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Asymmetric γ-Deprotonation and Homoaldol Reaction of 1,3-Dien-2-yl Carbamates: Stereo- and Regiochemistry

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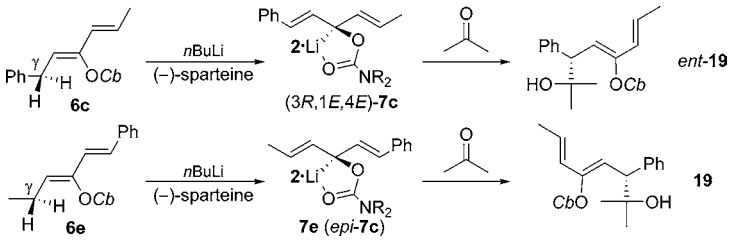
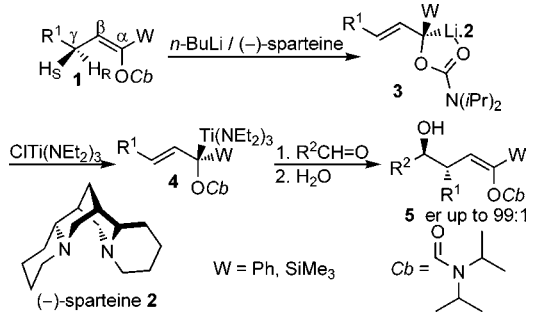
ABSTRACT



Lithium compounds 7 are configurationally stable intermediates obtained by deprotonation of 1,3-dien-2-yl carbamates 6 with *n*-butyllithium/(–)-sparteine with a high degree of enantiotopic differentiation at the γ-position. They react with electrophiles regioselectively giving highly enantioenriched products. Starting with different isomers or changing the double-bond geometries in 6 leads to either of the enantiomers.

The asymmetric homoaldol reaction of 1-metalated 2-alkenyl carbamates provides a flexible approach to 4-hydroxy-1-alken-1-yl carbamates,[1a] which can be transformed into a manifold of target molecules.[1] As we found recently,[2] the deprotonation of (*Z*)-1-alken-1-yl carbamates **1** by *n*-butyllithium/(−)-sparteine **2** proceeds smoothly by removal of the γ-*pro-R*-H leading to essentially stereohomogeneous five-membered lithium enolates **3**, as long as a slightly carbanion-stabilizing substituent W (e.g., aryl[2a,c] or trimethylsilyl[2b]) is present in **1** (Scheme 1). Addition of aldehydes or ketones to form stereohomogeneous adducts **5** is particularly rewarding after lithium−titanium exchange.

Scheme 1. Transmetalation and Homoaldol Reaction of **1**



A vinylic group in position α should also be capable of sufficient kinetic acidification of the γ-protons in diene **6**; however, the lithiated intermediate **7** now exhibits two positions for γ-attack leading to regioisomers **8** and **9**

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† Dr. Roland Fröhlich performed the X-ray analyses.

(1) Reviews: (a) Hoppe, D.; Hense, T. *Angew. Chem.* **1997**, *109*, 2376; *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2282. (b) Hoppe, D.; Marr, F.; Brüggemann, M. *Organolithiums in Enantioselective Synthesis*; Hodgson, D. M., Ed.; Topics in Organometallic Chemistry; Springer-Verlag: Berlin, 2003; Vol. 5, p 61. (c) Beak, P.; Johnson, T. A.; Kim, D. D.; Lim, S. H. In *Organolithiums in Enantioselective Synthesis*; Hodgson, D. M., Ed.; Topics in Organometallic Chemistry; Springer-Verlag: Berlin, 2003; Vol. 5, p 134. (d) Hoppe, D.; Christoph, G. In *Chemistry of Organolithium Compounds*; Rappoport, Z., Marek, I., Eds.; John Wiley & Sons Ltd.: Chichester, U.K., 2004; Vol. 2, p 1055. (e) Ahlbrecht, H.; Beyer, U. *Synthesis* **1999**, 365.

(2) (a) Hoppe, D.; Seppi, M.; Kalkofen, R.; Reupohl, J.; Fröhlich, R. *Angew. Chem.* **2004**, *116*, 1447; *Angew. Chem., Int. Ed.* **2004**, *43*, 1423. (b) Hoppe, D.; Reuber, J.; Fröhlich, R. *Org. Lett.* **2004**, *6*, 783. (c) Hoppe, D.; Reuber, J.; Fröhlich, R. *Eur. J. Org. Chem.* **2005**, *14*, 3017. (d) Hoppe, D.; Kalkofen, R.; Brandau, S.; Ünaldi, S.; Fröhlich, R. *Eur. J. Org. Chem.* **2005**, *21*, 4571.

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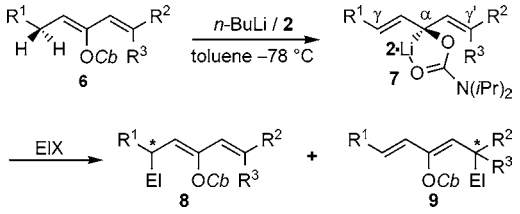
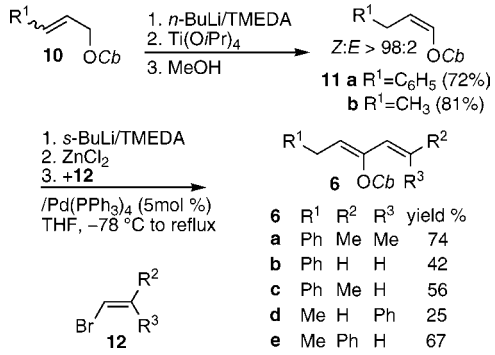
Scheme 2. Lithiation of **6** and Reaction with Electrophiles



(Scheme 2). Further, it is questionable if configurational stability is still given due to extended conjugation in the pentadienyl anion of **7**.

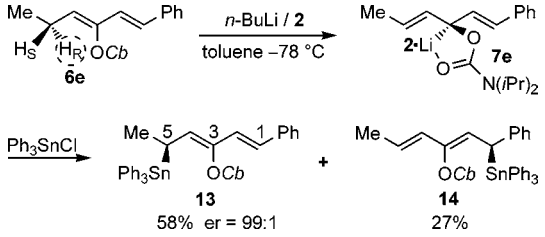
Dienes **6** are synthesized in a straightforward manner. After complete isomerization of allyl carbamates[3] **10** to vinyl carbamates **11** via lithiation, lithium−titanium exchange,[4] and protonation, the (*Z*)-enol carbamates **6** are obtained after vinylic lithiation[5] of **11**, transmetalation to zinc, and Negishi coupling[5c,6] (Scheme 3).

Scheme 3. Synthesis of Dienes **6**



Deprotonation of dienyl carbamate **6e** with *n*-butyllithium/(−)-sparteine (**2**) in toluene at −78 °C proceeds smoothly within 1 h. Trapping with Ph_3SnCl provides two separable regioisomers **13** and **14**[7] in a ratio of 68:32 and an er of 99:1 for **13** (Scheme 4). An X-ray crystal structure analysis with anomalous diffraction revealed the (5*S*,1*E*,3*Z*) configuration of **13** (Figure 1). Because all stannylations of lithiated 2-alkenyl carbamates are known to take place in an *anti*-S_E'

Scheme 4. Stannylation of **6e** with Ph_3SnCl



process,[8] the lithium intermediate **7e** has the (*S*)-configuration; this is formed by removal of the encircled proton (*pro-R* in **6e**). The structures of the further substitution products are based on this result, combined with the known or proven stereochemical courses of the reactions.

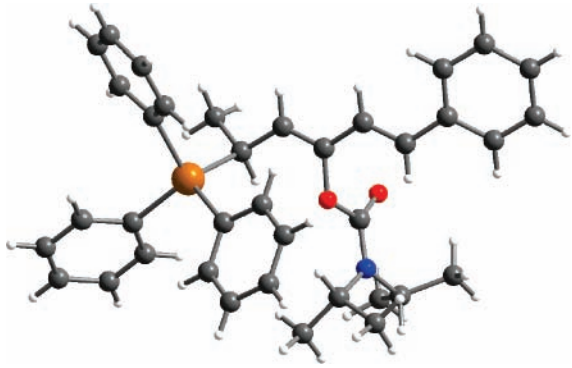
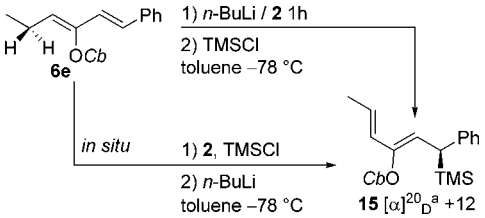


Figure 1. X-ray structure of **13**.[9]

The lithium intermediates derived from **6** are configurationally stable under the reaction conditions: after the (−)-sparteine-mediated deprotonation of **6e** (toluene, −78 °C) and reaction with $(CH_3)_3SiCl$, the silane **15** is obtained with the same enantiomeric purity (er = 98:2) after a standing time of 1 h (73%) or in situ trapping (Scheme 5). **15** is assigned the (*S*)-configuration because all silylations of lithiated 2-alkenyl carbamates are known to take place in an *anti*-S_E' process.

Scheme 5. Configurational Stability of **6**



[a] c = 0.76, 1.05 in $CHCl_3$; er = 98:2.

(3) (a) Hoppe, D.; Hanko, R.; Brönneke, A.; Lichtenberg, F.; van Hülsen, E. *Chem. Ber.* **1985**, *118*, 2822. (b) Hoppe, D.; Behrens, K.; Fröhlich, R.; Meyer, O. *Eur. J. Org. Chem.* **1998**, 2397.

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

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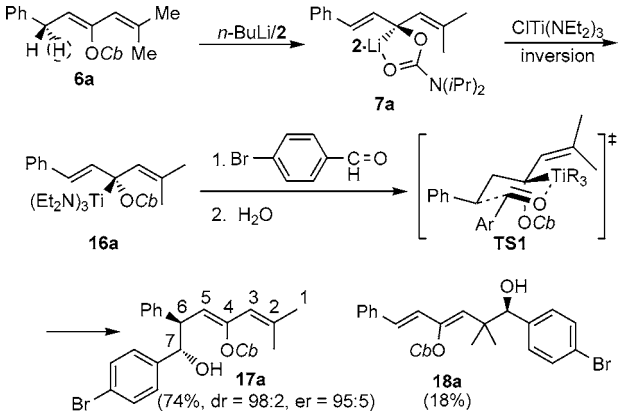
(6) Negishi, E.; Zeng, X.; Tan, Z.; Qian, M.; Hu, Q.; Huang, Z. In *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; de Meijere, A., Diedrich, F., Eds.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2004; Vol. 2, p 815.

(7) **14** decomposes easily not allowing complete analysis.

(8) Paulsen, H.; Graeve, C.; Hoppe, D. *Synthesis* **1996**, 141.

Similarly, carbamate **6a** was deprotonated and subjected to a metal exchange with $(Et_2N)_3TiCl$, and the titanium intermediate **16a** was intercepted by *p*-bromobenzaldehyde to give two regioisomeric homoaldol adducts **17a** and **18a** (92%, ratio of 80:20; Scheme 6). Again, the absolute

Scheme 6. Transmetalation and Homoaldol Reaction of **6a**



configuration of the major regioisomer **17a** (6*R*,7*S*,4*Z*; Figure 2) could be determined by X-ray analysis. Because the

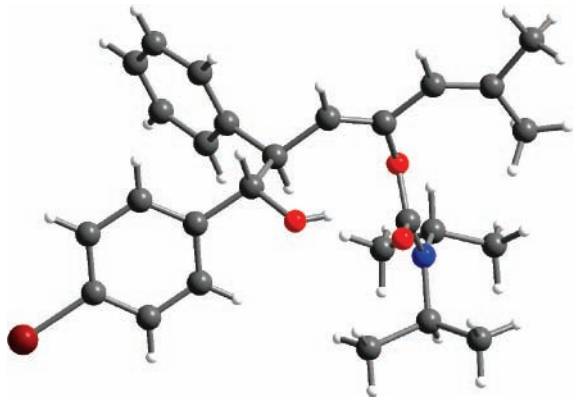
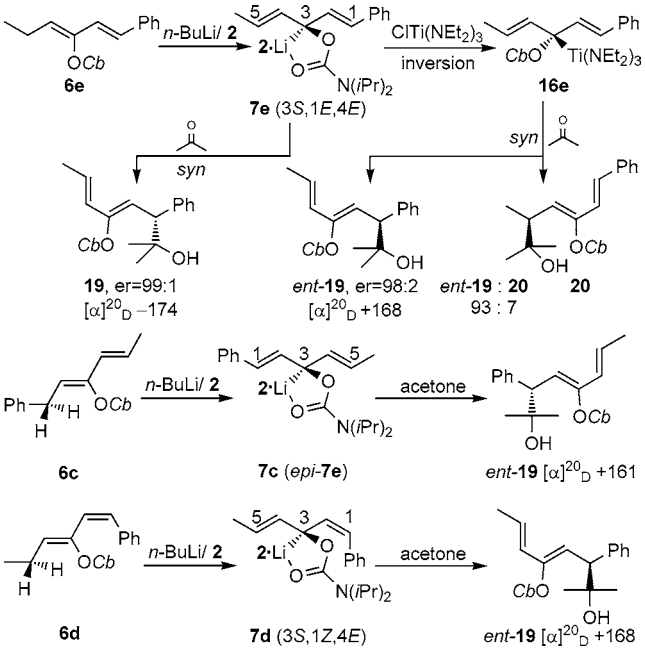


Figure 2. X-ray structure of **17a**.[9]

lithium−titanium exchange of (−)-sparteine allyllithium complexes proceeds (with no known exception) with inversion of configuration[4,10] and the addition step occurs in a suprafacial manner,[11] the lithium intermediate **7a** must have the (*S*)-configuration; this is formed by removal of the encircled proton (*pro-S* in **6a**). This is in agreement with the result extracted from the stannylation reaction.

Interesting features were uncovered from the homoaldol reaction of the lithium (**7e**) and titanium (**16e**) intermediates

Scheme 7. Homoaldol Reactions of **6** with Acetone



with acetone (Scheme 7). Both enantiomers can be obtained by applying either **7e** or **16e**. This also substantiates the *syn*-S_E' addition of acetone to **7e**.

The sense of enantioselectivity can also be directed by the used starting regioisomer or the configuration of its "terminal" double bond (Scheme 7). Asymmetric deprotonation of **6c** and addition of acetone yield *ent*-**19** (er = 94:6, yield 86%). When (1*Z*)-**6d** is subjected to the same reaction conditions, again *ent*-**19** (er = 96:4, yield 93%) is produced arising from the Li compound (3*S*,1*Z*,4*E*)-**7d**. The latter result again provides clear evidence for a *syn*-S_E' mode of ketone addition, which now has to approach from the *Si*-face of the styryl moiety. In addition, configurational stability of the C1−C2 bond against torsion at low temperature must be concluded.

Concerning the regiochemistry, the following rules are extracted from the above examples and some more entries in Table 1 and Scheme 8. The lithium intermediates **7** are preferentially attacked at the terminus adjacent to the phenyl residue where the highest electron and charge density are expected. In the covalently bound titanium compounds **16**,

Table 1. Substitution of **6e** with Different Electrophiles via **7e**

El	product(s)	yield %[a]	er [b]	$[\alpha]^{20}_D$ [c]
Me_3Si	**15**	73	98:2	+12
$Me_2C(OH)$	**19**	88	99:1	−174
Me	**9ea**[d,e]	93	93:7	+266
*t*BuC(O)	**9eb:8eb**[d] (98:2)	91	97:3	−150
Ph_3Sn	**13:14** (68:32)	85	99:1	+7[f]

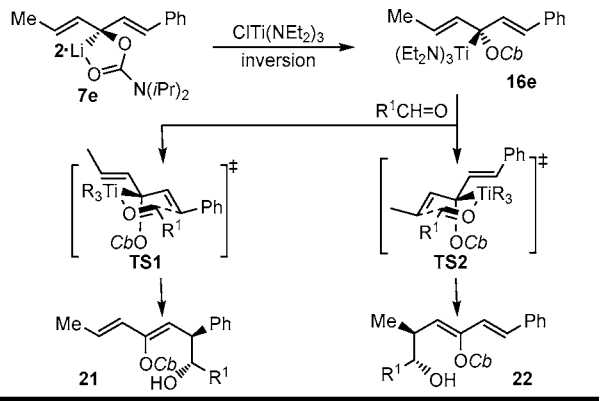
[a] Total yield. [b] Major product determined on chiral HPLC. [c] $c = 0.65-1.05$, in $CHCl_3$. [d] Refers to Scheme 2: R^1 = Me, R^2 = Ph. [e] The absolute configuration has not been determined yet. [f] Taken from the major product.

(9) Crystal structure data of **13** and **17** are available in the Supporting Information.

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

(11) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920.

Scheme 8. Homoaldol Reactions of **6e**



R^1	product(s)	yield % [a]	er [b] (dr [c])	$[\alpha]^{20}_D$ [d]
*t*Bu	**21a**[e]	89	99:1 (>98:2)	+ 430
*i*Pr	**21b:22b** (66:34)	64	99:1 (>98:2)	+ 390

[a] Total yield. [b]Major product determined on chiral HPLC. [c]By ^{1}H NMR. [d] c = 0.62−0.84, in $CHCl_3$ (major product). [e]X-ray structure available in the Supporting Information.

this effect is still seen to a lower extent, but the steric situation gains in influence by increasing bulkiness of the attacking carbonyl compound. Surprisingly, no electrophilic substitution product arising from attack of the "central position" of the "pentadienyl anion" has ever been found by us, although this is the preferred center of reactivity in 3-unsubstituted compounds.[12]

The alcohol **21a** was oxidized to the ketone leading to *ent*-**9eb** (6*S*,2*E*,4*Z*; er = 99:1; $[\alpha]^{20}_D$ = +154). This substantiates the syn-S_E' addition of pivaloyl chloride to **7e** forming ketone **9eb**.

In conclusion, the facile construction of geometrically defined dienyl carbamates **6**, combined with highly stereoselective asymmetric deprotonation and substitution reactions, allows for a flexible synthesis of stereohomogeneous substituted 1,3-dienes.

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Supporting Information Available: Experimental procedures, spectroscopic data, X-ray crystal analyses of compounds **13**, **17a**, and **21a**, and ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

OL061005P

(12) Schlosser, M.; Zellner, A. *Synlett* **2001**, 1016.