Stereochemistry of the intramolecular carbolithiation of vinyl sulfides

Reinhard W. Hoffmann,*[a] Ralf Koberstein,[a] Bruno Remacle[b] and Alain Krief[b]

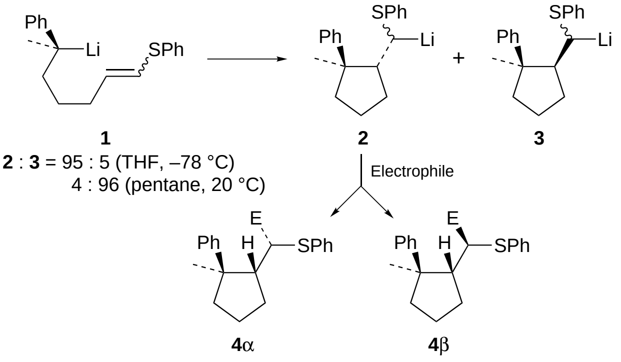
[a] *Fachbereich Chemie der Philipps-Universität Marburg, Hans-Meerwein-Strasse, 35032 Marburg, Germany*
[b] *Department of Chemistry, Facultés Universitaires Notre-Dame de la Paix, 61, rue de Bruxelles, 5000 Namur, Belgium*

Intramolecular carbolithiation of vinyl sulfides to generate configurationally stable α-durylthioalkyllithium compounds at −105 °C in THF showed carbolithiation to be non-stereospecific regarding the newly formed lithium bearing stereocentre.

The intramolecular carbolithiation of alkenes,[1] *i.e.* the addition of an organolithium entity across a C=C double bond is of interest, because it leads to carbo- and hetero-cycles with a stereochemically defined substitution pattern.[2] The detailed mechanism of the carbolithiation reaction is as yet not well-understood.

Cyclization of **1** in THF led to the *trans*-isomer **2** in high diastereoselectivity[3,4] (Scheme 1). Trapping of **2** by electrophiles generated two diastereoisomeric products **4α** and **4β**, the ratio of which depended on the electrophile used.[3] This demonstrates that the configurational stability of the α-phenylthioalkyllithium species **2** is too low to allow any conclusions regarding the initial configuration of the lithium-bearing stereocentre in **2**. Such information could, however, be obtained if a lithium-bearing stereocentre of higher configurational stability could be generated in the carbolithiation reaction. Previous studies[5] have indicated that α-durylthioalkyllithium compounds (duryl = 2,3,5,6-tetramethylphenyl) have a significantly higher barrier to enantioisomerization than α-phenylthioalkyllithium compounds. We therefore prepared the (*E*)- and (*Z*)-durylthio compounds **5**,† hoping to uncover further stereochemical details of the carbolithiation reaction of the derived benzyllithium compounds **6** (Scheme 2).

In order to preserve the initial configuration at the newly formed lithium-bearing stereocentre in **7** and **8**, we treated the seleno compound **5** with *tert*-butyllithium at −105 °C in THF. Quenching after 10 min with precooled CD_3OD in a two compartment reaction vessel[6] showed that cyclization of **6** to **7** and **8** had occurred. The relative configuration of **9** at the ring carbon atoms corresponds to that of **4**, as supported by a crystal structure analysis of **9c**. The relative configuration of **9a** and **10a** at the exocyclic carbon atom is assigned by the similarity of their ^{1}H NMR spectra to that of **4** (E = D). The ratio of the two diastereoisomeric deuterated compounds **9a** and **10a** was determined by ^{2}H NMR spectroscopy.

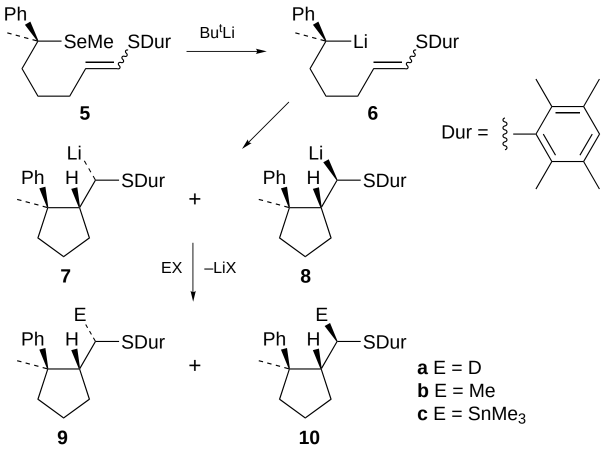


Scheme 1

Entries 1 and 2 of Table 1 show that carbolithiation occurred in an essentially stereospecific manner, when starting from a sample enriched in (*Z*)-**5**. Carbolithiation in the *E* series (entries 3 and 4) led to the α- and β-diastereoisomers **9a** and **10a** in a 4 : 6 ratio. The differences between the two series of experiments, and the fact that the time between carbolithiation and trapping had no influence on the diastereoisomer ratio of **9a** : **10a** indicates that the α-durylthioalkyllithium compounds **7** and **8** are configurationally stable under the reaction conditions. The diastereoisomer ratio is therefore kinetically controlled. Warming of the reaction mixture to −78 °C before quenching led to equilibration of **7** and **8**. Subsequent trapping then reflects the thermodynamic ratio of **7** and **8** (*cf.* entries 11–13 of Table 1). Moreover, dilution (entry 5) or trapping with methyl iodide to give **9b** and **10b** (entries 6 and 7) had no effect on the **9** : **10** ratio. For the carbolithiation reactions to occur at these low temperatures and with this stereochemistry, THF (a lithium-coordinating solvent) is essential. The reaction does also proceed in pentane at low temperatures, but only in the presence of at least one equivalent of THF.

The seemingly stereospecific cyclization of (*Z*)-**6** to **7** is in line with a concerted *syn*-addition of carbon and lithium to the double bond, but does not prove such a mechanism. The non-stereospecific cyclization of (*E*)-**6** suggests, however, a different scenario for the carbolithiation reaction in THF.

Carbolithiation reactions are greatly facilitated by all factors which help to detach the lithium from the carbon atom at the migration origin, *e.g.* an allyl-[7] or benzyl-lithium[3,4,8] entity at the migration origin, complexation assisted carbolithiation[9,10] and addition of lithium coordinating co-solvents.[10,11] This suggests that the carbon–lithium bond at the migration origin has to be broken first, in the extreme with the formation of a solvent separated ion pair **11**, a process favoured at lower temperatures.[12] C–C Bond formation, *i.e.* the cyclization, then proceeds in the carbanion part of the ion pair to give the ion pairs **12** and **13** (Scheme 3). The choreography of the cyclisation is probably such that C_i, S, C_α and the lone pair are initially antiperiplanar in **12** and **13**, in order to stabilize the transition state of the cyclization by delocalization of the negative charge

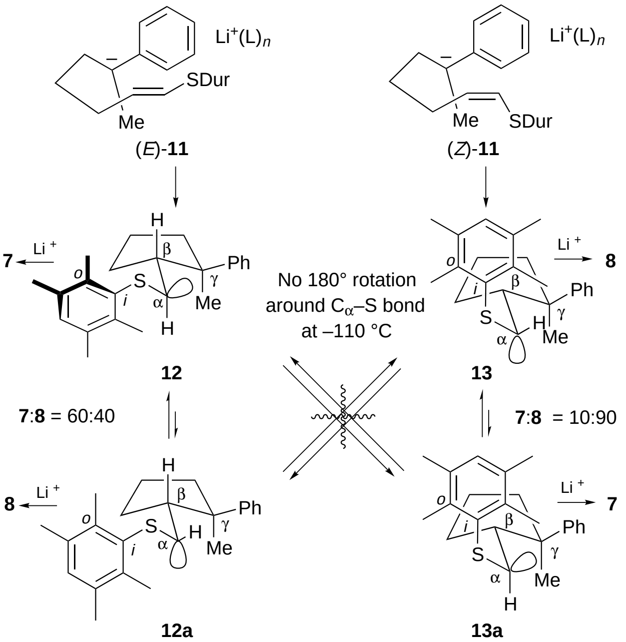


Scheme 2

Table 1 Results of some carbolithiation experiments

Entry[a]	T/°C[b]	Solvent	Substrate **5** E : Z	Electrophile	t/min[c]	Product Yield (%)	**9** : **10**
1	−105	THF	13 : 87	CD_3OD (neat)	10		88 : 12
2	−105	THF	13 : 87	CD_3OD (neat)	60		88 : 12
3	−107	THF	98 : 2	CD_3OD (neat)	5.5		41 : 59
4	−104	THF	98 : 2	CD_3OD (neat)	20	70	41 : 59
5[d]	−106	THF	98 : 2	CD_3OD (2.74 M in THF)	15 + 30		41 : 59
6	−106	THF	13 : 87	MeI (2.01 M in THF)	30		90 : 10
7	−104	THF	98 : 2	MeI (neat)	20	70	43 : 57
8	−107	THF + HMPA (4 equiv.)	15 : 85	CD_3OD (0.95 M in THF)	15	67	86 : 14
9	−104	THF + HMPA (1 equiv.)	98 : 2	CD_3OD (1.06 M in THF)	20		41 : 59
10[e]	−103	Pentane + THF (1 equiv.)	98 : 2	CD_3OD (1.06 M in THF)	50	70	42 : 58
11	−78	THF	13 : 87	CD_3OD (neat)	90	62	94 : 6
12	−78	THF	98 : 2	CD_3OD (neat)	90		94 : 6
13	−78	THF	13 : 87	MeI (2.01 M in THF)	90	81	94 : 6

[a] Reactions were normally carried out with a 0.20 M solution of **5** in THF and with 1.2 equiv. of a 1.6 M solution of $\mathrm{Bu^tLi}$ in pentane. [b] All reactions were carried out with $\mathrm{Bu^tLi}$ and substrate solutions precooled to the given temperature. [c] Time between the start of the reaction and the addition of the electrophile (‘15 + 30’ means that the substrate was added over 15 min to the $\mathrm{Bu^tLi}$ solution and stirred for further 30 min before CD_3OD was added). [d] Substrate concentration: 0.02 M, $\mathrm{Bu^tLi}$ concentration: 0.08 M. [e] Substrate concentration: 0.10 M.



Scheme 3

into the S–C_i σ*-orbital. Next, a rotation about the C_α–C_β bond ensues to render the groups S–C_α–C_β–C_γ antiperiplanar, due to the quaternary nature of C_γ. Thus, the cyclization of (*E*)-**11** and (*Z*)-**11** leads to two distinct ion pairs **12** and **13**. Interconversion between the ion pairs **12** and **13** would require carbanion inversion and rotation about the C_α–S bond, a process which should be slow at −110 °C,[5] but could be viable at −78 °C. The change in the stereochemistry of the carbolithiation reaction is then attributed to an inversion at the carbanion centre, which is calculated to have a rather low (<2.5 kcal mol^{-1}) activation barrier.[13] This inversion to give **12a** and **13a** could therefore be competitive with or faster than the collapse of the ion pairs **12** and **13** to the configurationally stable organolithium compounds **7** and **8**. It should be noted, however, that the same stereoselectivity is observed in the absence or presence of HMPT and that further experiments may be needed to prove or to modify the interpretation given.

The carbolithiation of vinyl sulfides in THF was found to be non-stereospecific regarding formation of the new lithium-bearing stereocentre. This suggests that carbolithiation proceeds in a non-concerted fashion, in which collapse of an ion pair determines the configuration of the lithium-bearing centre at the migration terminus.

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Footnotes and References

* E-mail: rwho@ps1515.chemie.uni-marburg.de

† The starting materials (*Z*)- and (*E*)-**5** were prepared using routes similar to the ones outlined in ref. 6.

1 W. F. Bailey and T. V. Ovaska, *Advances in Detailed Reaction Mechanisms*, ed. J. M. Coxon, JAI Press, Greenwich, CT, vol. 3, 1994, pp. 251–273. For more relevant studies, see I. Goldham and R. Hufton, *Tetrahedron Lett.*, 1995, **36**, 2157; *Tetrahedron*, 1996, **52**, 12 541; I. Goldham, R. Hufton and D. J. Snowden, *J. Am. Chem. Soc.*, 1996, **118**, 5322; M. P. Cooke and J.-J. Huang, *Synlett*, 1997, 535; W. F. Bailey, X. L. Jiang and C. E. McLeod, *J. Org. Chem.*, 1995, **60**, 7791; W. F. Bailey and E. R. Punzelan, *Tetrahedron Lett.*, 1996, **37**, 5435; W. F. Bailey and M. W. Carson, *Tetrahedron Lett.*, 1997, **38**, 1329.

2 L. R. Subramaniam, *Methoden der Organischen Chemie (Houben-Weyl)*, ed. M. Hanack, Thieme, Stuttgart, vol. E19d, 1933, pp. 744–747.

3 A. Krief, B. Kenda and B. Remacle, *Tetrahedron*, 1996, **52**, 7435.

4 A. Krief and P. Barbeaux, *J. Chem. Soc., Chem. Commun.*, 1987, 1214; A. Krief, B. Kenda, C. Maertens and B. Remacle, *Tetrahedron*, 1996, **52**, 7465.

5 R. W. Hoffmann, R. K. Dress, T. Ruhland and A. Wenzel, *Chem. Ber.*, 1995, **128**, 861.

6 H. C. Stiasny and R. W. Hoffmann, *Chem. Eur. J.*, 1995, 619.

7 A. Krief, D. Derouane and W. Dumont, *Synlett.*, 1992, 907.

8 A. Krief and P. Barbeaux, *Tetrahedron Lett.*, 1991, **31**, 417.

9 G. W. Klumpp, *Recl. Trav. Chim. Pays-Bas*, 1986, **105**, 1; B. Mudryk and T. Cohen, *J. Org. Chem.*, 1991, **56**, 5761; R. F. Schmitz, F. J.-J. de Kanter, M. Schakel and G. W. Klumpp, *Tetrahedron*, 1994, **50**, 5933; F. Chen, B. Mudryk and T. Cohen, *Tetrahedron*, 1994, **50**, 12 793.

10 B. Mudryk and T. Cohen, *J. Am. Chem. Soc.*, 1993, **115**, 3855.

11 R. L. Funk, G. L. Bolton, K. M. Brummond, K. E. Ellestad and J. B. Stallman, *J. Am. Chem. Soc.*, 1993, **115**, 7023; W. F. Bailey, X.-L. Jiang and C. E. McLeod, *J. Org. Chem.*, 1995, **60**, 7791; W. F. Bailey and X.-L. Jiang, *J. Org. Chem.*, 1996, **61**, 2596.

12 J. Smid, *Ions and Ion Pairs in Organic Reactions*, ed. M. Szwarc, Wiley-Interscience, New York, vol. 1, ch. 3, 1972, pp. 106–110; G. Boche and F. Heidenhain, *J. Am. Chem. Soc.*, 1979, **101**, 738.

13 R. K. Dress, T. Rölle and R. W. Hoffmann, *Chem. Ber.*, 1995, **128**, 673.

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