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ON THE CONFIGURATIONAL STABILITY OF α-PHENYLSELENO-ALKYL-LITHIUM COMPOUNDS

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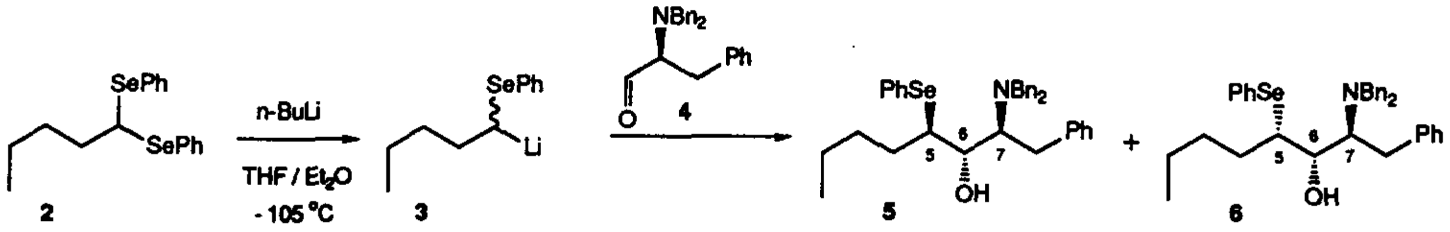
Summary: Using a test based on kinetic resolution the α-phenylseleno-alkyllithium compounds **3** have been shown to undergo enantiomer equilibration at -105°C with a rate comparable to that of their addition to aldehydes. At -125°C in Me-THF as solvent, the α-phenylseleno-alkyllithium compounds **10** were found to be configurational stable for at least 6 hours.

Chiral α-heterosubstituted alkyl-lithium compounds **1** could serve as valuable reagents in stereoselective synthesis, provided they are configurationally stable. This holds for the MOM derivatives **1a**,[1] which Still [1a] showed to be configurationally stable up to -30°C in THF.

1 a: X = OMOM   **c**: X = Br
b: SPh   **d**: SePh

The related phenylthio derivatives **1b** equilibrate fairly rapidly at -78°C in THF,[2] but individual stereoisomers of **1b** may be trapped selectively by fast intramolecular processes.[3] As far as the corresponding bromo derivatives **1c** go, recent results [4] suggest them to be configurationally stable at -110°C in a Trapp solvent mixture.[5] Moreover, the phenylseleno derivatives **1d** appeared to equilibrate rapidly at -78°C in ether.[6] This is in line with similar observations by Krief [7] and Reich [8] on α-phenylseleno-cyclohexyllithium derivatives in THF at -78°C. We would like to show here that compounds of the type **1d** equilibrate at a measureable rate at -105°C in THF/ether mixtures and are configurationally stable at -120°C in methyltetrahydrofuran for at least several hours.

We have recently developed a test,[9] by which the rate of configurational equilibration of an organolithium compound **1** can be compared to the rate of trapping of **1** by an electrophile. The test is based on kinetic resolution and can be applied to the racemic organolithium compounds **1**. In order to get information on the α-phenylseleno-pentyl-lithium reagent **3**, it was generated from the selenoacetal **2** and treated at -105°C with racemic N,N-dibenzyl-phenylalaninal **4**.[10] Due to the high asymmetric induction from the stereogenic centre in the aldehyde only two diastereomeric products **5** and **6** (instead of four isomers) were obtained in 97% yield. While the



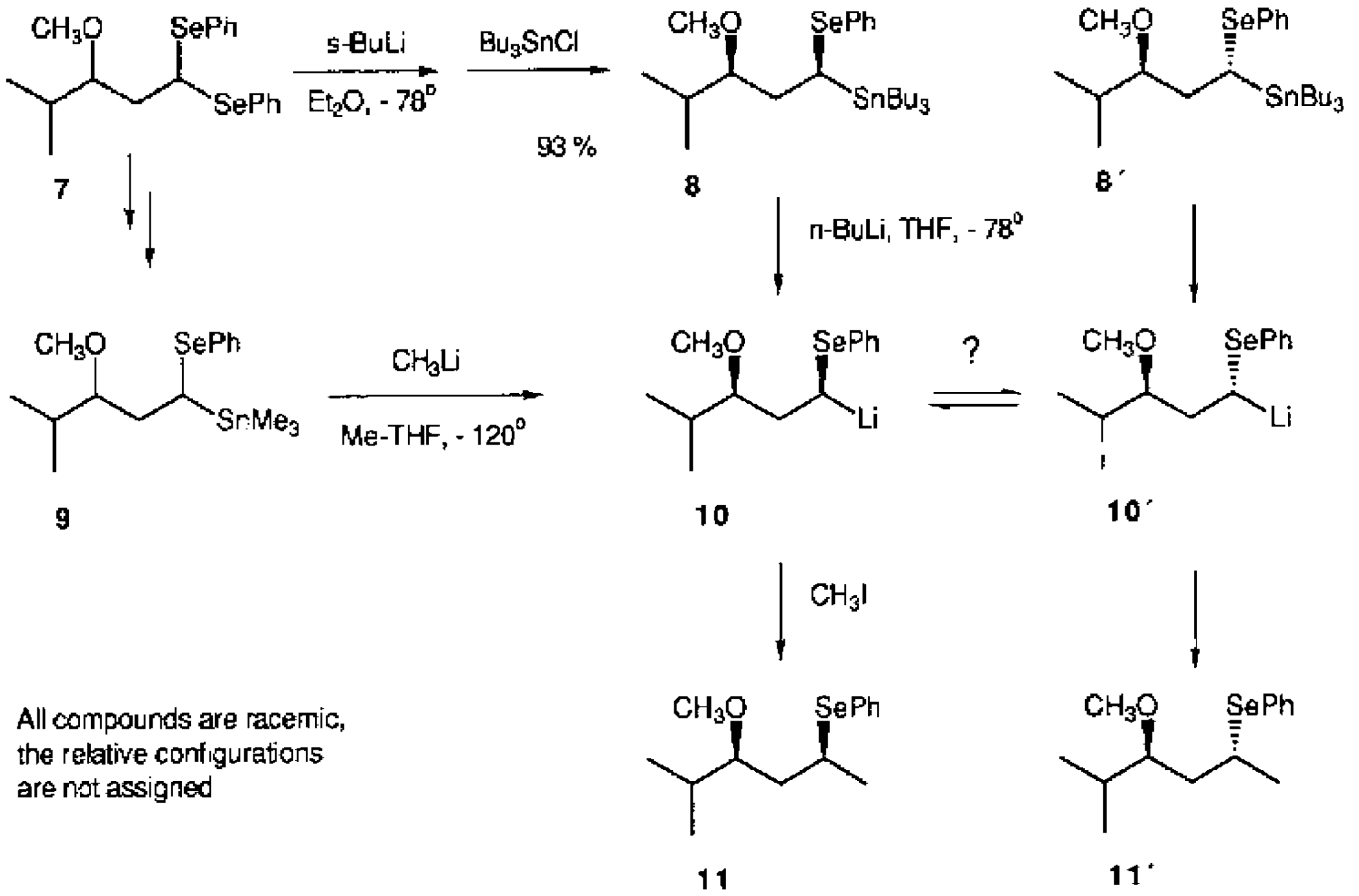
	rac - 4	93 %	68	:	32
	(S) - 4	97 %	53	:	46
Inverse Addition to	(S) - 4	83 %	50	:	50

configuration of the products has not been ascertained, precedent[10] suggests that the adducts **5** and **6** have the same relative configuration at C-6 and C-7. The diastereomer ratio was determined by analytical HPLC to be 68:32 (stereoisomers unassigned).

This level of kinetic resolution in the reaction of e.g. (S)-**3** with (S)-**4** and (R)-**4** is sufficient and optimal for carrying out the test experiments. To this end, the organolithium compound **3** was trapped by enantiomerically pure (S)-**4**, giving again the products **5** and **6**, but in a different ratio (54:46). The mere fact, that the two experiments gave different product ratios, is evidence that the equilibration of $\mathbf{3} \rightleftharpoons$ ent-**3** is slower than the addition of **3** to the aldehyde **4**. The product ratio of the second experiment approaches the value of 50:50, which would result on complete reaction of both enantiomers of **3**, provided they are configurationally stable. A value between 50:50 and that defined by kinetic resolution (68:32) could also result, if the rates of trapping of **3** by the aldehyde **4** and of the enantiomer equilibration of **3** are of the same magnitude. In this case, a higher rate of trapping, e.g. a higher aldehyde concentration, should bring the product ratio closer to 50:50. We therefore added the lithium compound **3** to a 10.4-fold excess of the aldehyde **4**. The ratio of the products varied over several runs between 50:50 and 53:47.

This test indicated qualitatively that the individual enantiomers of **3** have sufficient life times at -105°C to be trapped by electrophiles without racemisation. More quantitative information was sought using the classical technique[1, 2] starting from individual isomers of **1d** which contain a further stereogenic center as an internal reference point: The seleno acetal **7** was converted into the diastereomeric tin-seleno compounds **8** (unassigned ratio 36:64) which were separated by MPLC.

Tin-lithium exchange on **8** with n-butyllithium required ca. 2 h at -100°C in THF. Subsequent trapping of the resulting organolithium compounds **10** with acetone proceeded only in low yield (45%) due to concomitant enolization. Much higher yields (90-95%) were attained by trapping of **10** with methyl iodide. Starting from a 1:2 mixture of **8** the two diastereomers of **11** were obtained in a 3:1 ratio (by ^{13}C-NMR, structures unassigned). Starting from the individual isomers of **8** mixtures of **11** of the same diastereomeric



All compounds are racemic, the relative configurations are not assigned

composition (75:25) were obtained. Thus, the α-phenylselenoalkyl-lithium compounds **10** had fully equilibrated over a 2 h period in THF at -100°C.

Experiments at still lower temperatures required a different solvent (methyl-THF) and a tin-precursor, from which the organolithium compounds **10** can be generated more rapidly. Thus, a mixture of the trimethyltin derivatives **9** was obtained as above in 93% yield (37:63 diastereomer ratio). Addition of this mixture at -120°C to methyllithium in methyl-THF followed after 6 h by CH_3I (45 min) gave the seleno compounds **11** in 79% yield in a 38:62 ratio. The diastereomeric tin derivatives **9** could be separated by MPLC. The minor one took 6 h to react with methyllithium at -120°. Quenching with CH_3I gave a 16:84 diastereomer ratio of **11**. The major diastereomer of **9** reacted over 2 h with methyllithium at -120°C. Trapping with CH_3I gave a 92:8 diastereomer ratio of **11**. Therefore equilibration between the diastereomeric lithium compounds **10** had occurred to only a small extent. This happened probably during the addition of the insufficiently precooled (-78°C) solution of **9**, as reaction of the major diastereomer of **9** with methyllithium at -120°C and quenching <u>after 3 or 6 h</u> resulted in identical 92:8 product ratios of **11**. This value does not represent the thermodynamic ratio of the lithio compounds **10** in methyl-THF, because starting from either isomer of **8** equilibrated mixtures of **10** could be generated by treatment with n-butyllithium in methyl-THF at -78°C. Slow cooling to -120°C followed by quenching with CH_3I gave the diastereomers of **11** in a 65:35 ratio, representing the thermodynamic ratio of the organolithium epimers **10**. Hence, the individual isomers of **10** must be stable for more than 3 h at -120°C in methyl-THF.

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Representative NMR-data: ^{1}H NMR (300 MHz, $CDCl_3$); ^{13}C NMR (75 MHz, $CDCl_3$). **5/6** major diasteromer: 0.92 (t, J = 7.1 Hz, 3H), 1.10 - 1.35 (m, 5H), 1.52 - 1.72 (m, 1H), 2.19 (broad d, 1H), 2.96 (dd, J = 14.2 and 5.1 Hz, 1H), 3.09 (dd, J = 14.2 and 6.8 Hz, 1H), 3.20 (dt, J = 5.3 and 7.0 Hz, 1H), 3.53 (s, 4H), 3.66 (m, 1H), 4.01 (m, 1H), 7.08 - 7.49 (m, 20H). - 14.1, 22.7, 27.8, 31.0, 33.0, 53.4, 54.0, 60.5, 74.6, 125.7 - 129.6, 134.8, 139.5, 141.7. - Minor diasteromer: 0.75 (t, J = 7.1 Hz, 3H), 0.96 - 1.28 (m, 5H), 1.35 - 1.49 (m, 1H), 2.81 - 2.99 (m, 3H), 3.05 (dd, J = 13.9 and 7.3 Hz, 1H), 3.19 (dt, J = 2.5 and 6.7 Hz, 1H), 3.66 and 3.78 (AB-system, J = 14.2 Hz, 4H), 3.81 (m, 1H), 7.25 - 7.48 (m, 20H). - 13.8, 22.1, 29.9, 31.5, 31.6, 54.6, 56.2, 60.5, 73.0, 125.7 - 129.6, 135.1, 140.1, 140.9. - **11** major diastereomer: 17.0, 18.2, 24.0, 29.7, 37.3, 38.5, 57.7, 84.0, 127.3, 128.8, 129.1, 135.1. - Minor diastereomer: 17.3, 17.9, 21.7, 29.7, 35.8. 38.0, 57.1, 83.5, 127.2, 128.8, 129.5, 134.6.

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