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(–)-Sparteine-Mediated Stereoselective Intramolecular Carbolithiation of Alkynes

Martin Oestreich, Roland Fröhlich[+], Dieter Hoppe*

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

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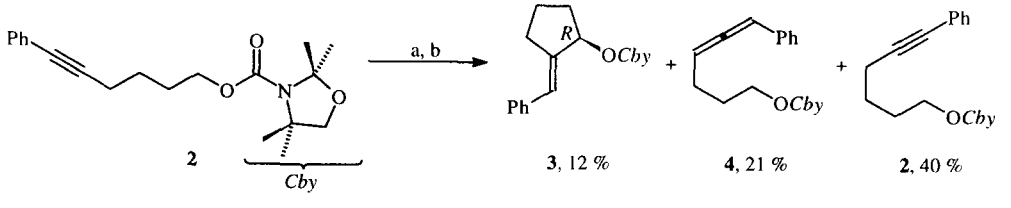
Abstract: The asymmetric deprotonation mediated by the chiral base *s*-butyllithium/(–)-sparteine of 4-substituted 5-hexynyl carbamates permits the synthesis of enantioenriched carbanionic pairs which undergo a regioselective 5-*exo-dig* ring closure with the triple bond acting as an internal electrophile. The functionalized five-membered rings are formed with complete stereoselectivity in high yields.

The asymmetric deprotonation of carbamate esters derived from primary alkanols with the chiral base *s*-butyllithium/(–)-sparteine (*s*-BuLi/**1**) and the subsequent stereospecific electrophilic substitution of the carbanionic intermediates by *external* electrophiles represent a powerful tool for the synthesis of enantioenriched secondary alkanols.[1] An extension of this method is the employment of carbon-carbon multiple bonds as *internal* electrophiles corresponding to an intramolecular carbolithiation. Bailey and others have already demonstrated for achiral substrates that especially double bonds[2] but also triple bonds[3] can serve as good electrophiles. Therefore, our interest is focussed on the fusion of the concepts of the *asymmetric deprotonation* and the *intramolecular carbolithiation*. In this context, we have recently reported the first example of an enantioselective intramolecular carbolithiation starting from achiral 6-phenyl-5-hexenyl carbamates which cyclize stereoselectively in the presence of *s*-BuLi/**1** in moderate yields to give substituted cyclopentanols incorporating three defined adjacent stereocenters.[4,5]

If the same concept is applied to the corresponding alkyne **2** the relatively high thermodynamic acidity of the propargylic protons competes with the kinetic acidity of the protons at the carbon bearing the activating hydroxy group. Thus, after treatment of the 6-phenyl-5-hexynyl carbamate (**2**) with *s*-BuLi/**1** not only the desired cyclization product **3** but also the allene **4** were isolated in poor yields (Scheme 1).



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

Scheme 1

During our studies we recognized that the cyclization behaviour of 6-phenyl-5-hexenyl carbamates is dramatically enhanced if a substituent is introduced in allylic position. The chiral 4-substituted carbamate **5** derived from (*S*)-glutamic acid (**8**) cyclizes with good stereoselectivity yielding **6** in 70 % (Scheme 2).

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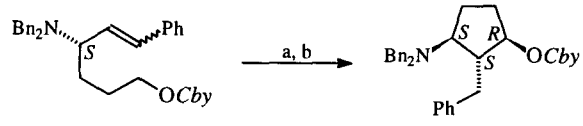
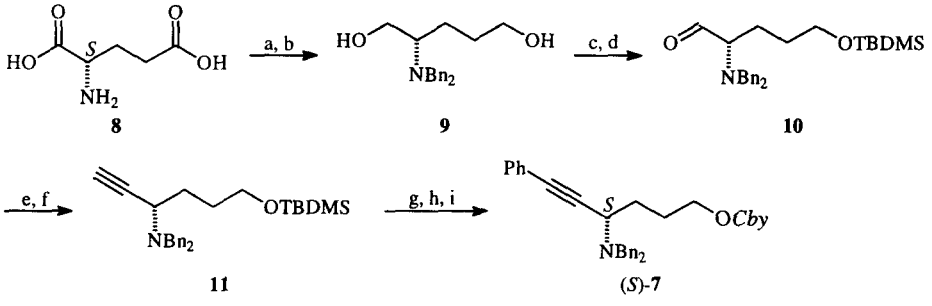


5 6, 70 %, > 95 % ds

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

Scheme 2

Consistently we introduced several propargylic substituents in the carbamate **2** to investigate whether this effect proves to be generally applicable to alkynes. The 4-amino-6-phenyl-5-hexynyl carbamate (*S*)-**7** was prepared starting from (*S*)-glutamic acid (**8**) using a regioselective silylation[6] of the intermediate diol **9**. The terminally substituted triple bond was introduced by Corey's formyl→ethynyl conversion[7] (**10**→**11**) with a subsequent sp-sp^2 coupling reaction known as the Sonogashira reaction[8] (Scheme 3).

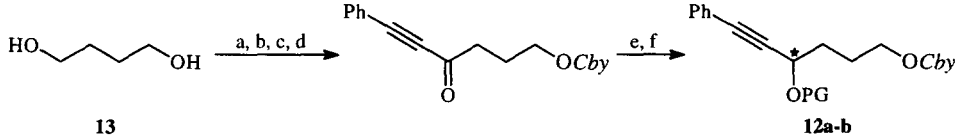


8 **9** **10** **11** (*S*)-**7**

a) 4.5 equiv. BnBr, 2.25 equiv. K_2CO_3, 2.25 equiv. NaOH, MeOH/H_2O (1:1), reflux, 80 %; b) 1.6 equiv. $LiAlH_4$, THF, reflux, 97 %; c) 1.2 equiv. TBDMSCl, 0.5 equiv. DMAP, 1.0 equiv. Et_3N, CH_2Cl_2, reflux, 76 %; d) Swern, 90 %; e) 2.0 equiv. CBr_4, 4.0 equiv. PPh_3, CH_2Cl_2, 0 °C, 69 %; f) 2.0 equiv. *n*-BuLi, -78 °C → rt, 85 %; g) 1.0 equiv. PhI, 1.0 mol% $(Ph_3P)_2PdCl_2$, 0.5 mol% CuI, Et_3N, rt, 94 %; h) 3.0 equiv. TBAF, THF, rt, 94 %; i) 1.2 equiv. *Cby*Cl, 1.2 equiv. NaH, THF, reflux, 88 %.

Scheme 3

The synthesis of several 4-hydroxy-6-phenyl-5-hexynyl carbamates **12a-b** was accomplished in a straightforward manner starting from 1,4-butanediol **13** with Brown's Alpine-Borane® reduction[9] as the key step; both enantiomers of **12** could be synthesized with an enantiomeric excess of 90 %, determined via esterification with Mosher's reagent[10] (Scheme 4).



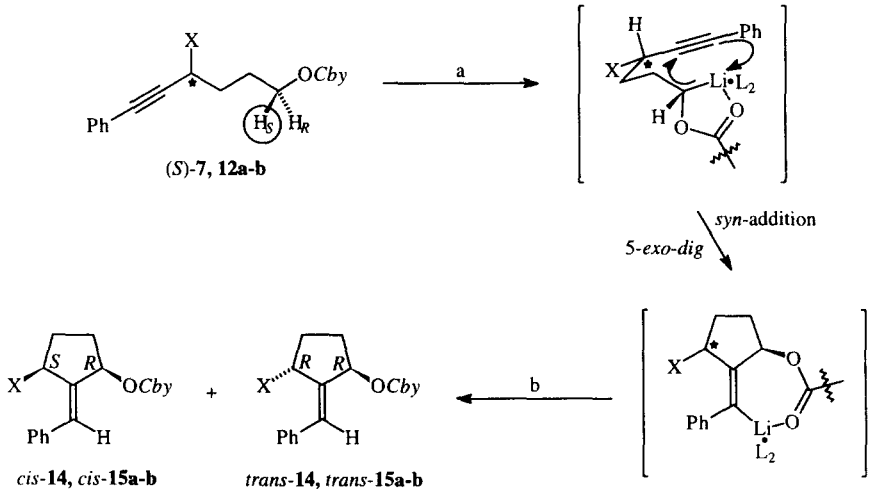
13 **12a-b**

a) 0.33 equiv. *Cby*Cl, 0.35 equiv. NaH, THF, reflux, 87 %; b) Swern, 89 %; c) 1.3 equiv. phenylacetylene, 1.25 equiv. *n*-BuLi, THF, -78 °C → -20 °C → rt, 95 %; d) MnO_2, CH_2Cl_2, reflux, 82 %; e) 2.0 equiv. Alpine-Borane®, acetaldehyde, 2.2 equiv. ethanolamine, no solvent, rt, 87 %; f) PG = Tr: 1.1 equiv. TrCl, 1.5 equiv. Et_3N, 0.05 equiv. DMAP, CH_2Cl_2, reflux, 54 %; PG = TBDPS: 1.1 equiv. TBDPSCl, 1.1 equiv. Et_3N, 0.5 equiv. DMAP, CH_2Cl_2, reflux, 98 %.

Scheme 4

When the precursor (*S*)-**7** was analogously treated with *s*-BuLi/**1** in Et_2O the desired cyclization product *cis*-**14**[11a] could be isolated in 70 % yield (Table 1, entry 1), again showing the enhancing effect of a substituent in

the 4-position of 5,6-unsaturated alkenyl and alkynyl carbamates (Schemes 2 and 5); the formation of the allene was not observed. The other carbamates (*S*)-**12a** and (*S*)-**12b** also reveal this smooth cyclization behaviour undergoing the ring closure nearly quantitatively to yield the functionalized cyclopentylidene derivatives *cis*-**15a** and *cis*-**15b** (Table 1, entries 2 and 5); a crystal structure of *cis*-**15a**[12] allowed the determination of the relative configuration and proved that the chiral base *s*-BuLi/**1** selectively removes the *pro*-*S*-proton in (*S*)-**7** and **12a-b**. The *cis*:*trans* ratios of the cyclization products obviously correspond to the enantiomeric excess in the particular precursor; thus, the new stereocenter is formed highly stereoselectively.



(*S*)-**7**, **12a-b**

cis-**14**, *cis*-**15a-b** *trans*-**14**, *trans*-**15a-b**

a) 1.5 equiv. *s*-BuLi/L_2 (L_2 = (–)-sparteine (**1**) *or* TMEDA (**16**)[a]), Et_2O, -78 °C, 18-22 h; b) 2.0 equiv. MeOH, -78 °C → rt.

Scheme 5

In order to investigate the role of the existing stereocenter the (*R*)-configurated precursor (*R*)-**12a** and the racemates *rac*-**12a** and *rac*-**12b** were cyclized by the typical procedure (Table 1, entries 3, 4 and 6). These experiments furnished the cyclization products *trans*-**15a**, **15a** and **15b** exclusively in *cis*:*trans* ratios which are directly related to the ratio of the enantiomers of compounds (*R*)-**12a**, *rac*-**12a** and *rac*-**12b**. The fact that the cyclizations of the racemic carbamates *rac*-**12a** and *rac*-**12b** gave the products with *cis*:*trans* ratios of 50:50 in all cases exhibits that there is no kinetic resolution of the enantiomers operating (Table 1, entries 4 and 6).

Table 1: Stereoselective Cyclization of the Precursors (*S*)-**7** and **12a-b**[11]

entry	precursor	X	ratio of the enantiomers	configuration at C★	diamine	major product	*cis*:*trans* ratio 1*R*,3*S* : 1*R*,3*R*	yield (%)
1	(*S*)-**7**	NBn_2	> 99 : 1	*S*	**1**	*cis*-**14**	> 99 : 1	70
2	(*S*)-**12a**	OTr	95 : 5	*S*	**1**	*cis*-**15a**	95 : 5	88
3	(*R*)-**12a**	OTr	5 : 95	*R*	**1**	*trans*-**15a**	5 : 95	99
4	*rac*-**12a**	OTr	50 : 50	*R*, *S*	**1**	**15a**	50 : 50	80
5	(*S*)-**12b**	OTBDPS	95 : 5	*S*	**1**	*cis*-**15b**	95 : 5	90
6	*rac*-**12b**	OTBDPS	50 : 50	*R*, *S*	**1**	**15b**	50 : 50	96
7	(*S*)-**12b**	OTBDPS	95 : 5	*S*	**16**	*epi*-**15b**[a]	50 : 50	89

[a] In this case the diastereomers *cis*-**15b** (1*R*,3*S*) and *ent*-*trans*-**15b** (1*S*,3*S*) are formed with an enantiomeric excess of 90 %.

If the cyclization precursor (*S*)-**12b** is treated with *s*-BuLi in the presence of an achiral diamine such as TMEDA (**16**), the formation of the new stereocenter proceeds not being affected by the existing one; compound *epi*-**15b** is obtained in high yield but with a *cis*:*trans* ratio of 50:50 (Table 1, entry 7).

In summary, we have shown that the intramolecular addition of a chiral carbanion to a triple bond occurs in a *syn*-fashion and is completely regioselective; the 5-*exo*-*dig* cyclization product is formed exclusively. This method represents an extension to the intramolecular carbolithiation of alkenes[4] allowing the stereoselective synthesis of substituted enantiopure cyclopentanoid building blocks.

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[+] Crystal structure analysis

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11. (a) Compound *cis*-**14**: ^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm) = 1.33-1.60 (7s, 12H, 4CH_3 (*Cby*)); 1.78-1.85 (m, 1H, 5-Hα); 1.96-2.04 (m, 2H, 4-Hα, 5-Hβ); 2.18-2.28 (m, 1H, 4-Hβ); 3.24 (2d, 2H, ^{2}J = 12.6 Hz, NCH_2); 3.70 (2s, 2H, CH_2 (*Cby*)); 3.85 (m, 2H, NCH_2); 4.20 (m, 1H, 3-H); 5.56 (m, 1H, 1-H); 6.92 (m, 1H, 6-H); 7.02-7.04 (m, 3H, Ph); 7.16-7.40 (m, 12H, Ph); ^{13}C-NMR (150 MHz, $CDCl_3$): δ (ppm) = 24.1/24.2/25.2/25.3/25.4/25.5/26.6/26.7 (4CH_3 (*Cby*)); 22.1 (C-4); 30.3/30.4 (C-5); 54.8/54.9 (NCH_2); 59.5/60.8 (N$C(CH_3)_2$ (*Cby*)); 60.4 (C-3); 76.0/76.4 (OCH_2 (*Cby*)); 80.3 (C-1); 94.6/96.0 (N$C(CH_3)_2$O (*Cby*)); 126.8/127.1/127.6/127.9/128.3/128.7/129.3/130.3/135.9/136.0/139.2 (Ph, C-2); 141.7/141.8 (C-6); 151.9/152.6 (*C*=O); $[\alpha]^{25}_{D}$ = -76.6 (c = 0.15, $CHCl_3$); (b) All isolated compounds gave satisfactory analytical and spectroscopic data.
12. Crystal structure data of *cis*-**15a**: Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre.