Asymmetric Synthesis

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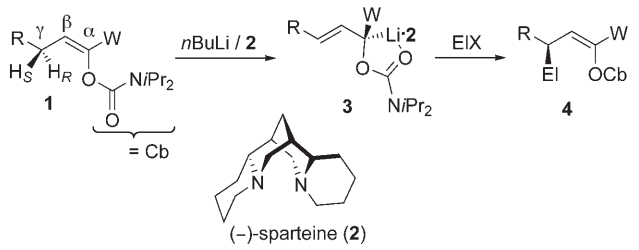
Stereo- and Regiochemical Divergence in the Substitution of a Lithiated Alk-1-en-3-yn-2-yl Carbamate: Synthesis of Highly Enantioenriched Vinylallenes or Alk-3-en-5-yn-1-ols**

*Roland Bou Chedid, Michael Brümmer, Birgit Wibbeling, Roland Fröhlich, and Dieter Hoppe**

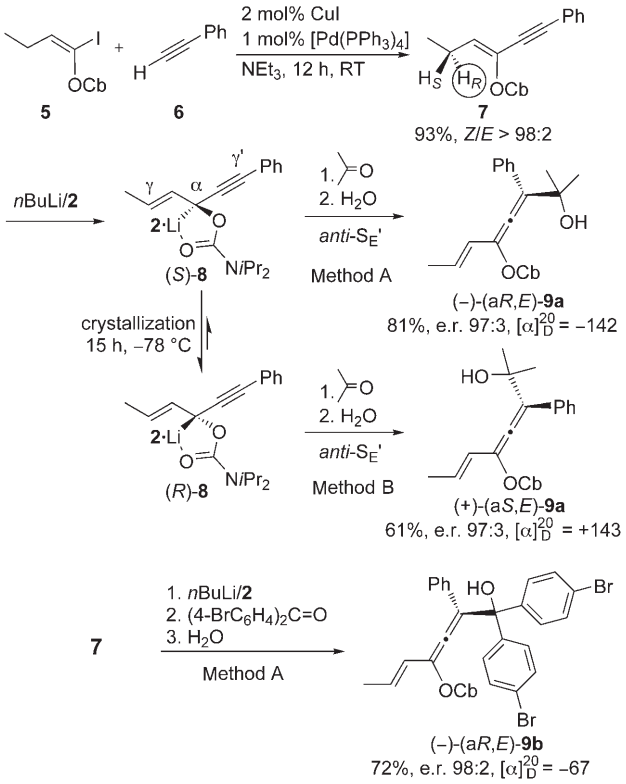
Dedicated to Professor Lutz F. Tietze on the occasion of this 65th birthday

We recently found that (*Z*)-1-alken-1-yl *N*,*N*-diisopropylcarbamates **1** bearing an anion-stabilizing group W are deprotonated in the γ position by *n*-butyllithium/(−)-sparteine (**2**) with high enantiotopos differentiation, leading to configurationally stable lithium chelates **3** (Scheme 1).[1] Trapping **3** with electrophiles gives rise to highly enantioenriched substitution products, such as **4**. Aryl,[1] triorganosilyl,[2] and 1-alkenyl[3] groups were found to be suitable substituents W.



Scheme 1. Lithiation of **1** and substitution with electrophiles (El).

In our current investigations on the alk-1-en-3-yn-2-yl carbamate **7** (the position designations refer to the relative positions in the molecule) we uncovered unprecedented features:[4] The course of the hydroxyalkylation of the corresponding lithium compounds can be directed selectively in four different directions by simple means. The starting material **7** was prepared by Sonogashira coupling[5] of (*E*)-1-iodo-1-butenyl carbamate **5** with phenylethyne (**6**) (Scheme 2). Enyne **7** was allowed to react with *n*BuLi/**2** in toluene at −78 °C for 30 s[6] to form the lithium chelate **8** before acetone was added (Scheme 2, Method A). The S_E' addition of intermediate **8** has two possible regiochemical courses: addition at the γ position (allylmetal reactivity) and at the γ′ position (propargylmetal reactivity). The γ′ product (−)-(a*R*,*E*)-**9a**[7] was isolated in 81 % yield and with an e.r. of 97:3. When pentane/toluene was used (Scheme 2, Method B), a brownish precipitate was observed. After 15 h, when the slurry was treated with acetone, the opposite enantiomer (+)-(a*S*,*E*)-**9a**[7] was obtained in 61 % yield and with an e.r. of 97:3.



Scheme 2. Synthesis and deprotonation of **7** to give **8** and its subsequent addition to a carbonyl compound. For Methods A and B, see the Experimental Section. $[\alpha]_D^{20}$ in deg cm^3 g^{-1} dm^{-1}.

Addition of the kinetically controlled lithium intermediate (*S*)-**8** to 4,4′-dibromobenzophenone afforded (a*R*,*E*)-**9b** (Scheme 2) according to an X-ray analysis with anomalous dispersion.[8,9] It can thus be concluded that the lithium species **8** add in *anti*-S_E' processes to carbonyl compounds.

In another series of experiments, the lithium intermediates (*S*)-**8** and (*R*)-**8** were subjected to lithium–titanium exchange prior to acetone addition (Scheme 3). We found that (*S*)-**8** reacted via (*S*)-**10** to afford the homoaldol product

[*] Dr. R. Bou Chedid, M. Brümmer, B. Wibbeling,[+] Dr. R. Fröhlich,[+] Prof. Dr. D. Hoppe
Organisch-Chemisches Institut
Westfälische Wilhelms-Universität Münster
Corrensstrasse 40, 48149 Münster (Germany)
Fax: (+49) 251-83-36531
E-mail: dhoppe@uni-muenster.de

[+] X-ray crystal structure analyses

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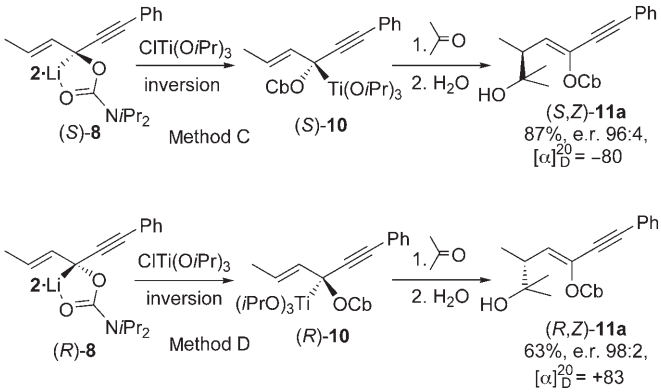
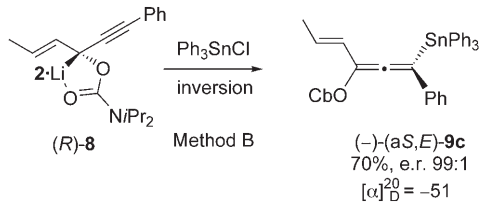


Scheme 3. Transmetalation of **8** and its subsequent reaction with acetone. For Methods C and D, see the Experimental Section. $[\alpha]_D^{20}$ in deg cm^3 g^{-1} dm^{-1}.

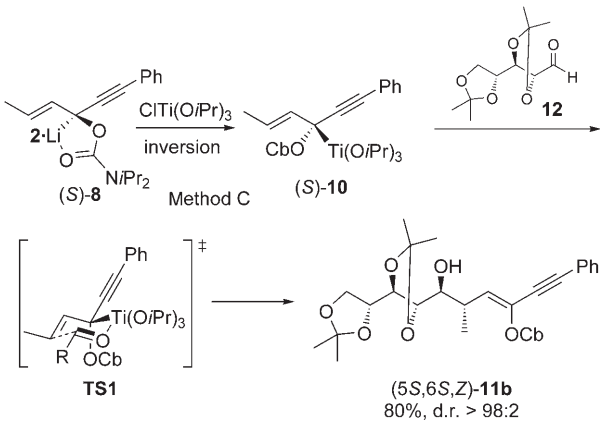
(*S*)-**11a**[7] (Method C) with high e.r., whereas (*R*)-**8** provided the other enantiomer (*R*)-**11a** via (*R*)-**10** (Method D).

From these results we conclude that (*S*)-**8** is the kinetically controlled lithium intermediate, which is transformed over extended reaction times to the epimer (*R*)-**8**; this is enforced by the selective crystallization of (*R*)-**8**.[10,14a] Apparently, the carbanionic lithium compounds (*S*)- and (*R*)-**8** add in *anti*-S_E' fashion stereospecifically to acetone, and the more electron-rich allenic position next to the phenyl ring is more reactive.[10] However, covalently bound titanium compounds **10** prefer a *syn* addition via a chairlike Zimmerman–Traxler transition state,[11] avoiding a linear C3 component in the ring.[12]

The absolute configurations of the products and the lithium intermediates were verified by the following experiments (Schemes 4 and 5): Trapping the selectively crystallized



Scheme 4. Stannylation of (*R*)-**8**. $[\alpha]_D^{20}$ in deg cm^3 g^{-1} dm^{-1}.



Scheme 5. Homoaldol reaction with the chiral aldehyde **12**.

lithium intermediate (*R*)-**8** by reaction with triphenyltin chloride afforded the crystalline allenylstannane **9c**. An X-ray analysis of **9c** with the anomalous dispersion technique revealed its a*S* configuration.[9,13] Since in other examples, stannylation reactions of propargyllithium/(–)-sparteine complexes were shown to proceed in an *anti*-S_E' manner,[14] the lithium intermediate possesses the *R* configuration.

The "kinetic" lithium compound (*S*)-**8** was transmetalated with inversion by reaction with $ClTi(OiPr)_3$[15] and then added to 2,3:4,5-di-*O*-isopropylidene-D-ribose[16] (**12**) to form the stereohomogeneous homoaldol product **11b**. The configuration of **11b** in the solid state could be determined by an X-ray analysis to be 5*S*,6*S*,*Z*.[9,17]

Previously we[18] and others[19] demonstrated that chiral α-(carbamoyloxy)allyltitanium compounds react with chiral aldehydes with strict chirality transfer from the Zimmerman–Traxler transition state. Thus we deduce that the titanium intermediate **10** has *S* configuration, and **10** must be formed from (*S*)-**8** with inversion of configuration.

In conclusion, the (–)-sparteine-mediated lithiation of the alkenyl carbamate **7** proceeds with efficient enantiotopic differentiation at the γ position. Slow epimerization takes place with longer reaction times to form essentially completely the other epimer having opposite configuration at the metal-bearing center. Lithium–titanium exchange proceeds with inversion of the configuration. Whereas the stereospecific addition of the lithium intermediates **8** to a carbonyl compound proceeds in an *anti*-S_E' manner and produces highly enantioenriched hydroxyvinylallenes,[20] the titanium intermediates **10** give rise to enantioenriched homoaldol products (alk-3-en-5-yn-1-ols) in both absolute configurations through a *syn*-S_E' addition via a Zimmerman–Traxler transition state.[11] Some examples are listed in Table 1.[21] This is the first example of highly enantioenriched vinylallenes produced from achiral precursors.[22]

Table 1: Products of the reactions of **8** with some electrophiles.

Electrophile (Method)	Product[a]	Yield	e.r. (d.r.[b])	$[\alpha]_D^{20}$[c]
Ph_3SnCl (A)	(a*R*,*E*)-**9c**	80%	96:4	+42
cyclohexanone (B)	(a*S*,*E*)-**9d**	57%	97:3	+107
isobutyraldehyde (C)	(5*S*,6*R*,*Z*)-**11c**	80%	97:3 (>98:2)	−72
isobutyraldehyde (D)	(5*R*,6*S*,*Z*)-**11c**	69%	98:2 (98:2)	+74

[a] See the Supporting Information for the structures. [b] Where applicable. [c] In deg cm^3 g^{-1} dm^{-1}.

Experimental Section

Method A: A solution of (–)-sparteine (95 mg, 0.36 mmol, 1.2 equiv) in toluene (2 mL) was cooled to −78 °C. *n*BuLi (0.23 mL of 1.6 M, 0.36 mmol, 1.2 equiv) was added slowly, and the reaction mixture was stirred for 10 min. A solution of the carbamate **7** (90 mg, 0.3 mmol) in toluene (0.5 mL) was cooled down to −78 °C and added quickly while the reaction mixture was stirred efficiently. The reaction mixture turned dark brown within seconds. Immediately afterwards (in less than 30 s), a solution of the electrophile (0.90 mmol, 3 equiv) in toluene (0.5 to 2 mL) already cooled down to −78 °C was added quickly. After 15 min, the reaction was quenched at −78 °C with MeOH (0.3 mL) and HCl (2 M, 1 mL), and warmed up to room temperature. The organic phase was separated and the aqueous phase washed three times with diethyl ether (DE). The combined organic

phases were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by column chromatography (*n*-pentane (PE)/DE) furnished the corresponding product.

Method B: A solution of (−)-sparteine and *n*BuLi in PE (2.0 mL) was prepared according to Method A. A solution of the carbamate **7** (90 mg, 0.3 mmol) in PE/toluene (0.5 mL each) was added slowly with a syringe which was then washed twice with PE (0.2 mL each time). The reaction mixture was stirred vigorously. The formation of precipitate started within 2 h. After 15 to 16 h, a heavy precipitate in a brown solution had formed. The electrophile (0.90 mmol, 3 equiv) was then added slowly in PE (1 mL), or in toluene (1 mL) if it was not soluble in PE. After 3 h, the reaction was quenched, and workup was performed as described for Method A.

Method C: Carbamate **7** (0.3 mmol, 90 mg) was deprotonated as described in Method A. Immediately afterwards (in less than 30 s), ClTiPT (1.5 equiv, 1M in toluene) already cooled down to −78 °C was added quickly. After 20 min, the electrophile (0.90 mmol, 3 equiv) in toluene (1 mL) was added dropwise. The reaction was quenched after 3 h, and the workup was performed as described for Method A.

Method D: Carbamate **7** (0.3 mmol) was deprotonated as described in Method B. ClTiPT (1.5 equiv, 1M in toluene) was then added dropwise and the reaction mixture stirred for another 20 min. The electrophile (0.90 mmol, 3 equiv) was then added slowly in PE (1 mL), or in toluene (1 mL) if it was not soluble in PE. After 3 h, the reaction was quenched at −78 °C and warmed up to room temperature. The workup was performed as described for Method A.

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[6] Since we expected configurational instability of **8**, we chose the short deprotonation time.

[7] For the elucidation of the absolute configuration, see the experiments described below.

[8] X-ray crystal structure analysis of (a*R*,*E*)-**9b**: see Figure 1 in the Supporting Information; $C_{32}H_{33}Br_2NO_3$, $M = 639.41$, colorless crystal $0.07 \times 0.06 \times 0.03$ mm^3, $a = 11.532(1)$, $b = 16.105(1)$, $c = 16.190(1)$ Å, $V = 3006.9(4)$ Å^3, $\rho_{calcd} = 1.412$ g cm^{-3}, $\mu = 3.669$ mm^{-1}, empirical absorption correction ($0.783 \le T \le 0.898$), $Z = 4$, orthorhombic, space group $P2_12_12_1$ (No. 19), $\lambda = 1.54178$ Å, $T = 223$ K, ω and ϕ scans, 18136 reflections collected ($\pm h$, $\pm k$, $\pm l$), $[(\sin\theta)/\lambda] = 0.59$ Å^{-1}, 4832 independent ($R_{int} = 0.075$) and 4270 observed reflections [$I \ge 2\sigma(I)$], 349 refined parameters, $R = 0.045$, $wR^2 = 0.115$, Flack parameter −0.09(3), max. residual electron density 0.37 (−0.36) e Å^{-3}, hydrogen atoms calculated and refined as riding atoms.

[9] Data sets were collected with Nonius KappaCCD diffractometers, in case of Mo radiation equipped with a rotating anode generator. Programs used: data collection COLLECT (Nonius B. V., 1998), data reduction Denzo-SMN (Z. Otwinowski, W. Minor, *Methods Enzymol.* **1997**, *276*, 307–326), absorption correction SORTAV (R. H. Blessing, *Acta Crystallogr. Sect. A* **1995**, *51*, 33–37; R. H. Blessing, *J. Appl. Crystallogr.* **1997**, *30*, 421–426) and Denzo (Z. Otwinowski, D. Borek, W. Majewski, W. Minor, *Acta Crystallogr. Sect. A* **2003**, *59*, 228–234), structure solution SHELXS-97 (G. M. Sheldrick, *Acta Crystallogr. Sect. A* **1990**, *46*, 467–473), structure refinement SHELXL-97 (G. M. Sheldrick, Universität Göttingen, **1997**), graphics SCHAKAL (E. Keller, Universität Freiburg, **1997**). CCDC-626814, 626815, and 630362 contain 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.

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[12] Only traces of the other regioisomer **9** or **11**, if at all, were evident by TLC or ^{1}H NMR spectroscopy.

[13] X-ray crystal structure analysis for (a*S*,*E*)-**9c**: see Figure 2 in the Supporting Information; $C_{37}H_{39}NO_2Sn$, $M = 648.38$, colorless crystal $0.40 \times 0.30 \times 0.10$ mm^3, $a = 7.888(1)$, $b = 16.454(1)$, $c = 13.132(1)$ Å, $\beta = 105.42(1)°$, $V = 1643.0(3)$ Å^3, $\rho_{calcd} = 1.311$ g cm^{-3}, $\mu = 0.809$ mm^{-1}, empirical absorption correction ($0.738 \le T \le 0.924$), $Z = 2$, monoclinic, space group $P2_1$ (No. 4), $\lambda = 0.71073$ Å, $T = 198$ K, ω and ϕ scans, 10555 reflections collected ($\pm h$, $\pm k$, $\pm l$), $[(\sin\theta)/\lambda] = 0.67$ Å^{-1}, 6681 independent ($R_{merge} = 0.036$) and 6353 observed reflec-tions [$I \ge 2\sigma(I)$], 375 refined parameters, $R = 0.024$, $wR^2 = 0.058$, Flack parameter −0.04(1), max. residual electron density 0.48 (−0.62) e Å^{-3}, hydrogens calculated and refined as riding atoms.

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[17] X-ray crystal structure analysis for (5*S*,6*S*,*Z*)-**11b**: see Figure 3 in the Supporting Information; $C_{30}H_{43}NO_7$, $M = 529.65$, colorless crystal $0.35 \times 0.30 \times 0.30$ mm^3, $a = 8.829(1)$, $b = 10.252(1)$, $c = 16.728(1)$ Å, $\beta = 94.11(1)°$, $V = 1510.2(2)$ Å^3, $\rho_{calcd} =$

1.165 g cm^{-3}, $\mu = 0.666$ mm^{-1}, empirical absorption correction ($0.800 \le T \le 0.825$), $Z = 2$, monoclinic, space group $P2_1$ (No. 4), $\lambda = 1.54178$ Å, $T = 223$ K, ω and ϕ scans, 13534 reflections collected ($\pm h$, $\pm k$, $\pm l$), $[(\sin\theta)/\lambda] = 0.59$ Å^{-1}, 4827 independent ($R_{merge} = 0.031$) and 4760 observed reflections [$I \ge 2\sigma(I)$], 353 refined parameters, $R = 0.043$, $wR^2 = 0.121$, Flack parameter −0.0(2), max. residual electron density 0.44 (−0.16) e Å^{-3}, hydrogens calculated and refined as riding atoms.

[18] a) D. Hoppe, G. Tarara, M. Wilckens, P. G. Jones, D. Schmidt, J. J. Stezowski, *Angew. Chem.* **1987**, *99*, 1079; *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 1034; b) D. Hoppe, G. Tarara, M. Wilckens, *Synthesis* **1989**, 83; c) D. Hoppe, F. Rehders, *Synthesis* **1992**, 859; d) D. Hoppe, F. Rehders, *Synthesis* **1992**, 865; e) D. Hoppe, S. Kollmann, R. Fröhlich, *Synthesis* **2007**, 731.

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[20] Other derivatives of **7**, where the Ph is replaced by *n*Bu, TMS, or Cy groups, were also investigated by us. The regioselectivity has proven to be the same as in **7**. The reaction conditions for the synthesis of both enantiomers have not yet been optimized.

[21] Several further examples have not been included.

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