ORGANIC LETTERS

2001
Vol. 3, No. 8
1221−1224

Synthesis of Enantiomerically Enriched Allenes by (−)-Sparteine-Mediated Lithiation of Alkynyl Carbamates

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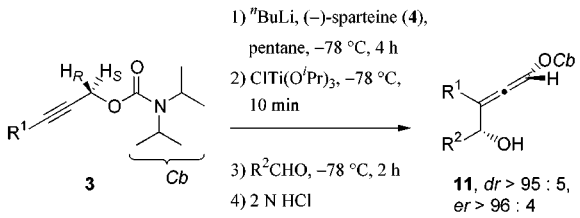
Received February 14, 2001

ABSTRACT



The α-deprotonation of alkynyl carbamates 3 with the chiral base (−)-sparteine (4)/*n*-butyllithium, transmetalation with ClTi(O^{i}Pr)$_3$, and subsequent substitution with an aldehyde results in the formation of enantioenriched 4-hydroxyallenyl carbamates 11. Stereoselection is determined by dynamic resolution of the lithium/(−)-sparteine complexes by selective crystallization.

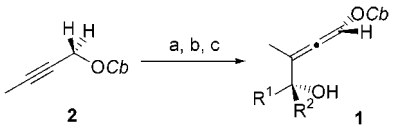
Optically active allenes are an important class of compounds. They are useful building blocks for the synthesis of various complex compounds.[1] As a consequence, there is a growing demand for the asymmetric synthesis of chiral allenes.[2,3]

A method for the synthesis of racemic allenyl carbamates **1** has been developed in our research group (Scheme 1).[4] After α-deprotonation of 2-butynyl *N*,*N*-diisopropylcarbamate **2** with *n*-butyllithium, transmetalation with Ti(O^{i}Pr)$_4$, and subsequent addition onto aldehydes or ketones, the 4-hydroxyallenyl carbamates **1** were isolated with good yields and with excellent diastereomeric ratios.

Further investigations of optically active secondary 2-alkynyl carbamates revealed that the formation of allenyl carbinols proceeds with a high degree of chirality transfer.[5]

Herein, we report the synthesis of chiral allenyl carbamates via asymmetric deprotonation of prochiral 2-alkynyl carbamates by the (−)-sparteine method.[6] Deprotonation of the 2-alkynyl carbamates **3a**−**c** with (−)-sparteine **(4)**/*n*-butyllithium in toluene at −78 °C and trapping the intermediate ion pairs **5** and *epi*-**5** by carboxylation or silylation led to only slightly enantioenriched products **6a**−**f** (Table 1). These results may be interpreted by two explanations: Either the deprotonation proceeds with a low degree of enantiotopic selectivity or the ion pairs **5** and *epi*-**5** are not configuration-

Scheme 1. Synthesis of Racemic Allenyl Carbamates **1**[a]



[a] (a) ^{n}BuLi, Et$_2$O, −78 °C, 15 min; (b) Ti(O^{i}Pr)$_4$, −78 °C, 10 min; (c) R^{1}R^{2}C═O.

[†] X-ray analysis.

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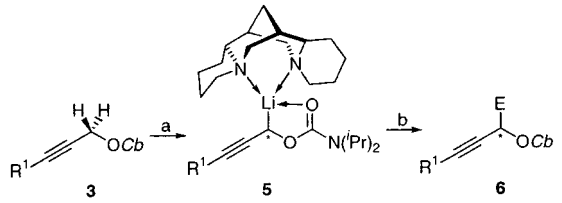
10.1021/ol0157104 CCC: $20.00
Published on Web 03/29/2001

Table 1. Asymmetric Deprotonation of Prochiral 2-Alkynyl Carbamates **3**



a. ^{n}BuLi, (−)-sparteine (**4**), toluene, −78 °C, 0.5 h. b. E-X.

substrate	R^1	E−X	product	yield (%)	ee (%)	$[\alpha]_D$[a]
3a	Me_3Si	CO_2/CH_2N_2	**6a**	77	17[b]	*c*
3b	^{t}Bu	CO_2/CH_2N_2	**6b**	78	23[b]	*c*
3c	^{n}Pr	CO_2/CH_2N_2	**6c**	82	2[b]	+0.4
3a	Me_3Si	Me_3SiCl	**6d**	80	*d*	+20.4
3b	^{t}Bu	Me_3SiCl	**6e**	86	31	+25.1
3c	^{n}Pr	Me_3SiCl	**6f**	80	6	+5.0

[a] CH_2Cl_2, 22 °C. [b] The excess enantiomer has (*S*)-configuration, see Figure 1. [c] $[\alpha]_D$: see Table 2. [d] The enantiomeric excess was not determined.

ally stable in solution and equilibrate under the reaction conditions.[7,8]

When the deprotonation was carried out in pentane as solvent, a crystallization was observed, and carboxylation or silylation yielded the highly enantioenriched products **6a**,**b**,**d**,**e**; the sense of chirality remained unchanged (Table 2). An excess of the electrophile is necessary to achieve

Table 2. Asymmetric Deprotonation of **3** with Selective Crystallization of One Epimer of the Lithiated 2-Alkynyl Carbamates **5**

substrate	R^1	E−X	product	yield (%)	ee (%)	$[\alpha]_D$[a]
3a	Me_3Si	CO_2/CH_2N_2	**6a**	72	85	+40.9
3a	Me_3Si	Me_3SiCl[b]	**6d**	67	*c*	+79.2
3b	^{t}Bu	CO_2/CH_2N_2	**6b**	77	76	+40.2
3b	^{t}Bu	Me_3SiCl[b]	**6e**	74	93	+72.8

[a] CH_2Cl_2, 22 °C. [b] 10 equiv of Me_3SiCl. [c] The enantiomeric excess was not determined.

highly enantioenriched products. After silylation of the lithiated *tert*-butyl-substituted alkynyl carbamate **5b** with only 3 equiv of chlorotrimethylsilane, the product **6e** has only an enantiomeric excess of 34% ee instead of 93% ee with 10 equiv. The origin of stereoselection is a dynamic resolution[9] of the lithium−(−)-sparteine complexes **5** by selective crystallization, as we had found previously for lithiated allyl carbamates[10] and 1-methylindene.[11] The lithiated trimethylsilyl-substituted alkynyl carbamate **5a** crystallizes within 5 min after addition of the chiral base; for the lithiated *tert*-butyl-substituted compound **5b**, crystallization takes up to 1 h. Although we tried different solvents and concentrations, we were unable to find conditions for the crystallization of the lithiated *n*-propyl-substituted alkynyl carbamate **5c**.

The absolute configuration of the acid **7**, obtained from **3a** by asymmetric lithiation and carboxylation, was elucidated by X-ray analysis and found to be (*S*) (Figure 1).

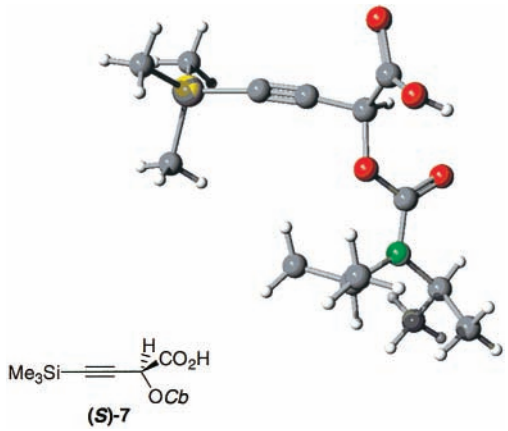


Figure 1. Crystal structure analysis of (*S*)-2-(*N*,*N*-diisopropylcarbamoyloxy)-4-(trimethylsilyl)but-3-ynoic acid (**7**).[12]

Lithiated propargylic derivatives can exist in two tautomeric forms in equilibrium—as a propargyl or allenyllithium reagent.[1,13] The regioselectivity in the reaction of the lithiated alkynyl carbamates with electrophiles leads to the conclusion that the lithium intermediate is a propargylic ion pair and not an allenic one. The chelating carbamate group holds the lithium ion in the α-position; this corresponds to lithiated allyl carbamates.[14]

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(5) Dreller, S.; Dyrbusch, M.; Hoppe, D. *Synlett* **1991**, 397.

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(7) After lithiodestannylation of (+)-4,4-dimethyl-1-(trimethylstannyl)-pent-2-ynyl *N*,*N*-diisopropylcarbamate **(6g)** (≥95% ee) with (−)-sparteine/^{n}BuLi in toluene at −78 °C and subsequent quenching with chlorotrimethylsilane, we isolated (+)-**6e** in an enantiomeric excess of 40%.

(8) We obtained (+)-**6e** in 22% ee after asymmetric deprotonation of **3b** in the presence of chlorotrimethylsilane (in situ procedure).

(9) For review, see: Caddick, S.; Jenkins, K. *Chem. Soc. Rev.* **1996**, *25*, 447.

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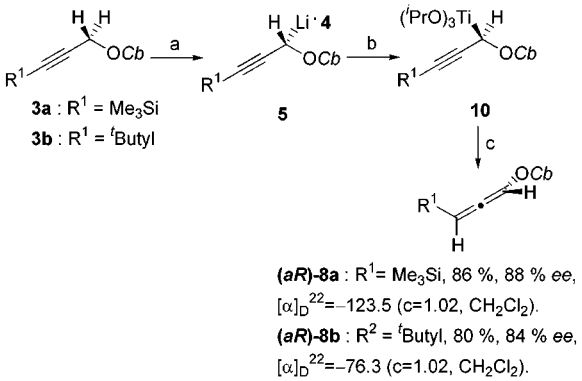
After transmetalation of the suspension of the lithium salts **5a** or **5b** with $ClTi(O^iPr)_3$ (1 M precooled solution in toluene) followed by acetic acid, the highly enantioenriched allenes **8a** and **8b**, respectively, were obtained (Scheme 2). For (−)-

Scheme 2. Synthesis of Chiral Allenyl Carbamates **8**[a]

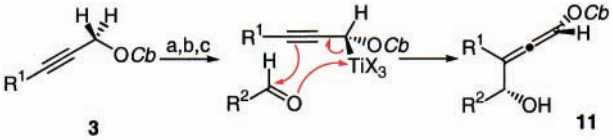


[a] (a) ^{n}BuLi, (−)-sparteine (**4**), pentane, −78 °C, 4 h; (b) $ClTi(O^iPr)_3$, −78 °C, 10 min; (c) 1 M H_3CCO_2H, −78 °C, 10 min.

8b, the application of Lowe−Brewster rules[15] predict the (*aR*)-configuration.[16]

The addition of an aldehyde to the titanium intermediate **10** results in the formation of highly enantioenriched allenyl carbinols **11** (Table 3).

Table 3. Synthesis of Chiral Allenyl Carbinols **11**



a. ^{n}BuLi, (–)-sparteine (**4**), pentane, –78 °C, 4 h.
b. $ClTi(O^iPr)_3$, –78 °C, 10 min. c. R^2CHO, –78 °C, 2 h.

substrate	R^1	R^2	product[a]	yield (%)	ee (%)	$[\alpha]_D$[b]
3a	Me_3Si	^{i}Pr	**11a**	76	>95	−64.3
3a	Me_3Si	Me	**11b**	73	93	−61.6
3a	Me_3Si	Ph	**11c**	86	>95[c]	−226.5
3b	^{t}Bu	^{i}Pr	**11d**	80	*d*	+26.6
3b	^{t}Bu	Me	**11e**	70	93[c]	+23.6
3b	^{t}Bu	Ph	**11f**	86	>95[c]	−203.8

[a] Diastereoselectivity was determined by ^{1}H NMR analysis of the crude product: dr > 95:5. [b] CH_2Cl_2, 22 °C. [c] The enantiomeric excess was determined by an ^{1}H NMR shift experiment of the corresponding acetate. [d] The enantiomeric excess was not determined.

^{1}H NMR analysis of the crude product gave evidence of only one diastereomer. The relative and absolute configurations were elucidated by X-ray analysis of the *N*-phenylurethane **12** of the adduct **11a** (Figure 2).

The high simple diastereoselectivity of the carbonyl addition to titanated alkynyl carbamates results from a Zimmerman−Traxler transition state.[17] The pericyclic nature

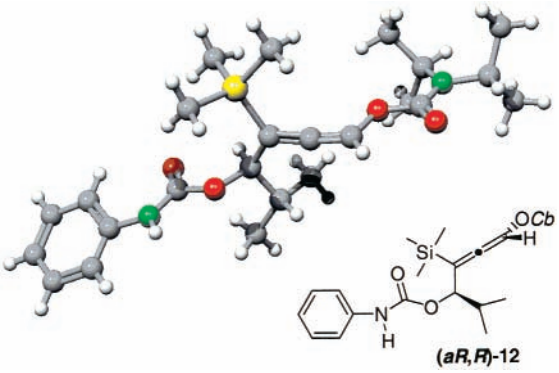
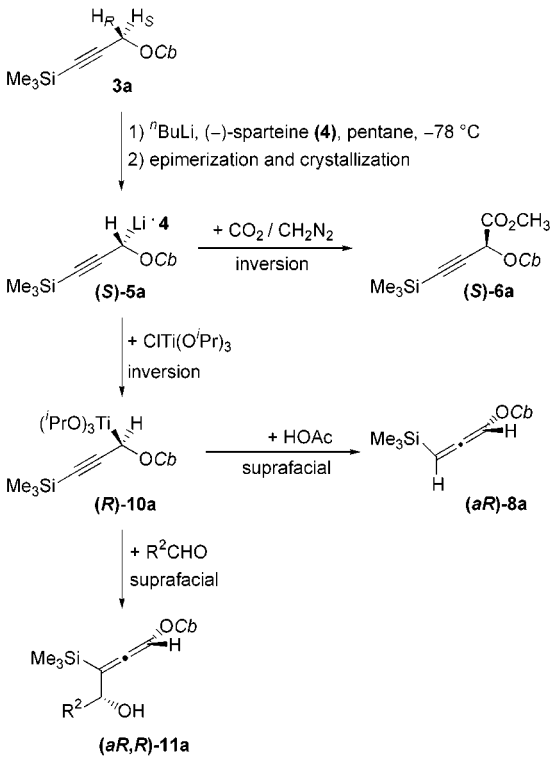


Figure 2. Crystal structure analysis of (*aR*,*R*)-*O*-[4-(*N*,*N*-diisopropylcarbamoyloxy)-1-isopropyl-2-(trimethylsilyl)buta-2,3-dienyl] *N*-phenyl urethane (**12**).[12]

of the addition step requires a suprafacial mode and is the origin for an efficient transfer of central to axial chirality.[18]

Thus, the titanium intermediate (*R*)-**10a** is the direct precursor of the (*aR*)-configured allene moiety in the products **8a** and **11a**−**c** (Scheme 3). It is reasonable to assume that the lithium−titanium exchange in the (−)-sparteine complexes **5** proceeds with inversion (as has been found for related allyllithium compounds[10b]) and the crystallizing epimer **5a** has the (*S*)-configuration. The formation of the carboxylation product (*S*)-**6a** as the major product from **5a**

Scheme 3. Mechanism of the Asymmetric Deprotonation and Substitution of 2-Alkynyl Carbamates[a]



[a] Only the major stereoisomers are shown.

is in accordance with this hypothesis, since we regularly found inversion in these reactions.[19]

Work is in progress to expand this method of asymmetric allene synthesis to further 2-alkynyl carbamates **3**. We are currently applying the chiral allenes in a modified Nazarov cyclization.[20]

Acknowledgment. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. C.S.-F. gratefully acknowledges a fellowship of the Fonds der Chemischen Industrie. We thank Mrs. K. Gottschalk for her outstanding experimental assistance.

Supporting Information Available: Detailed experimental procedures with spectroscopic data for all compounds and crystal data of **7**, **9**, and **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0157104

(12) Crystals suitable for X-ray diffraction analysis were grown by slow evaporation of an ethereal solution.

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(16) This assumption was certified during a synthesis based on (*aR*)-**8b** (see: Schultz-Fademrecht, C.; Hoppe, D.; Tius, M. A. Manuscript in preparation). We achieved an X-ray structure of (*aS*)-4,4-dimethyl-1-(trimethylstannyl)penta-1,2-dienyl *N*,*N*-diisopropylcarbamate (**9**). This was prepared by α-deprotonation of (*aR*)-**8b** and subsequent substitution of the lithiated allenyl carbamate with chlorotrimethylstannane.

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