Asymmetric Synthesis

Highly Enantiomerically Enriched Ketone Homoenolate Reagents Prepared by (−)-Sparteine-Mediated γ-Deprotonation of Achiral 1-Alkenyl Carbamates**

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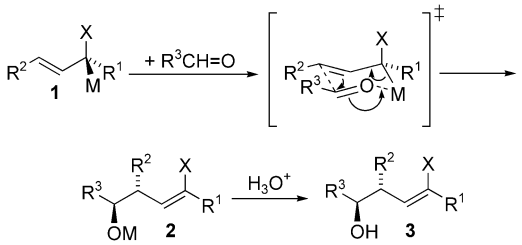
Dedicated to Professor Manfred T. Reetz on the occasion of his 60th birthday

Enantiomerically enriched, 1-hetero-substituted 2-alkenylmetal compounds **1** (e.g., M = Li, Ti(O*i*Pr)$_3$, Ti(NEt$_2$)$_3$) are powerful homoenolate reagents.[1] They react with aldehydes and ketones with virtually complete 1,3-transfer of chirality to form optically active homoaldol products **2**[2] (Scheme 1).[3] In



Scheme 1. Addition of homoenolate reagents to aldehydes.

the best homoenolate reagents **1** the substituent X is a complexing *N*,*N*-dialkylcarbamoyloxy group[2a–d] or a *tert*-butoxycarbonylamino group,[2e] both of which enhance the kinetic acidity in the deprotonation of the allylic precursor and are able to hold the counterion in compound **1** at the α-position.

The first known chiral allyllithium derivative configurationally stable below −70 °C was generated by deprotonation of an enantiomerically enriched, secondary allylic carbamate by *n*-butyllithium/*N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA).[4] We also reported on the preparation of lithium compounds **1** obtained by kinetic resolution of racemic precursors by deprotonation with *n*-butyllithium/(−)-sparteine.[5,6] Lithium carbanions **1** (R^1 = H) derived from primary precursors could be generated by enantiotopos-differentiating deprotonation, but these only occasionally exhibit sufficient configurational stability.[2b,7] Alternatively, chiral auxiliaries were used for residue X.[8]

We now report on a surprising, simple, and efficient approach to 1-aryl ketone homoenolate reagents by enantiotopos-differentiating γ-deprotonation of 1-aryl-1-alkenyl *N*,*N*-diisopropylcarbamates by *n*-butyllithium/(−)-sparteine. When we attempted the asymmetric carbolithiation of enol carbamate **4a** (*Z*/*E* = 92:8)[10,11] and trapped the lithiated intermediate **6a** with acetone, we isolated the homoaldol product **8aa** in 69% yield and with 97% *ee* (Scheme 2). Subsequent experiments indicated that **8aa** has *R* configuration and is formed from the enantiomerically enriched homoenolate reagent (*S*)-**6a**. In turn, reagent (*S*)-**6a** arises from **4a** by deprotonation under the influence of the chiral base via the ternary complex **5a**. During the removal of the *pro*-*R* proton at C3 in the nine-membered cyclic transition state, the lithium cation migrates along the π system to position 1 to form the five-membered chelate (*S*)-**6a**. The prerequisites for intramolecular deprotonation are met only in the isomer (*Z*)-**4a**, since (*E*)-**4a** remains unchanged. Carbamates **4b–d** react analogously. The electrophiles **7** investigated—the dialkyl ketones **7a** and **7b**, triphenyltin chloride (**7c**), the acid chlorides **7d** and **7e**, the arene carboxaldehydes **7h** and **7i**, and alkanal **7l**—are added exclusively at the γ-position (Table 1).

The reactions of **4a** with triphenyltin chloride (**7c**) and *p*-bromobenzaldehyde (**7h**) (and subsequent oxidation of *ent*-**8ah**) afforded crystalline products *ent*-**8ac** and *ent*-**8af**, respectively, each with >90% *ee*. In X-ray crystal structure analyses with anomalous dispersion[12] both of them had the *S* configuration (Figure 1).

Since all of the investigated stannylations of allyllithium[13] and benzyllithium[14] derivatives proceed in an antarafacial manner by *anti*-S$_E$′ or stereoinvertive processes, the carbanionic intermediate **6a** has to be assigned the 1*S* configuration. Our experiments (Scheme 3) indicate that even *p*-bromobenzaldehyde (**7h**) undergoes an *anti*-S$_E$′ addition. Further evidence for this unusual result was provided by the following experiments: The lithium cation in **6a** was exchanged by reaction with chlorotris(diethylamino)titanium[15] (inversion of configuration), and the resulting *ent*-**9a** added onto aldehyde **7h** (*syn* addition).[2] Oxidation of the epimeric secondary alcohols *ent*-**8ah** yielded the ketone *ent*-**8af**, which was identical to a sample obtained from the lithium intermediate. This fact means that an antarafacial reaction step—the carbonyl addition—is involved in the lithium pathway B, as well.[16] In contrast, **6a** and acetone (**7a**) (Scheme 4) yield opposite enantiomers (*S*)-*ent*-**8aa** (pathway B) and (*R*)-**8aa** (pathway A), demonstrating that the lithium intermediate **6a** adds to dialkyl ketones in a *syn*-S$_E$′ process. The acylation by means of methyl chloroformate (**7e**) also proceeds predominantly in a *syn*-S$_E$′ process, as could be shown by transformation of the carboxylic ester (−)-**8ae** into alcohol (+)-**8aa** (Scheme 4).

The addition of the lithium compound **6a** to 2,2-dimethylpropanal (**7l**) and 2,2-dimethylpropanoyl chloride (**7d**) is also a *syn*-S$_E$′ process, as was concluded from an experiment similar to that depicted in Scheme 3. The aliphatic ketones, aldehydes, and acid chlorides are added to the lithium–

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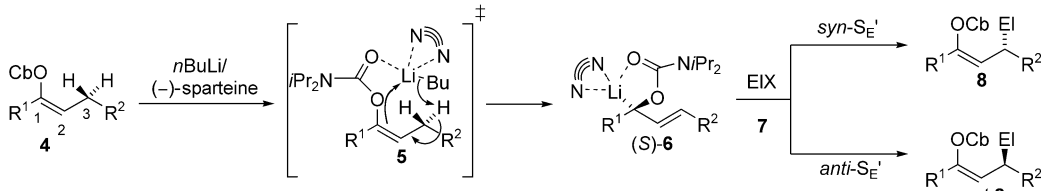
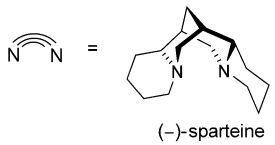


4	R^1	R^2
(*Z*)-**4a**	C_6H_5	CH_3
(*Z*)-**4b**	C_6H_5	C_2H_5
(*Z*)-**4c**	2-naphthyl	CH_3
(*Z*)-**4d**	4-ClC_6H_4	C_2H_5



Scheme 2. Enantiotopos-differentiating γ-deprotonation of the *pro-R* protons by means of the chiral base *n*BuLi/(−)-sparteine. For ElX (**7**) see Table 1, Cb = carbamoyl.

Table 1: Reaction of lithium compounds **6** with different electrophiles.

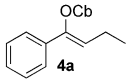
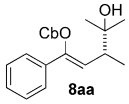
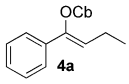
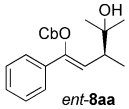
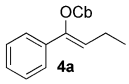
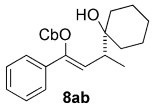
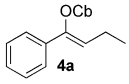
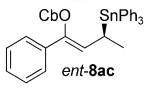
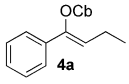
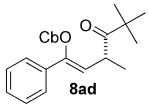
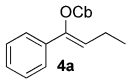
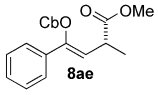
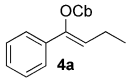
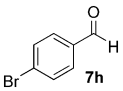
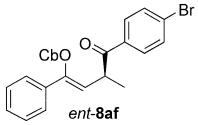
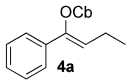
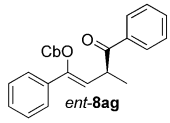
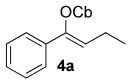
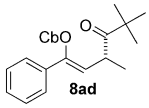
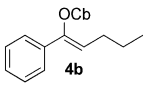
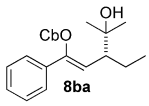
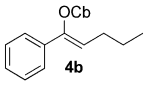
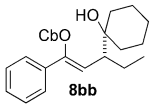
Entry	Starting materials		Product	Yield [%]	*ee* [%][a]	$[\alpha]_D^{20}$[a]
1	 **4a**	 **7a**	 **8aa**	69	97	+87
2[b]	 **4a**	 **7a**	 *ent*-**8aa**	80	92	−83
3	 **4a**	 **7b**	 **8ab**	57	93	+49
4	 **4a**	Ph_3SnCl **7c**	 *ent*-**8ac**	78	94	+54
5	 **4a**	 **7d**	 **8ad**	81	77	−91
6	 **4a**	 **7e**	 **8ae**	78	78	−52
7[c,d]	 **4a**	 **7h**	 *ent*-**8af**	49	>90	+64
8[c,d]	 **4a**	 **7i**	 *ent*-**8ag**	70	86	+85
9[c,d]	 **4a**	 **7l**	 **8ad**	73	86	−105
10	 **4b**	 **7a**	 **8ba**	74	>95	+84
11	 **4b**	 **7b**	 **8bb**	75	>90	+51

Table 1: (Continued)

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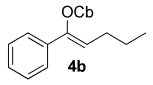
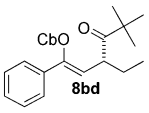
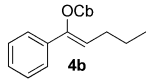
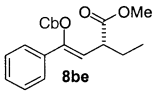
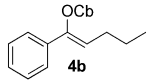
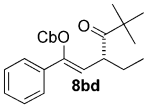
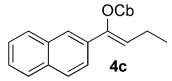
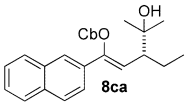
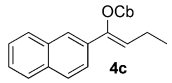
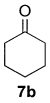
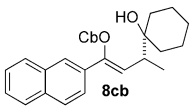
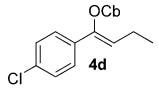
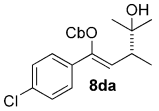
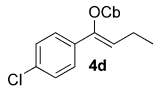
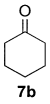
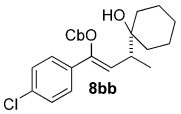
12	 **4b**	 **7d**	 **8bd**	83	>95	−120
13	 **4b**	 **7e**	 **8be**	76	92	−64
14[c,d]	 **4b**	 **7l**	 **8bd**	72	>95	−129
15	 **4c**	 **7a**	 **8ca**	77	88	+84
16	 **4c**	 **7b**	 **8cb**	58	>95	+63
17	 **4d**	 **7a**	 **8da**	50	>95	+81
18	 **4d**	 **7b**	 **8bb**	58	>95	+57

[a] $c = 0.5$–1.28, $CHCl_3$. [b] Lithium species **6a** was treated with 3 equiv $[ClTi(NEt_2)_3]$ (Scheme 5). [c] Mixture of diastereomeric homoaldol adducts (ca. 1:1). [d] Oxidation of the crude product with pyridinium dichromate (PDC).

sparteine complexes in a suprafacial manner.[17] Apparently the lithium cation provides electrophilic assistance for the addition of carbonyl electrophiles. Aromatic aldehydes such as **7h** and **7i** undergo *anti* additions (Table 1, entries 7, 8);

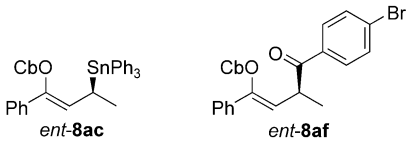
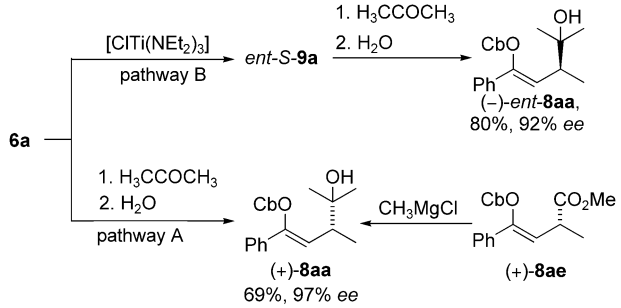
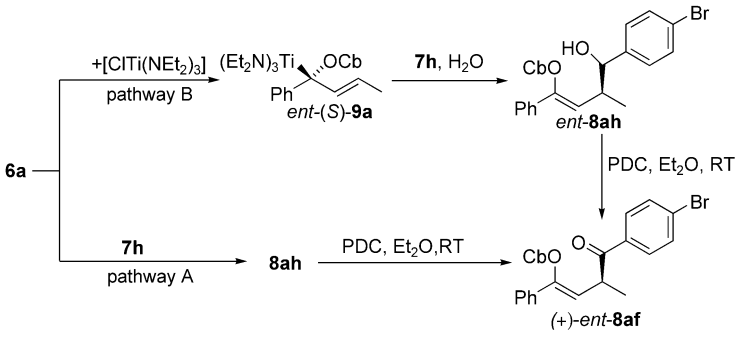


Figure 1. Formulas of the γ-products *ent*-**8ac** and *ent*-**8af**, which were analyzed by X-ray diffraction.

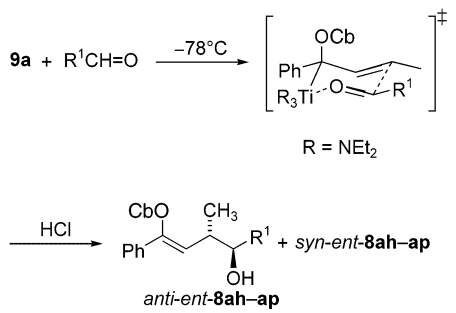


Scheme 4. Additions of (*S*)-**9a** and (*S*)-**6a** to acetone (**7a**) yield products of opposite configuration.

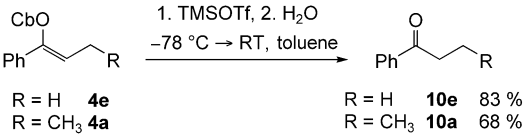


Scheme 3. Additions of (*S*)-**9a** and (*S*)-**6a** to *p*-bromobenzaldehyde (**7h**). Subsequent oxidation by pyridinium dichromate (PDC) leads to products of identical configuration.

presumably, an open-chain transition state is promoted by the formation of an intermediate π–π* complex.[18,14] Here, the approach from the face not covered by the solvated lithium cation is favored. The titanium compound (*S*)-**9a**, which generally is formed from **6a** with stereoinversion, adds to aldehydes reliably via a Zimmerman–Traxler transition state[19] and leads, combined with 1,3-chirality transfer, diastereoselectively to optically active homoaldol adducts *anti-ent*-**8** (Scheme 5, Table 2). Hydrolysis of 1-aryl-1-alkenyl carbamates to ketones is possible by treatment with trimethylsilyl triflate (TMSOTf) and subsequent addition of water (Scheme 6).



Scheme 5. Reaction of titanium compound (*S*)-**9a** with different aldehydes to form highly enantioenriched homoaldol products. See Table 2 for R^1.



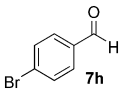
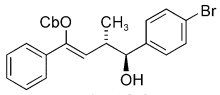
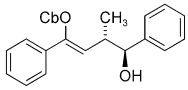
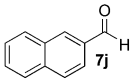
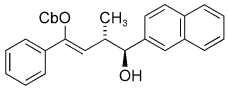
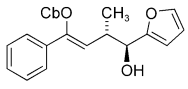
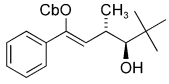
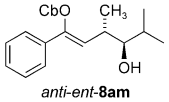
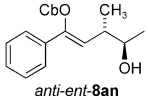
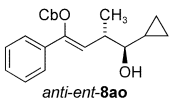
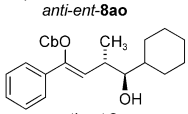
Scheme 6. Decarbamoylation of **4a** and **4e** by means of TMSOTf.

The (−)-sparteine-mediated γ-deprotonation of 1-alkenyl carbamates is an efficient and expandable approach to enantiomerically enriched homoenolate reagents starting from achiral precursors.[20] These react with the standard electrophiles investigated with high regio- and stereospecificity. From a mechanistic point of view, the highly stereoselective removal of a remote proton deserves particular attention.

Experimental Section

Synthesis of the homoaldol products *anti-ent*-**8ah**–**8ap**: To a solution of (−)-sparteine (0.353 g, 1.50 mmol) in dry toluene (2 mL) was added at −78 °C ca. 1.6 M butyllithium (1.4 mmol, 0.89 mL) in hexane. After the reaction mixture had been stirred for 10 min at −78 °C, a solution of carbamate **4a** (1.0 mmol) in toluene (1 mL) was added slowly. Stirring was continued for 1.5 h before a solution of $[ClTi(NEt_2)_3]$ (3.0 mmol) in toluene (2 mL) was added dropwise. After a transmetalation time of 2 h, the aldehyde **7** (3.0 mmol) was added at −78 °C, and stirring was continued for further 2 h. For workup, 2 N aq HCl (10 mL) was introduced to the flask. The aqueous phase was separated, and the aqueous solution was extracted with diethyl ether (3 × 25 mL, each). The combined organic extracts were

Table 2: Diastereo- and enantioselective homoaldol reaction, starting from **4a**.

Entry	Aldehyde	Product	Yield [%]	d.r.[a]	*ee* [%][a]	$[\alpha]_D^{20}$[b]
1	 **7h**	 *anti-ent*-**8ah**	66	95:5	97	−135
2	 **7i**	 *anti-ent*-**8ai**	71	98:2	95	−133
3	 **7j**	 *anti-ent*-**8aj**	49	97:3	93	−145
4	 **7k**	 *anti-ent*-**8ak**	82	97:3	95	−148
5	 **7l**	 *anti-ent*-**8al**	75	99:1	96	−73
6	 **7m**	 *anti-ent*-**8am**	78	99:1	94	−91
7	 **7n**	 *anti-ent*-**8an**	79	99:1	93	−95
8	 **7o**	 *anti-ent*-**8ao**	81	99:1	95	−100
9	 **7p**	 *anti-ent*-**8ap**	77	99:1	95	−85

[a] Determined by HPLC (column Chira Grom-2, solvent: hexane/2-propanol). [b] $c = 0.5$–1.25, $CHCl_3$.

dried over $MgSO_4$, and the solvents evaporated in vacuo. The crude product *anti-ent*-**8** was purified by flash chromatography on silica gel (diethyl ether/petroleum ether 1:1). For the yields and stereochemical purity see Table 2.

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Keywords: asymmetric synthesis · homoaldol reaction · lithium · sparteine · titanium

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[9] For the asymmetric γ-deprotonation of enamines see the ref. [1d] and, in particular, the contributions of the author cited therein.

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[12] X-ray crystal structure analysis of *ent*-**8ac**: $C_{35}H_{39}NO_2Sn$, $M_w = 624.36$, colorless crystal $0.35 \times 0.15 \times 0.10$ mm, $a = 10.625(1)$, $b = 14.474(1)$, $c = 11.047(1)$ Å, $\beta = 109.22(1)°$, $V = 1604.2(2)$ Å^3, $\rho_{calcd} = 1.293$ g cm^{-3}, $\mu = 65.52$ cm^{-1}, empirical absorption correction by ψ-scan data ($0.208 \le T \le 0.341$), $Z = 2$, monoclinic, space group $P2_1$ (no. 4), $\lambda = 1.54178$ Å, $T = 223$ K, $\omega/2\theta$ scans, 3591 reflections collected ($+h$, $+k$, $\pm l$), $(\sin\theta)/\lambda = 0.62$ Å^{-1}, 3407 independent ($R_{int} = 0.025$) and 3162 observed reflections [$I \ge 2\sigma(I)$], 3507 refined parameters, $R = 0.036$, $wR^2 = 0.097$, max. residual electron density 0.75 (-1.17) e Å^{-3}, Flack parameter $-0.003(9)$, hydrogen atoms calculated and refined as riding atoms. X-ray crystal structure analysis of *ent*-**8af**: $C_{24}H_{28}BrNO_3$, $M_w = 458.38$, colorless crystal $0.35 \times 0.20 \times 0.20$ mm, $a = 9.272(1)$, $b = 12.938(1)$, $c = 10.388(1)$ Å, $\beta = 112.00(1)°$, $V = 1155.4(2)$ Å^3, $\rho_{calcd} = 1.318$ g cm^{-3}, $\mu = 26.07$ cm^{-1}, empirical absorption correction via SORTAV ($0.462 \le T \le 0.624$), $Z = 2$, monoclinic, space group $P2_1$ (no. 4), $\lambda = 1.54178$ Å, $T = 223$ K, ω?and φ scans, 7530 reflections collected ($\pm h$, $\pm k$, $\pm l$), $[(\sin\theta)/\lambda] = 0.59$ Å^{-1}, 3077 independent ($R_{int} = 0.028$) and 2886 observed reflections [$I \ge 2\sigma(I)$], 268 refined parameters, $R = 0.029$, $wR^2 = 0.077$, max. residual electron density 0.22(-0.27) e Å^{-3}, Flack parameter $-0.030(18)$, hydrogens calculated and refined as riding atoms. Data sets were collected with an Enraf-Nonius CAD4 and Nonius KappaCCD diffractometers. Programs used: data collection EXPRESS (Nonius B.V., 1994) and COLLECT (Nonius B.V., 1998), data reduction MolEN (K. Fair, Enraf-Nonius B.V., 1990) and Denzo-SMN (Z. Otwinowski, W. Minor, *Methods Enzymol.* **1997**, *276*, 307), absorption corrections for CCD data SORTAV (R. H. Blessing, *Acta Crystallogr. Sect. A* **1995**, *51*, 33; R. H. Blessing, *J. Appl. Crystallogr.* **1997**, *30*, 421), structure solution SHELXS-97 (G. M. Sheldrick, *Acta Crystallogr. Sect. A* **1990**, *46*, 467), structure refinement SHELXL-97 (G. M. Sheldrick, Universität Göttingen, **1997**, E. Keller, Graphik SCHAKAL, Universität Freiburg, **1997**). CCDC-219962 and CCDC-219961 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

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[16] Previously, only *syn*-S_E' additions of aldehydes have been reported.[1]

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