Pergamon

Tetrahedron Letters 40 (1999) 1881–1884

TETRAHEDRON LETTERS

(–)-Sparteine-Mediated Stereoselective Intramolecular Conjugate Addition Reactions of Dienes and Enynes

Martin Oestreich and Dieter Hoppe*

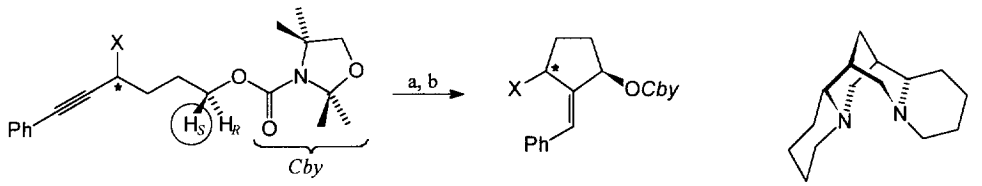
Organisch-chemisches Institut, Westfälische Wilhelms-Universität Münster, Corrensstraße 40, D-48149 Münster, Germany, Fax +251-83-39772

Received 15 December 1998; accepted 7 January 1999

Key words: *asymmetric deprotonation, (–)-sparteine, intramolecular carbolithiation, conjugate addition, chiral cyclopentanes*

Abstract: Enantioenriched carbanionic pairs generated by the asymmetric deprotonation of carbamate esters with the chiral base *s*-butyllithium/(–)-sparteine undergo smoothly intramolecular conjugate addition reactions to dienes and enynes in high yields.

The addition of a carbon-metal bond to a carbon-carbon multiple bond has become an important tool for the formation of new carbon-carbon bonds particularly when controlling the relative and absolute configuration of the formed products.[1] In this context, the enantioselective intermolecular[2] as well as intramolecular[3,4] carbolithiation of carbon-carbon multiple bonds has attracted considerable attention in recent years. We have accomplished the first enantioselective intramolecular carbolithiation of alkenes[3a] by the fusion of the concepts of the *intramolecular carbolithiation*[1,5] and the *asymmetric deprotonation*[6]. Additionally, the efficiency of this method was demonstrated with the extension to alkynes of type **2** in which a bulky substituent X in the propargylic position prevents the abstraction of the remaining propargylic proton by the chiral base *s*-BuLi/(–)-sparteine (*s*-BuLi/**1**) (Scheme 1).[3b]



2, *er* = 95:5->99:1, X = NBn_2, OTr, OTBDPS

dr = 95:5->95:5, *E*/*Z* = >95:5, 70-99 %

1: (–)-sparteine

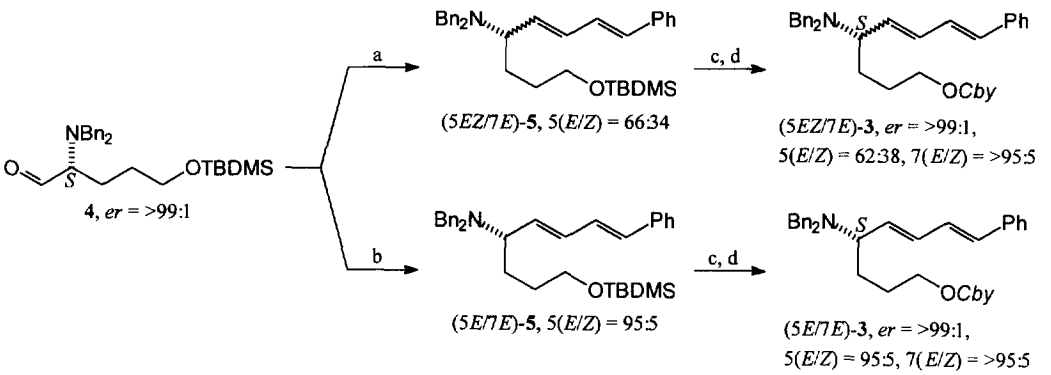
a) 1.5 equiv. *s*-BuLi/**1**, Et_2O, –78 °C, 18-22 h; b) 2.0 equiv. MeOH, –78 °C → rt.

Scheme 1

In this paper we wish to report the stereoselective intramolecular conjugate addition of a chiral α-oxyalkyllithium, generated by the asymmetric deprotonation, to dienes and enynes, respectively; similar systems were investigated by Normant's and Cooke's groups in an achiral fashion.[7]

The dienes (5*EZ*,7*E*)-**3** and (5*E*/7*E*)-**3** were chosen as model systems taking advantage of an allylic substituent which has proven to suppress the abstraction of acidified protons.[3b] Compounds **3** were prepared starting form the aldehyde **4**[3b] derived from (*S*)-glutamic acid. The diene moiety was introduced either by a Wittig[8] (**4**→(5*EZ*/7*E*)-**5**) or a Horner-Emmons[9] reaction (**4**→(5*E*/7*E*)-**5**) with the corresponding cinnamyl derivatives (Scheme 2).

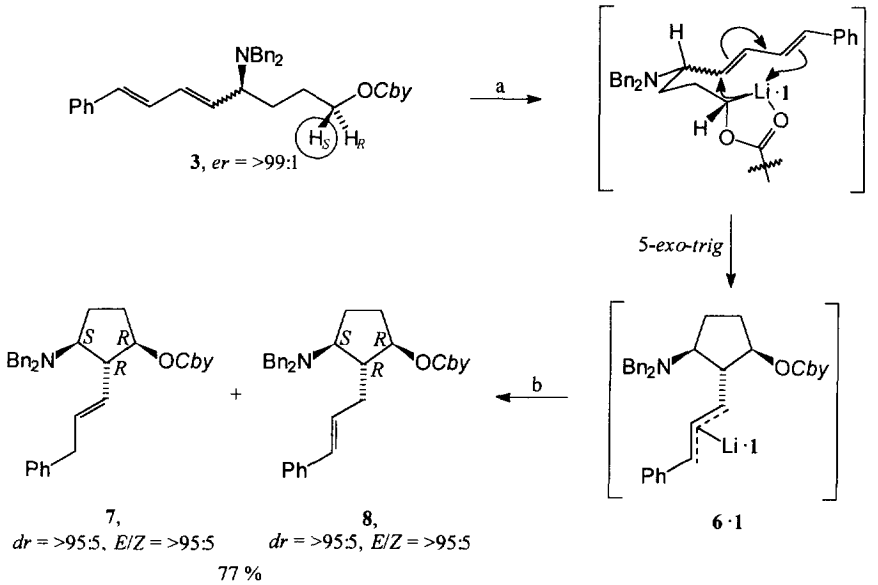
0040-4039/99/$ - see front matter
PII: S0040-4039(99)00092-1



a) 2.0 equiv. (*E*)-cinnamyltriphenylphosphonium chloride, 1.85 equiv. KO*t*-Bu, Et_2O, −18 °C → rt, 84 %; b) 2.0 equiv. (*E*)-diethyl cinnamylphosphonate, 1.85 equiv. LDA, THF, −78 °C → rt, 98 %; c) 3.0 equiv. TBAF, THF, rt, 5(*EZ/7E*)-**4**: 88 %, 5(*E/7E*)-**4**: quant.; d) 1.2 equiv. *Cby*Cl, 1.3 equiv. NaH, THF, reflux, 5(*EZ/7E*)-**4**: 65 %, 5(*E/7E*)-**4**: 63 %.[10b]

Scheme 2

When the cyclization precursor (5*EZ/7E*)-**3** was treated with *s*-BuLi/**1** in Et_2O at −78 °C the desired 5-*exo-trig* ring closure proceeded via the intermediate η^3-lithiumallyl complex **6•1** yielding after protonation with MeOH the regioisomeric products **7** and **8** in a ratio of 66:34 (Scheme 3, Table 1, entry 1). In order to check the influence of the proton source on the product distribution AcOH (1M in Et_2O) was used instead of MeOH; although methoxide is a by far stronger base than acetate there was no significant change observed (Table 1, entry 2).



a) 1.5 equiv. *s*-BuLi/**1**, Et_2O, −78 °C, 21-23 h; b) 1.5 equiv. ROH, −78 °C → rt.

Scheme 3

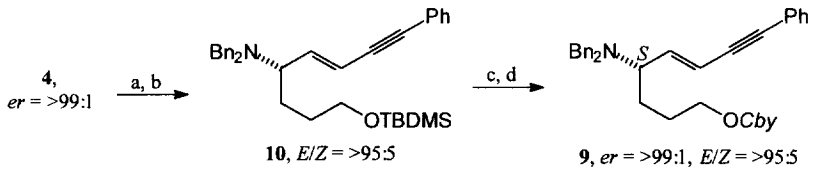
The cyclization of (5*E/7E*)-**3** with two stereodefined double bonds afforded the products **7** and **8** in a ratio of 68:32 (Table 1, entry 3). This confirmed our findings that the configuration of a double bond in the 5-position has no effect on the stereochemistry of the cyclization product.[3a] The fact that **7** and **8** are formed *E*-selectively suggests that **6•1** exists as an *exo,exo*-η^3-allyl complex.[11]

Table 1: Stereoselective Cyclization of the Precursors (5*EZ*/7*E*)-**3** and (5*E*/7*E*)-**3**[10a]

entry	diene[a]	reaction time	proton source ROH	*E*/*Z* ratio[a] of **7**	*E*/*Z* ratio[a] of **8**	ratio of regioisomers[a] **7**:**8**
1	(5*EZ*/7*E*)-**3**	20	MeOH	>95:5	>95:5	64:36
2	(5*EZ*/7*E*)-**3**	21	AcOH[b]	>95:5	>95:5	69:31
3	(5*E*/7*E*)-**3**	23	MeOH	>95:5	>95:5	68:32

[a]The *E*/*Z* ratios and the ratio of regioisomers, respectively, were determined by ^{1}H NMR spectroscopy; [b]1 M in Et_2O.

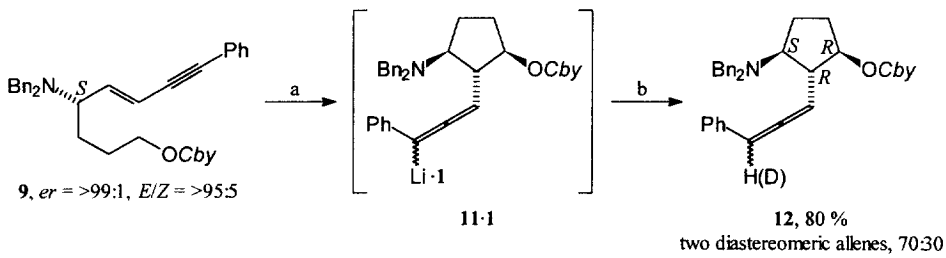
These promising results with the cyclization of the functionalized dienes **3** prompted us to synthesize the corresponding enyne **9**. By applying a Cr(II)-[12] and Pd(II)/Cu(I)-mediated[13] reaction sequence to the α-chiral aldehyde **4**[3b] which is transformed into the vinyl iodide and then cross-coupled with phenylacetylene following the Sonogashira protocol the enyne **10** could be isolated with excellent *E*-selectivity and in high yield (**4**→**10**) (Scheme 4).



a) 6.0 equiv. $CrCl_2$, 2.0 equiv. CHI_3, THF, 0 °C → rt, 79 %; b) 1.0 equiv. phenylacetylene, 1.0 mol% $(PPh_3)_2PdCl_2$, 0.5 mol% CuI, Et_3N, rt, 88 %; c) 3.0 equiv. TBAF, THF, rt, 98 %; d) 1.2 equiv. *Cby*Cl, 1.3 equiv. NaH, THF, reflux, 71 %.[10b]

Scheme 4

Analogously, we examined the cyclization behaviour of the enyne **9** which upon treatment with *s*-BuLi in the presence of **1** cleanly cyclized to an intermediate allenyllithium **11•1**. However, quenching with MeOH(D) gave a mixture of two diastereomeric allenes **12**[10c] in high yield (Scheme 5); the metallotropic equilibrium of the propargylic and the allenylic lithium species **11•1** is strongly in favour of the latter. This corresponds to an intramolecular 1,4-addition of a chiral carbanionic pair to an enyne functionality.



a) 1.5 equiv. *s*-BuLi/**1**, Et_2O, −78 °C, 21 h; b) 2.0 equiv.MeOH(D), −78 °C → rt.

Scheme 5

In summary, as in the case of alkynes the introduction of a sterically demanding substituent in the allylic position of conjugated systems such as dienes and enynes prevents the abstraction of the remaining allylic proton. Thus, carbamates containing a diene or enyne in the 5-position can be efficiently cyclized with stereoselective control of the substitution pattern of the formed carbocycles. This represents a further extension to the stereoselective intramolecular carbolithiation of alkenes[3a,c] and alkynes[3b] which was developed in our laboratories recently.

Acknowledgments: This work was generously supported by the Fonds der Chemischen Industrie (Kekulé Fellowship for M. O.) and the Deutsche Forschungsgemeinschaft. M. O. would like to thank K. Gottschalk for skillful technical assistance.

References and Notes

1. Review: Marek, I.; Normant, J. F. *Metal-catalyzed Cross-coupling Reactions*; Diederich, F.; Stang, P. J., Eds; Wiley-VCH, **1998**, pp. 271-337 and references cited therein.
2. (a) Klein, S.; Marek, I.; Poisson, J.-F.; Normant, J. F. *J. Am. Chem. Soc.* **1995**, *117*, 8853-8854; (b) Mück-Lichtenfeld, C.; Ahlbrecht, H. *Tetrahedron* **1996**, *52*, 10025-10042; (c) Norsikian, S.; Marek, I.; Poisson, J.-F.; Normant, J. F. *J. Org. Chem.* **1997**, *62*, 4898-4899.
3. (a) Woltering, M. J.; Fröhlich, R.; Hoppe, D. *Angew. Chem.* **1997**, *109*, 1804-1805; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1764-1766; (b) Oestreich, M.; Fröhlich, R.; Hoppe, D. *Tetrahedron Lett.* **1998**, *39*, 1745-1748; (c) Woltering, M. J.; Fröhlich, R.; Wibbeling, B.; Hoppe, D. *Synlett* **1998**, 797-800.
4. (a) Coldham, I.; Hufton, R.; Snowden, D. *J. Am. Chem. Soc.* **1996**, *118*, 5322-5323; (b) Tomooka, K.; Komine, N.; Nakai, T. *Tetrahedron Lett.* **1997**, *38*, 8939-8942; (c) Tomooka, K.; Komine, N.; Sasaki, T.; Shimizu, H.; Nakai, T. *ibid.* **1998**, *39*, 9715-9718.
5. Reviews: (a) Knochel, P. *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds; Pergamon Press, **1991**, Vol. 4, pp. 865-911; (b) Bailey, W. F.; Ovaska, T. V. *Advances in Detailed Reaction Mechanisms*; Coxon, J. M., Ed.; JAI Press, **1994**, Vol. 3, pp. 251-273 and references cited therein.
6. (a) Hoppe, D.; Hintze, F.; Tebben, P. *Angew. Chem.* **1990**, *102*, 1457-1459; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1422-1423. Reviews: (b) Hoppe, D.; Hense, T. *Angew. Chem.* **1997**, *109*, 2376-2410; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2282-2316; (c) Beak, P.; Basu, A.; Gallagher, D. J.; Park, Y. S.; Thayumanavan, S. *Acc. Chem. Res.* **1996**, *29*, 552-560.
7. (a) Lorthiois, E.; Marek, I.; Normant, J. F. *Tetrahedron Lett.* **1996**, *37*, 6693-6694; (b) Cooke, Jr., M. P.; Huang, J.-J. *Synlett* **1997**, 535-536.
8. Fitjer, L.; Quabeck, U. *Synth. Commun.* **1985**, *15*, 855-864.
9. Nicolaou, K. C.; Petasis, N. A.; Zipkin, R. E.; Uenishi, J. *J. Am. Chem. Soc.* **1982**, *104*, 5555-5557.
10. (a) Compounds **7** and **8**: colourless oil; R_F = 0.59 (Et_2O/hexanes = 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) of **7**: δ (ppm) = 1.25-1.92 (m, 15H, 4C*H*$_3$ (*Cby*), 4-H, 5-Hα); 1.98-2.09 (m, 1H, 5-Hβ); 2.65-2.80 (m, 1H, 2-H); 3.08 (dd, 1H, ^3J = 8.6 Hz, ^3J = 18.3 Hz, 3-H); 3.41 (d, 2H, ^3J = 6.7 Hz, 8-H); 3.54 (d, 2H, ^2J = 13.9 Hz, NC*H*H); 3.70 (s, 2H, CH_2 (*Cby*)); 3.82 (d, 2H, ^2J = 13.9 Hz, NCH*H*); 4.74 (dd, 1H, ^3J = 7.1 Hz, ^3J = 13.6 Hz, 1-H); 5.44 (dd, 1H, ^3J = 8.3 Hz, ^3J = 15.3 Hz, 6-H); 5.70 (dt, 1H, ^3J = 15.3 Hz, ^3J = 6.7 Hz, 7-H); 7.15-7.45 (m, 15H, Ph) and ^{1}H NMR (300 MHz, $CDCl_3$) of **8**: δ (ppm) = 1.25-1.92 (m, 16H, 4C*H*$_3$ (*Cby*), 4-H, 5-H); 2.12-2.24 (m, 1H, 2-H); 2.30 (dt, 1H, ^3J = 7.0 Hz, ^2J = 13.7 Hz, ^3J = 7.0 Hz, 6-Hα); 2.51 (ψ-dt, 1H, ^3J = 6.0 Hz, ^2J = 13.7 Hz, ^3J = 7.0 Hz, 6-Hβ); 2.90 (dd, 1H, ^3J = 8.3 Hz, ^3J = 17.4 Hz, 3-H); 3.47 (d, 2H, ^2J = 13.8 Hz, NC*H*H); 3.69 (s, breit, 2H, CH_2 (*Cby*)); 3.90 (d, 2H, ^2J = 13.8 Hz, NCH*H*); 4.81-4.86 (m, 1H, 1-H); 6.08 (dt, 1H, ^3J = 7.0 Hz, ^3J = 15.7 Hz, 7-H); 6.24 (d, 1H, ^3J = 15.7 Hz, 8-H); 7.15-7.45 (m, 15H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 24.1/25.3/26.7 (*C*H$_3$ (*Cby*)); 22.0/29.7 (C-4, C-5/**7**); 21.0/30.3 (C-4, C-5/**8**); 35.1 (C-6/**8**); 39.2 (C-8/**7**); 47.4 (C-2/**8**); 50.6 (C-2/**7**); 54.4 (N*C*H$_2$/**7**); 54.9 (N*C*H$_2$/**8**); 59.6/60.6 (N*C*(CH$_3$)$_2$ (*Cby*)); 63.0 (C-3/**7**); 63.5 (C-3/**8**); 76.1/76.3 (O*C*H$_2$ (*Cby*)); 78.2 (C-1) 94.8/95.8 (N*C*(CH$_3$)$_2$O, (*Cby*)); 125.9/126.1/126.7/126.9/128.1/128.2/128.5/128.6/128.7/131.1/140.1/140.6 (NCH$_2$*Ph*, Ph); 128.4 (C-7/**8**); 131.5 (C-7/**7**); 132.3 (C-8/**8**); 137.7 (C-6/**7**); 152.0/152.8 (*C*=O); $[\alpha]_D^{20}$ = −58.5 (c = 0.39, $CHCl_3$); IR (film): $\tilde{\nu}_{max}$ = 1700 (s, C=O); anal. calcd for $C_{36}H_{44}N_2O_3$: C, 78.23; H, 8.02; N, 5.07; found: C, 78.11; H, 7.93; N, 5.16; (b) all isolated compounds gave satisfactory analytical and spectroscopic data; (c) an impurity (5 %) was detected by ^{1}H NMR spectroscopy.
11. Boche, G.; Buckl, K.; Martens, D.; Schneider, D. R. *Liebigs Ann. Chem.* **1980**, 1135-1171.
12. (a) Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408-7410; (b) α-chiral aldehydes are not suffering epimerization: Nicolaou, K. C.; Piscopio, A. D.; Bertinato, P.; Chakraborty, T. K.; Minowa, N.; Koide, K. *Chem. Eur. J.* **1995**, *1*, 318-333.
13. (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467-4470; (b) review: Sonogashira, K. *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds; Pergamon Press, **1991**, Vol. 3, pp. 521-549.