4]^+$. $C_{24}H_{29}NO_4$ (395.49): calcd. C 72.89, H 7.39, N 3.54; found C 72.61, H 7.31, N 3.54. $[\alpha]_D^{20}$ = +22 (*c* = 0.57 in $CHCl_3$; 69% *op*, determined by conversion to **13**, see below). *rac*-**15** (yield 49%) was obtained in the same way by using 1.4 equiv. *rac-trans-N,N,N′,N′*-tetramethylcyclohexane-1,2-diamine/*n*-butyllithium for the deprotonation.

**(3*S*)-15 (GP2):** To a stirred solution of (–)-sparteine (**5**) (1.01 equiv., 0.51 mmol, 120 mg) in toluene (1.5 mL) was added 1.6 M *n*-butyllithium (1.01 equiv., 0.51 mmol, 0.32 mL) at –90 °C according to GP2. After 10 min, **6d** (1.0 equiv., 0.50 mmol, 169 mg) was added dropwise over 10 min and the clear deep red solution was stirred for 10 min. A solution of 3.0 equiv., 1.50 mmol, 142 mg) methyl chloroformate in toluene (0.5 mL) was added dropwise over 10 min. The mixture became pale yellow within 50 min and was quenched with a mixture of acetic acid (0.05 mL) and methanol (0.3 mL) at –90 °C. After warming to room temp. and dilution of the organic phase with diethyl ether it was dried with $MgSO_4$ and the solvent was removed in vacuo. Purification by column chromatography (pentane/diethyl ether, 9:1 → 4:1) furnished 130 mg (3*S*)-**15** (0.33 mmol, 72%) as a colourless oil. $[\alpha]_D^{20}$ = +31 (*c* = 0.79 in $CHCl_3$; 96% *op*; determined by conversion to **13**, see below).

**Homoaldol Reaction of 6d. Method A. General Procedure 3 (GP3):** A solution of (–)-sparteine (**5**) (1.2–1.4 equiv., 0.33–0.60 mmol) in toluene (1.5 mL) was cooled to –78 °C and 1.6 M *n*-butyllithium (1.2–1.4 equiv., 1.6 M in hexane, 0.33–0.60 mmol) was added dropwise. After 10 min, **6d** (1.0 equiv., 0.30–0.50 mmol) in toluene (1.1 mL) was added dropwise within 10 min under vigorous stirring. The deep red solution was stirred at this temperature for 20 min and then a solution of $ClTi(NEt_2)_3$ (1.5 equiv., 0.45–0.75 mmol) in toluene (0.5 mL) was added dropwise over 10 min. The dark reaction mixture was stirred for 30 min at –78 °C and then the aldehyde (3.0–4.0 equiv., 0.90–2.0 mmol), dissolved in toluene (0.5 mL), was added. Finally, the reaction mixture was stirred for 2–4 hours at –78 °C before it was quenched with a mixture of acetic acid (0.05 mL) and methanol (0.3 mL) at –78 °C. The solution was poured into a ice-cooled mixture of diethyl ether (15 mL) and 2 N aq. HCl (15 mL). The aqueous layer was extracted with diethyl ether (3 × 10 mL). The combined organic extracts was dried with anhydrous $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel flash column chromatography.

**Homoaldol Reaction of 6d. Method B. General Procedure 4 (GP4):** To a cooled (–90 °C) solution of (–)-sparteine (**5**) (1.2 equiv., 0.36 mmol) in toluene (1.5 mL) was added dropwise 1.6 M *n*-butyllithium (1.2 equiv., 0.36 mmol) . After 10 min, **6d** (1.0 equiv., 0.30 mmol) in toluene (1.1 mL) was added dropwise within 10 min under vigorous stirring. The deep red solution was stirred at –90 °C for additional 10 min and then a solution of $ClTi(NEt_2)_3$ (1.5 equiv., 0.45 mmol) in toluene (0.5 mL) was added dropwise over 10 min. The dark reaction mixture was stirred for 5 min at –90 °C. Then, a mixture of the aldehyde (4.0 equiv., 1.2 mmol) and Ti(O*i*Pr)4 (4.0 equiv., 1.2 mmol), dissolved in toluene (2.0 mL), was added dropwise over 15 min. Finally, the reaction mixture was stirred for 0.5–1.0 hour at –90 °C before it was quenched with a mixture of acetic acid (0.05 mL) and methanol (0.3 mL) at –90 °C. The solution was poured into an ice cooled mixture of diethyl ether (15 mL) and 2 N aq. HCl (20 mL). The aqueous layer was extracted with diethyl ether (3 × 10 mL). The combined organic extracts were dried with anhydrous $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel flash column chromatography.

**(3*R*)-13:** According to GP3 (–)-sparteine (**5**) (1.2 equiv., 0.36 mmol, 84 mg) was dissolved in toluene (1.5 mL) and cooled to –78 °C before 1.6 M *n*-butyllithium (1.2 equiv., 0.36 mmol, 0.23 mL) and subsequently **6d** (1.0 equiv., 0.30 mmol, 101 mg) was added. The reaction mixture was stirred for 30 min after which $ClTi(NEt_2)_3$ (1.5 equiv., 0.45 mmol, 135 mg) was added. The solution was stirred for 30 min at –78 °C and then acetone (4.0 equiv., 0.90 mmol, 55 mg), dissolved in toluene (0.5 mL), was added. The reaction was quenched after 4 h. Flash chromatography yielded 104 mg (0.26 mmol, 88%) (3*R*)-**13** as a colourless oil. $[\alpha]_D^{20}$ = –42 (*c* = 1.32 in $CHCl_3$, 73% *op*).

**(1*Z*,3*R*,4*R*)-4-Hydroxy-6-methyl-1,3-diphenyl-1-heptenyl *N*,*N*-Diisopropylcarbamate (17a). Method B. GP4:** Compound **6d** (1.0 equiv., 0.30 mmol, 101 mg) was lithiated with (–)-sparteine (**5**) (1.2 equiv., 0.36 mmol, 84 mg) and 1.6 M *n*-butyllithium (1.2 equiv., 0.36 mmol, 0.23 mL) at –90 °C as described by GP4. After titanation with a solution of $ClTi(NEt_2)_3$ (1.5 equiv., 0.45 mmol, 135 mg) in toluene (1 mL), the intermediate was trapped with a mixture of 3-methylbutanal (3.0 equiv., 0.90 mmol, 78 mg) and $Ti(OiPr)_4$ (3.0 equiv., 0.90 mmol, 256 mg) in toluene (2.0 mL). The solution was then stirred for additional 30 min at –90 °C before the reaction was stopped at –90 °C. After work up and chromatography of the crude product (pentane/$Et_2O$, 4:1 → 2:1), 87 mg (0.21 mmol, 68%) (1*Z*,3*R*,4*R*)-**17a** were obtained as a colourless solid. $R_F$ = 0.38 (pentane/$Et_2O$, 1:1). m.p. 141 °C (pentane/$Et_2O$). $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 0.75/0.77 [d, $^3J_{H,H}$ = 6.8 Hz, 6 H, $CH_2CH(CH_3)$], 1.02–1.11 [m, 2 H, $CH_2CH(CH_3)$], 1.18–1.30 (m, 12 H, O*Cb*-$CH_3$), 1.75–1.82 [m, 1 H, $CH_2CH(CH_3)$], 2.83 (d, $^3J_{H,OH}$ = 5.1 Hz, 1 H, OH), 3.50 (dd, $^3J_{H,H}$ = 10.5/7.5 Hz, 1 H, CqCHC*H*Ph), 3.84–4.04 (m, 3 H, C*H*OH/O*Cb*-CH), 6.09 (d, $^3J_{H,H}$ = 10.5 Hz, 1 H, CqC*H*CHPh), 7.13–7.38 (m, 10 H, aryl-H) ppm. $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 20.5 [21.6] (O*Cb*-$CH_3$), 21.6/23.8 [$CH_2CH(CH_3)_2$], 24.5 [$CH_2CH(CH_3)_2$], 44.9 [$CH_2CH(CH_3)_2$], 46.6 [46.8] (O*Cb*-CH), 50.2 (CqCH*C*HPh), 73.1 (*C*HOH), 118.4 (Cq*C*HCHPh), 125.9/126.6/128.0/128.3/128.4/128.7 (aryl-CH), 135.7/141.8 (aryl-Cq), 147.6 (Cq), 153.4 (O*C*ON) ppm. IR (KBr): $\tilde{\nu}$ = 3479, 1672 $cm^{-1}$. ESI-MS (*m*/*z*) = 424.3 $[M + H]^+$, 446.3 $[M + Na]^+$, 869.5 $[2M + Na]^+$. $C_{27}H_{37}NO_3$ (423.59) calcd. C 76.56, H 8.80, N 3.31; found C 76.18, H 8.67, N 3.05. $[\alpha]_D^{20}$ = –81 (*c* = 1.07 in $CHCl_3$; 91% *ee*). Shift experiment (300 MHz): 8 mol-% Eu(hfc)$_3$ in $CDCl_3$, $\Delta\delta$ = 0.15 ppm, [CH, $I_H$ ($\delta$ = 7.60 ppm): $I_T$ ($\delta$ = 7.65 ppm) = 4.5:96.5]. Compound *rac*-**17a** [yield 80%, m.p. 126 °C (pentane/$Et_2O$)] was obtained in the same way by using 1.2 equiv. *rac-trans-N,N,N′,N′*-tetramethylcyclohexane-1,2-diamine/*n*-butyllithium for the deprotonation.

**(1*Z*,3*R*,4*R*)-4-Hydroxy-5-methyl-1,3-diphenyl-1-hexenyl *N*,*N*-Diisopropylcarbamate (17b). Method A. GP3:** According to GP3 a solution of (–)-sparteine (**5**) (1.2 equiv., 0.36 mmol, 84 mg) in toluene (1.5 mL) was cooled to –78 °C. 1.6 M *n*-butyllithium (1.2 equiv., 0.36 mmol, 0.23 mL) was added followed by a solution of **6d** (1.0 equiv., 0.30 mmol, 101 mg) in toluene (1.0 mL) after 10 min and the solution was stirred for 20 min. A solution of $ClTi(NEt_2)_3$ (1.5 equiv., 0.45 mmol, 135 mg) in toluene (0.5 mL) was added and the reaction mixture was stirred for additional 30 min before 2-methylpropanal (4.0 equiv., 1.20 mmol, 86 mg) was added. The

solution was stirred for additional 2 h and then the reaction was quenched at –78 °C. After work up and chromatography (pentane/$Et_2O$, 1:1) 102 mg (0.25 mmol, 83%) (1*Z*,3*R*,4*R*)-**17b** were afforded. $R_F$ = 0.47 (pentane/$Et_2O$, 1:1). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 0.88/0.98 (d, $^3J_{H,H}$ = 6.9 Hz, 6 H, *i*Pr-$CH_3$), 1.28–1.90 (m, 13 H, *i*Pr-CH/O*Cb*-$CH_3$), 3.31 (d, $^3J_{H,OH}$ = 4.5 Hz, 1 H, OH), 3.77–3.79 (m, 2 H, CHC*H*Ph/C*H*OH), 4.10 (sept, $^3J_{H,H}$ = 6.8 Hz, 2 H, O*Cb*-CH), 6.19 (d, $^3J_{H,H}$ = 10.5 Hz, 1 H, C*H*CHPh), 7.22–7.47 (m, 10 H, aryl-H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 14.6/20.4 (*i*Pr-$CH_3$), 20.4 [22.1] (O*Cb*-$CH_3$), 29.7 (*i*Pr-CH), 46.4 [47.1] (O*Cb*-CH), 47.3 (CH*C*HPh), 79.1 (*C*HOH), 119.4 (*C*HCHPh), 124.9/126.6/127.8/128.1/128.3/128.8 (aryl-CH), 135.5/141.6 (aryl-Cq), 147.1 (Cq), 153.9 (O*C*ON) ppm. IR (KBr): $\tilde{\nu}$ = 3412, 1677 $cm^{-1}$. ESI-MS: (*m*/*z*) = 410.4 $[M + H]^+$, 432.3 $[M + Na]^+$, 448.3 $[M + K]^+$. $C_{26}H_{35}NO_3$ (409.56): calcd. C 76.25, H 8.61, N 3.42; found C 76.08, H 8.56, N 3.41. $[\alpha]_D^{20}$ = –117 (*c* = 1.08 in $CHCl_3$; 89% *ee*). Shift experiment (300 MHz): 5.3 mol-% Eu(hfc)$_3$ in $CDCl_3$, $\Delta\delta$ = 0.16 ppm, [CH, $I_H$ ($\delta$ = 6.50 ppm): $I_T$ ($\delta$ = 6.66 ppm) = 5.5:94.5]. Compound *rac*-**17b** [yield 84%, m.p. 126 °C (pentane/$Et_2O$)] was obtained in the same way by using 1.4 equiv. *rac-trans-N,N,N′,N′*-tetramethylcyclohexane-1,2-diamine/*n*-butyllithium for the deprotonation.

**(1*Z*,3*R*,4*R*)-17b (Method B, GP4):** Compound **6d** (1.0 equiv., 0.30 mmol, 101 mg) was lithiated with (–)-sparteine (**5**) (1.2 equiv., 0.36 mmol, 84 mg) and 1.6 M *n*-butyllithium (1.2 equiv., 0.36 mmol, 0.23 mL) at –90 °C as described by GP4. After titanation with a solution of $ClTi(NEt_2)_3$ (1.5 equiv., 0.45 mmol, 135 mg) in toluene (1 mL), the intermediate was trapped with a mixture of 2-methylpropanal (4.0 equiv., 1.20 mmol, 86 mg) and $Ti(OiPr)_4$ (4.0 equiv., 1.20 mmol, 284 mg) in toluene (2.0 mL). The solution was then stirred for an additional hour at –90 °C before the reaction was stopped at –90 °C. Work up and chromatography of the crude product (pentane/$Et_2O$, 4:1 → 2:1) yielded 100 mg (0.24 mmol, 81%) (1*Z*,3*R*,4*R*)-**17b**. M.p. 132 °C (pentane/$Et_2O$). $[\alpha]_D^{20}$ = –138 (*c* = 0.99 in $CHCl_3$; 99% *op*).

**(1*Z*,3*R*,4*R*)-4-Cyclopropyl-4-hydroxy-1,3-diphenyl-1-butenyl *N*,*N*-Diisopropylcarbamate (17c). Method B. GP4:** Compound **6d** (1.0 equiv., 0.30 mmol, 101 mg) was lithiated with (–)-sparteine (**5**) (1.2 equiv., 0.36 mmol, 84 mg) and 1.6 M *n*-butyllithium (1.2 equiv., 0.36 mmol, 0.23 mL) at –90 °C as described by GP4. After titanation with a solution of $ClTi(NEt_2)_3$ (1.5 equiv., 0.45 mmol, 135 mg) in toluene (1 mL), the intermediate was trapped with a mixture of cyclopropanecarbaldehyde (3.0 equiv., 0.90 mmol, 63 mg) and $Ti(OiPr)_4$ (3.0 equiv., 0.90 mmol, 256 mg) in toluene (2.0 mL). The solution was then stirred for an additional hour before the reaction was stopped at –90 °C. After work up and chromatography of the crude product (pentane/$Et_2O$, 2:1 → 1:1) 78 mg (0.19 mmol, 64%) (1*Z*,3*R*,4*R*)-**17c** were obtained. $R_F$ = 0.22 (pentane/$Et_2O$, 1:1), m.p. 81 °C (pentane/$Et_2O$). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 0.04–0.23 (m, 4 H, *c*-propyl-$CH_2$), 0.60–0.67 (m, 1 H, *c*-propyl-CH), 1.09–1.24 (m, 12 H, O*Cb*-$CH_3$), 2.86 (br. s, 1 H, OH), 3.32 (ψt, $^3J_{H,H}$ = 10.5/7.2 Hz, 1 H, CHC*H*Ph), 3.58 (dd, $^3J_{H,H}$ = 7.2/10.5 Hz, 1 H, C*H*OH), 3.89 (sept, $^3J_{H,H}$ = 6.6 Hz, 2 H, O*Cb*-CH), 6.19 (d, $^3J_{H,H}$ = 10.5 Hz, 1 H, C*H*CHPh), 7.02–7.28 (m, 10 H, aryl-H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 1.0/2.5 (*c*-propyl-$CH_2$), 15.7 (*c*-propyl-CH), 20.5 [21.7] (O*Cb*-$CH_3$), 45.6 [46.9] (O*Cb*-CH), 50.7 (CH*C*HPh), 77.3 (*C*HOH), 118.2 (*C*HCHPh), 124.9/126.6/128.2/ 128.4/128.6 (aryl-CH), 135.7/141.5 (aryl-Cq), 147.4 (Cq), 153.6 (O*C*ON) ppm. IR (KBr): $\tilde{\nu}$ = 3469, 1673 $cm^{-1}$. ESI-MS: (*m*/*z*) = 408.3 $[M + H]^+$, 430.2 $[M + Na]^+$, 837.5 $[2M + Na]^+$. $C_{26}H_{33}NO_3$ (407.55): calcd. C 76.62, H 8.16, N 3.44; found C 76.51, H 8.18, N 3.18. $[\alpha]_D^{20}$ = –88 (*c* = 0.97 in $CHCl_3$; ≥ 95% *ee*). Shift experiment (300 MHz): 10 mol-% Eu(hfc)$_3$ in $C_6D_6$, $\delta$ (CH) = 7.87 ppm (major enantiomer appears at lower field). Compound *rac*-**17c** [yield 74%, m.p. 132 °C (pentane/$Et_2O$)] was obtained in the same way by using 1.2 equiv. *rac-trans-N,N,N′,N′*-tetramethylcyclohexane-1,2-diamine/*n*-butyllithium for the deprotonation.

**(1*Z*,3*R*,4*S*)-4-Hydroxy-5,5-dimethyl-1,3-diphenyl-1-hexenyl *N*,*N*-Diisopropylcarbamate (17d). Method A. GP3:** According to GP3 a solution of (–)-sparteine (**5**) (1.2 equiv., 0.60 mmol, 145 mg) in toluene (1.5 mL) was cooled to –78 °C. 1.6 M *n*-Butyllithium (1.2 equiv., 0.60 mmol, 0.38 mL) was added, followed by a solution of **6d** (1.0 equiv., 0.50 mmol, 169 mg) in toluene (1.0 mL) after 10 min and the solution was stirred for 20 min. A solution of $ClTi(NEt_2)_3$ (1.5 equiv., 0.75 mmol, 225 mg) in toluene (1.0 mL) was added and the reaction mixture was stirred for additional 30 min before 2,2-dimethylpropanal (4.0 equiv., 2.00 mmol, 173 mg) was added. The solution was stirred for additional 2.5 h and then the reaction was quenched at –78 °C. After work up and chromatography (pentane/$Et_2O$, 4:1 → 2:1) 158 mg (0.37 mmol, 75%) (1*Z*,3*R*,4*S*)-**17d** were afforded. $R_F$ = 0.65 (pentane/$Et_2O$, 1:1), m.p. 99 °C (pentane/$Et_2O$). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 0.87 (s, 9 H, *t*Bu), 1.25–1.38 (m, 12 H, O*Cb*-$CH_3$), 3.06 (d, $^3J_{H/OH}$ = 6.9 Hz, 1 H, OH), 3.68 (ψt, $^3J_{H,H}$ = 6.9, $^3J_{H/OH}$ = 6.9 Hz 1 H, C*H*OH), 3.93 (dd, $^3J_{H,H}$ = 10.5, 6.9 Hz, 1 H, CHC*H*Ph), 4.04 ($m_c$, 2 H, O*Cb*-CH), 6.22 (d, $^3J_{H,H}$ = 10.5 Hz, 1 H, C*H*CHPh), 7.13–7.41 (m, 10 H, aryl-H) ppm.$^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 20.4 [21.7] (O*Cb*-$CH_3$), 26.8 (*t*Bu-$CH_3$), 36.4 (*t*Bu-Cq), 45.7 (CH*C*HPh), 46.3 [46.9] (O*Cb*-CH), 82.1 (*C*HOH), 119.7 (*C*HCHPh), 124.8/126.3/ 127.9/128.0/128.3/128.6 (aryl-CH), 135.9/143.9 (aryl-Cq), 145.7 (Cq), 153.5 (O*C*ON) ppm. IR (KBr): $\tilde{\nu}$ = 3409, 1674 $cm^{-1}$. ESI-MS: (*m*/*z*) = 446.4 $[M + Na]^+$. $C_{27}H_{37}NO_3$ (423.59): calcd. C 76.56, H 8.80, N 3.31; found C 76.52, H 8.77, N 3.18. $[\alpha]_D^{20}$ = –132 (*c* = 1.02 in $CHCl_3$; 92% *ee*). Shift experiment (300 MHz): 10 mol-% Eu(hfc)$_3$ in $CDCl_3$, $\Delta\delta$ = 0.22 ppm, [CH, $I_H$ ($\delta$ = 6.66 ppm): $I_T$ ($\delta$ = 6.89 ppm) = 96:4]. Compound *rac*-**17d** [yield 77%, m.p. 141 °C (pentane/$Et_2O$)] was obtained in the same way by using 1.4 equiv. *rac-trans-N,N,N′,N′*-tetramethylcyclohexane-1,2-diamine/*n*-butyllithium for the deprotonation.

**(1*Z*,3*R*,4*S*)-17d (Method B, GP4):** Compound **6d** (1.0 equiv., 0.30 mmol, 101 mg) was lithiated with (–)-sparteine (**5**) (1.2 equiv., 0.36 mmol, 84 mg) and 1.6 M *n*-butyllithium (1.2 equiv., 0.36 mmol, 0.23 mL) at –90 °C as described by GP4. After titanation with a solution of $ClTi(NEt_2)_3$ (1.5 equiv., 0.45 mmol, 135 mg) in toluene (1 mL), the intermediate was trapped with a mixture of 2,2-dimethylpropanal (3.0 equiv., 0.90 mmol, 103 mg) and $Ti(OiPr)_4$ (3.0 equiv., 0.90 mmol, 256 mg) in toluene (2.0 mL). The solution was then stirred for an additional hour at –90 °C before the reaction was stopped at –90 °C. Work up and chromatography of the crude product (pentane/$Et_2O$, 6:1 → 4:1) yielded 117 mg (0.28 mmol, 92%) (1*Z*,3*R*,4*S*)-**17d**. $[\alpha]_D^{20}$ = –130 (*c* = 0.99 in $CHCl_3$; 91% *ee*). Shift experiment (300 MHz): 10 mol-% Eu(hfc)$_3$ in $CDCl_3$, $\Delta\delta$ = 0.24 ppm, [CH, $I_H$ ($\delta$ = 6.84 ppm): $I_T$ ($\delta$ = 7.08 ppm) = 96.5:4.5].

**(1*Z*,3*R*,4*S*)-4-(4-Bromophenyl)-4-hydroxy-1,4-diphenyl-1-butenyl *N*,*N*-Diisopropylcarbamate (17e). Method A. GP3:** According to GP3 a solution of (–)-sparteine (**5**) (1.2 equiv., 0.60 mmol, 145 mg) in toluene (1.5 mL) was cooled to –78 °C. 1.6 M *n*-Butyllithium (1.2 equiv., 0.60 mmol, 0.38 mL) was added followed by a solution of **6d** (0.50 mmol, 169 mg) in toluene (1.0 mL) after 10 min, and the solution was stirred for 20 min. A solution of 1.5 equiv., 0.75 mmol, 225 mg) $ClTi(NEt_2)_3$ in toluene (1.0 mL) was added, and the reaction mixture was stirred for additional 30 min before *p*-bromobenzaldehyde (4.0 equiv., 2.00 mmol, 370 mg) was added.

The solution was stirred for 2 h and afterwards the reaction was quenched at –78 °C. After work up and chromatography (pentane/$Et_2O$, 4:1 → 2:1) 153 mg (0.30 mmol, 59%) (1*Z*,3*R*,4*S*)-**17e** were afforded. $R_F$ = 0.25 (pentane/$Et_2O$, 2:1). M.p. 125 °C (pentane/$Et_2O$). $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 1.32–1.38 (m, 12 H, O*Cb*-$CH_3$), 3.66 (ψt, $^3J_{H/H}$ = 10.5/11.1 Hz, 1 H, CHC*H*Ph), 4.05–4.13 (m, 2 H, O*Cb*-CH), 4.57 (bd, $^3J_{H,OH}$ = 4.8 Hz, 1 H, OH), 4.81 (m, 1 H, C*H*OH), 6.31 (d, $^3J_{H,H}$ = 11.1 Hz, 1 H, C*H*CHPh), 6.87–7.47 (m, 14 H, aryl-H) ppm. $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 20.9 [22.1] (O*Cb*-$CH_3$), 47.1 [47.5] (O*Cb*-CH), 53.4 (CH*C*HPh), 78.2 (*C*HOH), 118.5 (*C*HCHPh), 121.1/125.4/127.3/128.4/128.6/128.7/128.9/129.0 (aryl-CH), 131.0/140.3/143.0 (aryl-Cq), 148.2 (Cq), 154.4 (O*C*ON) ppm. IR (KBr): $\tilde{\nu}$ = 3352, 1673 $cm^{-1}$ . ESI-MS: (*m*/*z*) = 544.3 $[M + Na]^+$. $C_{29}H_{32}BrNO_3$ (522.47): calcd. C 66.67, H 6.17, N 2.68; found C 66.54, H 6.15, N 2.60. $[\alpha]_D^{20}$ = –55 (*c* = 1.13 in $CHCl_3$; 89% *op*). Compound *rac*-**17e** [yield 80%, m.p. 122 °C (pentane/$Et_2O$)] was obtained in the same way by using 1.4 equiv. *rac-trans-N,N,N′,N′*-tetramethylcyclohexane-1,2-diamine/*n*-butyllithium for the deprotonation.

**(1*Z*,3*R*,4*S*)-17e (Method B, GP4):** Compound **6d** (1.0 equiv., 0.30 mmol, 101 mg) was lithiated with (–)-sparteine (**5**) (1.2 equiv., 0.36 mmol, 84 mg) and 1.6 M *n*-butyllithium (1.2 equiv., 0.36 mmol, 0.23 mL) at –90 °C as described by GP4. After titanation with a solution of $ClTi(NEt_2)_3$ (1.5 equiv., 0.45 mmol, 135 mg) in toluene (1 mL), the intermediate was trapped with a mixture of ) *p*-bromobenzaldehyde (3.0 equiv., 0.90 mmol, 167 mg) and $Ti(OiPr)_4$ (3.0 equiv., 0.90 mmol, 256 mg) in toluene (2 mL). The solution was then stirred for additional 30 min before the reaction was stopped at –90 °C. Work up and chromatography of the crude product (pentane/$Et_2O$, 2:1) yielded 121 mg (0.23 mmol, 77%) (1*Z*,3*R*,4*S*)-**17e**. $[\alpha]_D^{20}$ = –59 (*c* = 0.99 in $CHCl_3$; ≥ 95% *ee*). Shift experiment (300 MHz): 10 mol-% $Eu(hfc)_3$ in $CDCl_3$, $\delta$ (CH) = 6.02 ppm (major enantiomer appears at lower field).

**Conversion of (3*S*)-15 to (3*S*)-13:** To a stirred solution of (3*S*)-**15** (1.0 equiv., 0.15 mmol, 69% *op*) ($[\alpha]_D^{20}$ = +22, *c* = 1.13 in $CHCl_3$; 69% *op*) in 2.0 mL diethyl ether was added MeMgBr (3.0 M solution in THF, 3.0 equiv., 0.45 mmol, 0.15 mL) ). The reaction mixture was stirred for 1.5 hours before the reaction was stopped by the addition of 0.5 mL 2N HCl. The organic layer was diluted with 10 mL diethyl ether and was dried with $MgSO_4$. After removal of the solvent in vacuo, the residue was purified by column chromatography which furnished 30 mg (3*S*)-**13** (0.08 mmol, 51%). $[\alpha]_D^{20}$ = +40 (*c* = 1.42 in $CHCl_3$; 68% *op*).

**Conversion of (3*R*,4*S*)-17d to (3*R*)-14:** Pyridinium dichromate (2.0 equiv., 0.58 mmol, 218 mg) was suspended in $CH_2Cl_2$ (2.5 mL). Then a solution of (3*R*,4*S*)-**17d** (1.0 equiv., 0.29 mmol, 124 mg) ($[\alpha]_D^{20}$ = –132, *c* = 1.02 in $CHCl_3$; 92% *op*) was added to the stirred suspension at room temp. The mixture was stirred for additional 5 hours, then poured to 10 mL diethyl ether, and filtered through celite. The solvent was removed on a rotary evaporator. The resultant crude mixture was applied to silica gel purification. Elution with pentane/$Et_2O$, 6:1 yielded 43 mg (0.10 mmol, 35%) (3*R*)-**14**. $[\alpha]_D^{20}$ = –57 (*c* = 2.17 in $CHCl_3$; 92% *op*).

**Retro-Homoaldol Reaction; Conversion of (3*R*)-13 to (3*R*)-14:** To a stirred solution of (–)-sparteine (**5**) (1.5 equiv., 0.30 mmol, 69 mg) in toluene (1.0 mL) was added *n*-butyllithium (1.6 M in hexanes, 1.5 equiv., 0.30 mmol, 0.19 mL) at –78 °C. After 15 min a solution of (3*R*)-**13** (1.0 equiv., 0.20 mmol, 78 mg) ($[\alpha]_D^{20}$ = –49, *c* = 0.94 in $CHCl_3$; 85% *op*) in toluene (0.8 mL) was added slowly within 10 min. Pivaloyl chloride (5.0 equiv., 1.00 mmol, 121 mg) in toluene (0.3 mL) was added to the red solution over 10 min after 2 hours stirring at –78 °C. The reaction mixture was stirred for 1 hour before the pale yellow reaction mixture was quenched by addition of acetic acid (0.05 mL) and methanol (0.3 mL) at –78 °C. After warming to room temp., the organic phase was diluted with diethyl ether and dried with $MgSO_4$. The solvent was removed on a rotary evaporator and the resultant crude mixture was applied to flash column chromatography (pentane/$Et_2O$, 2:1). The purification furnished 18 mg (0.04 mmol, 21%) (3*R*)-**14** ($[\alpha]_D^{20}$ = –31, *c* = 0.32 in $CHCl_3$; 49% *op*) and 60 mg (0.15 mmol, 77%) (3*R*)-**13** ($[\alpha]_D^{20}$ = –48, *c* = 1.52 in $CHCl_3$; 83% *op*).

**Retro-Homoaldol Reaction. Conversion of (3*R*)-13 to (3*R*,4*S*)-17d:** (–)-Sparteine (**5**) (1.5 equiv., 0.23 mmol, 53 mg) in toluene (1.0 mL) was cooled to –90 °C and *n*-butyllithium (1.6 M in hexanes, 1.5 equiv., 0.23 mmol, 0.14 mL) was added to the stirred solution. After 15 min a solution of 1.0 equiv., 0.15 mmol, 60 mg) (3*R*)-**13** ($[\alpha]_D^{20}$ = –48, *c* = 1.52 in $CHCl_3$; 83% *op*) in toluene (0.8 mL) was added slowly within 10 min. 2,2-Dimethylpropanal (5.0 equiv., 0.75 mmol, 65 mg) in toluene (0.5 mL) was added to the red solution over 10 min after 2 hours stirring at –78 °C. The reaction mixture was stirred for 1 hour before the pale yellow reaction mixture was quenched by addition of acetic acid (0.05 mL) and methanol (0.3 mL) at –78 °C. After warming to room temp. the organic phase was diluted with diethyl ether and dried with $MgSO_4$. The solvent was removed on a rotary evaporator and purification of the residue by flash column chromatography (pentane/$Et_2O$, 2:1) yielded 2 mg (0.01 mmol, 3%) (3*R*,4*S*)-**17d**. $[\alpha]_D^{20}$ = –55 (*c* = 0.10 in $CHCl_3$; 38% *op*).

**X-ray Crystallographic Study. Structure Analysis for HOP2669:** Formula $C_{29}H_{32}BrNO_3$, *M* = 522.47, colorless crystal 0.35 × 0.20 × 0.10 mm, *a* = 10.652(1), *b* = 13.493(2), *c* = 37.419(6) Å, *V* = 5378.1(13) $Å^3$, $\rho_{calcd.}$ = 1.291 g $cm^{-3}$, 23.08 $cm^{-1}$, empirical absorption correction by ψ scan data (0.499 ≤ *T* ≤ 0.802), *Z* = 8, orthorhombic, space group $P2_12_12_1$ (No. 19), λ = 1.54178 Å, *T* = 223 K, ω/2θ scans, 6106 reflections collected (–*h*,–*k*,–*l*), [(sinθ)/λ] = 0.62 $Å^{-1}$, 6106 independent and 4145 observed reflections [$I \geq 2\sigma(I)$], 653 refined parameters, *R* = 0.047, $wR_2$ = 0.147, Flack parameter 0.00(3), two almost identical independent molecules in the asymmetric unit, max. residual electron density 0.34 (–0.51) e·$Å^{-3}$, hydrogen atoms calculated and refined as riding atoms. Data set was collected with an Enraf–Nonius CAD4 diffractometer. Programs used: data collection EXPRESS (Nonius B.V., 1994), data reduction MolEN (K. Fair, Enraf–Nonius B.V., 1990), structure solution SHELXS-97 (G.M. Sheldrick, *Acta Cryst., Sect. A* **1990**, *46*, 467–473), structure refinement SHELXL-97 (G. M. Sheldrick, University of Göttingen, 1997), graphics SCHAKAL (E. Keller, University of Freiburg, 1997).

CCDC-264159 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

## Acknowledgments

The support provided by the Deutsche Forschungsgemeinschaft, Sonderforschungsbereich 424, the Graduiertenkolleg "Hochreaktive Mehrfachbindungssysteme", and by the Fonds der Chemischen Industrie is gratefully acknowledged. J. Reuber thanks Mrs. Cornelia Weitkamp and Ms. Verena Hack for their excellent experimental assistance.

[1] Reviews: a) D. Hoppe, T. Hense, *Angew. Chem.* **1997**, *109*, 2376–2410; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2282–2316;

b) H. Ahlbrecht, U. Beyer, *Synthesis* **1999**, 365–390; c) D. Hoppe, F. Marr, M. Brüggemann in *Organolithiums in Enantioselective Synthesis*; Topics in Organometallic Chemistry (Ed.: D. M. Hodgson), Springer-Verlag: Berlin, **2003**, vol. 5, p. 61–138; d) D. Hoppe, G. Christoph, in *The Chemistry of Organolithium Compounds*, Asymmetric Deprotonation with Alkyllithium-(–)-Sparteine (Eds.: Z. Rappoport, I. Marek), John Wiley & Sons, **2004**, p. 1055–1164.

[2] a) D. Hoppe, *Angew. Chem.* **1984**, *96*, 930–946; *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 932–940; b) D. Hoppe, O. Zschage, *Angew. Chem.* **1989**, *101*, 67–69; *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 69–71; c) O. Zschage, D. Hoppe, *Tetrahedron* **1992**, *48*, 5657–5666; d) H. Paulsen, D. Hoppe, *Tetrahedron* **1992**, *48*, 5667–5670.

[3] a) D. Hoppe, T. Krämer, *Angew. Chem.* **1986**, *98*, 171–173; *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 160–162; b) T. Krämer, D. Hoppe, *Tetrahedron Lett.* **1987**, *28*, 5149–5152; c) T. Krämer, J.-R. Schwark, D. Hoppe, *Tetrahedron Lett.* **1989**, *30*, 7037–7040.

[4] O. Zschage, J.-R. Schwark, D. Hoppe, *Angew. Chem.* **1990**, *102*, 336–337; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 296–297.

[5] a) M. Seppi, R. Kalkofen, R. Reupohl, R. Fröhlich, D. Hoppe, *Angew. Chem.* **2004**, *116*, 1447–1451; *Angew. Chem. Int. Ed.* **2004**, *43*, 1423–1427; b) R. Kalkofen, S. Brandau, B. Wibbeling, D. Hoppe, *Angew. Chem.* **2004**, *116*, 6836–6838; *Angew. Chem. Int. Ed.* **2004**, *43*, 6667–6669.

[6] J. Reuber, R. Fröhlich, D. Hoppe, *Org. Lett.* **2004**, *6*; 783–786.

[7] F. Marr, R. Fröhlich, D. Hoppe, *Tetrahedron: Asymmetry* **2002**, *13*, 2587–2592.

[8] a) S. Retzow, Ph. D. Dissertation, Univ. of Kiel, **1993**; b) J. G. Peters, Ph. D. Dissertation, Univ. of Münster, **2000**.

[9] Enantiomeric ratios were not determined.

[10] Reviews: a) M. T. Reetz, *Organotitanium Reagents in Organic Synthesis* 1st ed.; Springer-Verlag: Berlin, **1986**; b) B. Weidmann, D. Seebach, *Angew. Chem.* **1983**, *95*, 12–26; *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 32–46; c) M. T. Reetz, *Organotitanium Chemistry*, *Organometallics* in *Synthesis* 2nd ed. (Ed.: M. Schlosser), Wiley: Chichester, **2002**, p. 817–923.

[11] Few retro reactions of homoallylic alcohols are known, see: a) R. A. Benkeser, W. G. Young, W. E. Broxterman, D. A. Jones, S. J. Piaseczynsky, *J. Am. Chem. Soc.* **1969**, *91*, 132–137; b) J. Nokami, K. Yoshizane, H. Matsuura, S. Sumida, *J. Am. Chem. Soc.* **1998**, *120*, 6609–6610; c) F. Barbot, P. Miginiac, *J. Organomet. Chem.* **1977**, *132*, 445–454; d) P. Jones, N. Millot, P. Knochel, *Chem. Commun.* **1998**, 2405–2406; e) K.-T. Tan, S.-S. Chng, H.-S. Cheng, T.-P. Loh, *J. Am. Chem. Soc.* **2003**, *125*, 2958–2963, and references cited therein.

[12] D. Hoppe, I. Hoppe, M. Marsch, K. Harms, G. Boche, *Angew. Chem.* **1995**, *107*, 2328–2330; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2158–2160.

[13] P. Beak, D. J. Pippel, G. A. Weisenburger, S. R. Wilson, *Angew. Chem.* **1998**, *110*, 2600–2602; *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 2522–2524.

[14] a) P. Beak, G. A. Weisenburger, N. C. Faibish, D. J. Pippel, *J. Am. Chem. Soc.* **1999**, *121*, 9522–9530; b) P. Beak, M. C. Whisler, L. Vaillancourt, *Org. Lett.* **2000**, *2*, 2655–2658.

[15] a) A. Basu, S. Thayumanavan, *Angew. Chem.* **2002**, *114*, 740–763; *Angew. Chem. Int. Ed.* **2002**, *41*, 716–738; b) S. Caddick, K. Jenkins, *Chem. Soc. Rev.* **1996**, 447–456.

Received: March 5, 2005