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Configurational Stability of Chiral Organolithium Compounds on the Time Scale of their Addition to Aldehydes

Reinhard W. Hoffmann, Manfred Julius, Fabrice Chemla, Thomas Ruhland, and Gerlinde Frenzen *

Philipps-Universität Marburg
Fachbereich Chemie
D - 35032 Marburg

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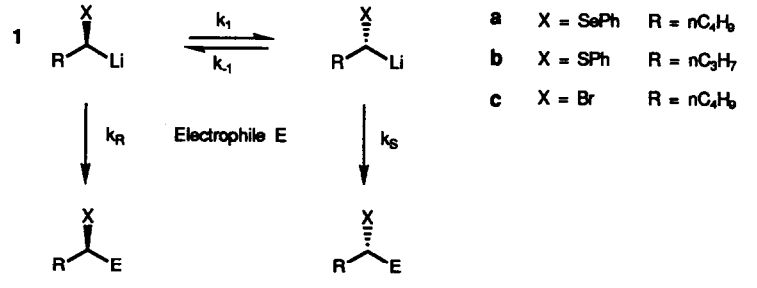
Abstract: *A test based on kinetic resolution has been applied to the α-bromo-, α-phenylseleno- and α-phenylthio-alkyllithium compounds 1, which shows that addition of these species to the chiral aldehyde 6 occurs faster than enantiomer equilibration of the organolithium compounds.*

Introduction

Chiral α-substituted organolithium compounds should be ideal synthons in stereoselective synthesis, provided they are configurationally stable and react with electrophiles in a stereodefined manner. The latter condition is generally given, substitution with retention of configuration is the rule.[2] Configurational stability on the other hand depends on the nature of the heteroatom X, the solvent, and foremost on the temperature. Notions begin to emerge[3] on the mechanism, by which such chiral organolithium compounds racemize.



Scheme 1

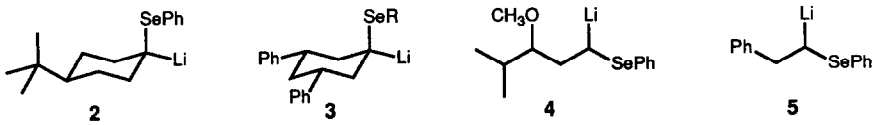
For preparative applications, the minimal information required is, whether a given chiral organolithium compound racemizes more slowly or more rapidly than it adds to an electrophile, for example an aldehyde. This particular information can be gathered by a test, recently introduced by Hoppe[4] and ourselves.[4,5] We detail here our studies on the α-phenylseleno-,[6] α-phenylthio-,[7] and α-bromo-substituted[8] alkyllithium reagents.

The test is based on kinetic resolution and has been described in detail elsewhere.[5,7] In short, the occurrence of sufficient kinetic resolution (k_R/k_S = 1.5 - 3) on reaction of a racemic organolithium compound 1

with a chiral electrophile is established in experiment (1) using the electrophile as a racemate. In a second experiment, "experiment (2)", the racemic organolithium compound **1** is added to the enantiomerically pure electrophile and the ratios of the diastereomeric products resulting from the two experiments are compared. If they are identical at conversions of >50% the organolithium compound is configurationally labile on the time scale set by the rate of its addition to the electrophile. If the diastereomer ratios differ in an analytically significant manner, enantiomer equilibration of the organolithium compound is slower than its addition to the electrophile.

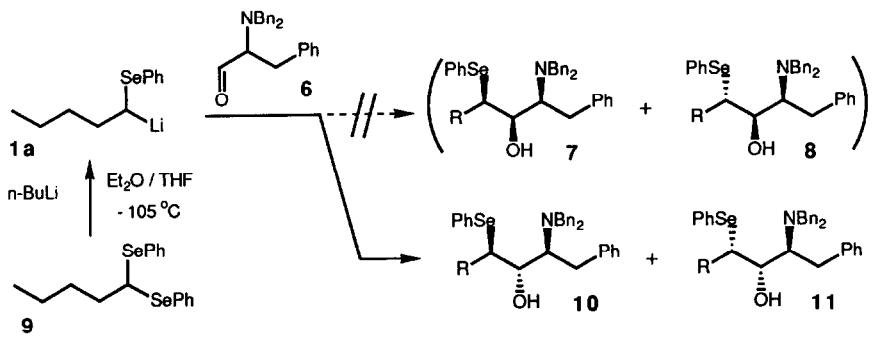
The α-Phenylseleno alkyllithium Compound 1a

Previous studies on the secondary α-phenylseleno-alkyllithium compound **2**[9] and **3**[10] revealed that these species are configurationally labile on a macroscopic time scale of minutes at -78°C. Trapping by standard electrophiles was found to be more rapid than diastereomer equilibration of **2** or **3**.



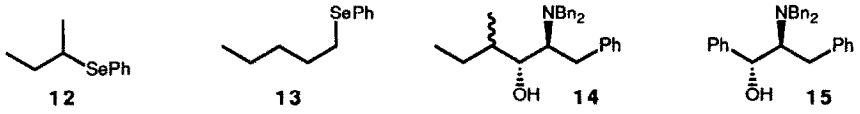
2 **3** **4** **5**

Regarding primary α-phenylseleno-alkyllithium compounds our own studies on compounds of type **4** indicate, that epimerisation is rapid at -100°C in THF, whereas it is slow over an hour at -120°C in methyl-THF.[6] Moreover, the enantiomerisation barrier of **5** has been determined by NMR-spectroscopic methods to be 12.4 kcal at 0°C in THF.[3] Thus, the α-phenylseleno-alkyllithium compounds are a well studied system, suitable for establishing the validity of the above mentioned test. We chose N,N-dibenzyl-phenylalaninal **6** [11] as the chiral electrophile, because it shows good reactivity towards a wide range of organolithium reagents.[12] On addition of simple organolithium reagents to **6** a new stereogenic center is created. However, asymmetric induction from the resident stereocenter in **6** is high, such that essentially only one diastereomeric adduct results. Therefore, on reaction of the chiral organolithium compound **1** with **6** we would expect the formation of only two adducts **10** and **11**, instead of a total of four possible adducts (including **7** and **8**).



The investigation was started with bis-phenylseleno-pentane **9**, prepared according to ref.[13]. The organolithium compound **1a** was liberated from the acetal by treatment with 1.2 equivalents of sec-butyllithium in a Trapp solvent mixture[14] at -80°C. 1.2 equivalents of the aldehyde rac-**6** was added. After a period of 1.5 h the mixture was hydrolysed. Chromatographic separation yielded 66% of the adducts **10** and **11** in a 67:33 ratio. In search for the other diastereomeric products **7** and **8**, 47% of **12**, 15% of **13**, 2% of a 1:1-

diastereomeric mixture of **14**, and 7% of **15** were obtained. The latter arises probably from phenyllithium generated from **12** and s-butyllithium. We found no noticeable amount of the adducts **7** or **8**. Moreover, the ^{77}Se-NMR-spectrum of the crude product from a reaction of **1a** (generated from **9** with n-butyllithium), with **6** showed a signal for **10** at 326 ppm, and for **11** at 293 ppm, but no further signals besides that of n-butyl-phenylselenide (298 ppm).



The test mentioned above can be carried out if the compounds obtained are **7** or **10** *and* **8** or **11**. The structures need not to be assigned. The test could not be carried out, if unexpectedly the two products were **7** *and* **10**, or **8** *and* **11**. For this reason we wanted to establish the identity of the products obtained at least in one case. The major diasteromer **10** crystallized. Hence, its structure could be assigned by X-ray crystal analysis, cf. fig. 1. The minor isomer, **11**, was converted into a crystalline 3,5-dinitrobenzoate, again allowing structural assignment by X-ray crystal structure analysis, cf. fig. 1.

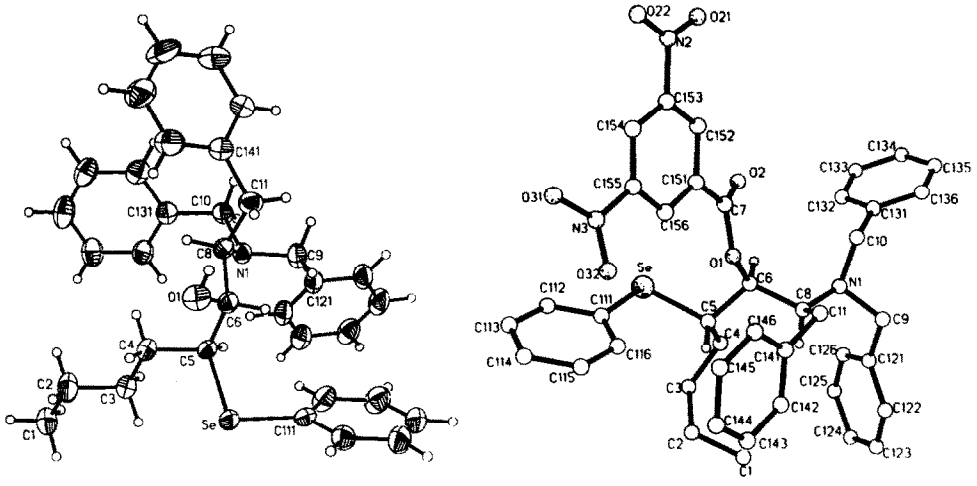
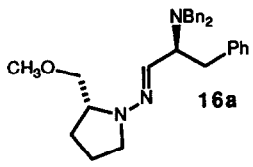


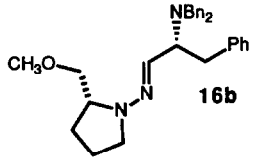
Fig. 1. X-Ray structures of (2S*,3S*,4R*)-2-(N,N-dibenzylamino)-1-phenyl-4-phenylseleno-3-octanol (**10**) and of (2S*, 3S*, 4S*)-2-(N,N-dibenzylamino)-3-(3,5-dinitrobenzoyloxy)-1-phenyl-4-phenylseleno-octane.[15]

This way it was secured that the diastereomeric products **10** and **11** obtained differed only in the configuration of the selenium-bearing carbon atom. It follows that the diastereomer ratio 67:33 reflects the kinetic resolution on reaction of **1a** with the aldehyde **6**. This kinetic resolution is in the optimal range[5] for carrying out the test. For experiment (2) of the test, enantiomerically pure aldehyde **6** is required. The aldehyde should maintain its enantiomeric purity during the test reaction, i.e. it should not (partially) racemize. In order to establish this fact, racemic aldehyde **6** was converted into a 1:1 mixture of the RAMP-hydrazones **16a** and **16b**, which showed distinguishable ^{1}H- and ^{13}C-NMR-data. Next, the α-phenylseleno-alkyllithium-compound **1a** was allowed to react with an excess of the (S)-aldehyde **6**. The recovered aldehyde was con-

verted into its RAMP-hydrazone **16**, which was shown by NMR-spectroscopy to be diastereomerically pure. Hence, there is no racemization of **6** under the reaction conditions. This conforms to findings by Drewes[16] that **6** does racemize to less than 1% on addition of methyllithium or phenylmagnesium bromide.



16a



16b

Finally, the test requires the accurate determination of the diastereomer ratio of **10** and **11**. This could be realized either by ^{77}Se-NMR-spectroscopy or by HPLC-analysis. The latter allowed also the determination of the yields of **10** and **11** with reference to 4,4-di-tert-butyl-biphenyl as an internal standard.

Armed with this information, experiment (2), e.g. reaction of **1a** with (S)-**6** has been run. Using the inverse addition technique recommended for experiment (2)[5] and a tenfold excess of (S)-**6** at -78°C the diastereomers **10** and **11** were generated in 93% yield and in a 56:44 ratio. The difference between the diastereomer ratio of experiment (1) and (2) clearly establishes that the organolithium compound **1a** is trapped more rapidly by the aldehyde **6** than is racemizes. This situation is defined by the ratio of two rate constants, k_1 and k_R or k_S respectively (cf. scheme 1). This ratio could be temperature- as well as solvent-dependent. For this reason the test runs were repeated at various temperatures in a Trapp solvent mixture and once in diethyl ether. The results are compiled in table 1.

Table 1

Diastereomer ratios **10/11** Obtained on Reaction of **1a** with 2 Equiv. of rac-**6** and with 10 Equiv. of (S)-**6**

Temp. (°C)	Solvent	Expt. (1) [a]		Expt. (2) [b]		
		Conversion (%)	Diastereomer ratio	Conversion (%)	Diastereomer ratio Found	Calculated[c]
-105	Trapp	93	68.5 : 31.5	83	53.0 : 47.0	54 : 46
-105	Et_2O	98	62.4 : 37.6	80	52.0 : 48.0	53 : 47
- 80	Trapp	93	67.4 : 32.6	93	56.1 : 43.9	52 : 48
- 40	Trapp	81	65.4 : 34.6	89	58.2 : 41.8	52 : 48

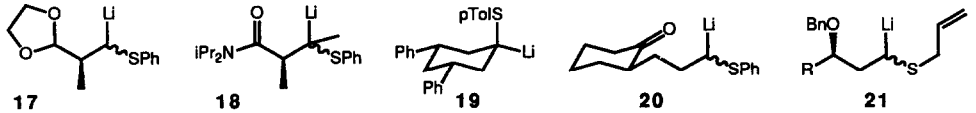
[a] Addition of rac-**6** to **1a**; [b] Additon of **1a** to S-**6**; [c] Calculated for configurationally "stable" **1a** based on the extent of conversion.

The data in table 1 show that the kinetic resolution (experiment (1)) is not markedly influenced by the temperature or by changing the solvent from a Trapp-solvent-mixture to diethyl ether. In all of the experiments (2) the diastereomer ratio approached the ultimate value of 50:50, but did not reach this value in any case. In fact, the diastereomer ratios for the -105°C runs of experiment (2) correspond within $\pm$ 2% to values calculated[5] based on conversion and the kinetic resolution factor. The diastereomer ratios of the experiments (2) carried out at higher temperatures (-80°C, -40°C), deviate increasingly (4%, 6%) from the calculated values. These deviations in the directions of the diastereomer ratios of experiment (1) are not large enough to

prove, but they suggest that the enantiomer interconversion rate of **1a** is at these higher temperatures no longer substantially, but only marginally faster than the rate of trapping of **1a** by the aldehyde **6**. This would be quite reasonable for a competition between an unimolecular racemization having a small negative activation entropy (-2.5 e.u.),[3] with a bimolecular reaction having probably a substantially more negative activation entropy.

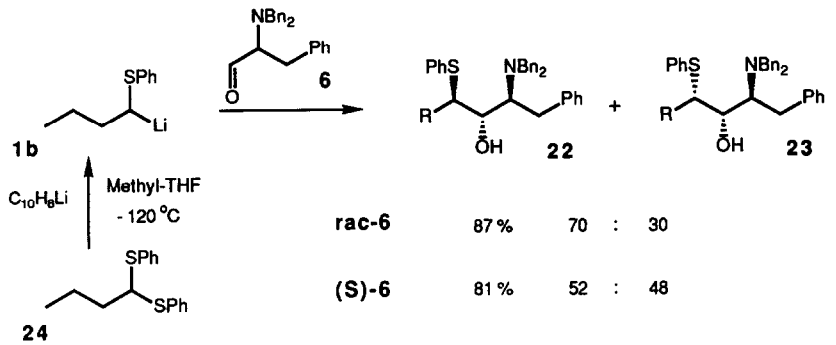
The α-Phenylthio-alkyllithium Compound 1b

Since the results with the α-phenylseleno-alkyllithium compound **1a** signaled that the rate of trapping by **6** is only marginally faster than the enantiomer equilibration we became interested in the situation with the analogous sulfur-substituted organolithium compound **1b**. Previous studies by McDougal on **17**[17] and by Beak on **18**[18] established that the compounds undergo diastereomer equilibration at -78°C in THF over a macroscopic time scale.



17 **18** **19** **20** **21**

Reich[10] showed that **19**, if generated in the presence of trimethylchlorosilane, is trapped by the latter reagent at a comparable rate to its epimerization. When trapping occurs in an intramolecular fashion, as with **20** [19] or **21** (2,3-sigmatropic rearrangement)[20] any epimerization of the α-thio-substituted organolithium compounds has been completely suppressed. Against this background it is of interest whether intermolecular trapping of **1b** by an aldehyde would be faster than the racemization or not. To clarify this point, the lithium compound **1b** was generated from the thioacetal **24**[21] in methyl-tetrahydrofuran. The resulting solution was cooled to -120°C and treated with the aldehyde rac-**6**. This gave in 87% yield two diastereomeric products, to which we assign the structures **22** and **23** in analogy to **10** and **11**.



It should be recalled that the above mentioned test does not require a structural assignment of the individual diastereomers. Their ratio (70:30) indicates the occurrence of sufficient kinetic resolution in this reaction. Next, experiment (2) using inverse addition of **1b** to the enantiomerically pure aldehyde **6** was carried out, leading to **22** and **23** in a 52:48 ratio. The difference in the diastereomer ratios establish that trapping of **1b** by **6** is faster than enantiomer equilibraton of **1b**.

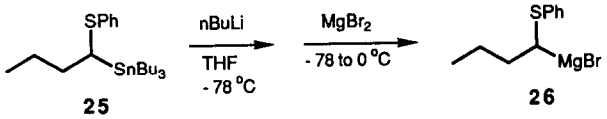
The test was then extended to include the corresponding Grignard reagent **26**. The latter was much less reactive than **1b** and required hours to react with the aldehyde rac-**6** at -40°C in THF. To our surprise, only a single diastereomer, **22**, was obtained. The yield increased from 29% after 5 h to 46% after 20 h. Further

extension of the reaction time to 60 h led to no further increase in yield. In order to attain higher yields, we turned to diethyl ether as solvent. Here, the reaction has to be carried out at 0°C to attain a yield of >50%. The results for the "test"-experiments carried out in diethyl ether or in dichloromethane are summarized below.

Diastereomer ratios **22** : **23** Obtained on Reaction of **26** with 2 Equiv. of rac-**6** and with 10 equiv. of (S)-**6**

Temp. (°C)	Solvent	Expt. (1) Conversion (%)	diastereomer ratio	Expt. (2) conversion(%)	Diastereomer ratio
0°	Et_2O	77	100 : 0	80	63 : 37
0°	CH_2Cl_2	61	100 : 0	49	71 : 29

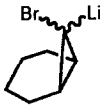
It is apparent that kinetic resolution on reaction of **26** with **6** is high (k_R/k_S > 10) since only one diastereomer, **22**, is formed. This high kinetic resolution would require an excessive reaction time in experiment (2) to reach conversions of >50%. The reaction time is, however, limited by the low chemical stability of **26** at 0°C. It is thus understandable, that the diastereomer ratio in experiment (2) did not reach the value 50:50 which would be expected for configurationally stable **26**. Rather the difference between 100:0 in experiment (1) and ≈ 70:30 in experiment (2) is sufficient to draw the conclusion that **26** adds at 0°C more rapidly to the aldehyde **6** than it racemizes. These results therefore suggest a considerable potential of chiral α-heterosubstituted Grignard reagents in stereoselective synthesis.



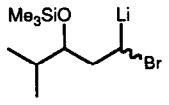
25 **26**

The α-Bromo-alkyllithium Compound 1c

The test on the configurational stability of chiral organolithium compounds could be applied as well to α-bromo-alkyllithium compounds.[22] Earlier studies had been made on a large set of α-bromo-cyclopropyl-lithium compounds such as **27**.[23]



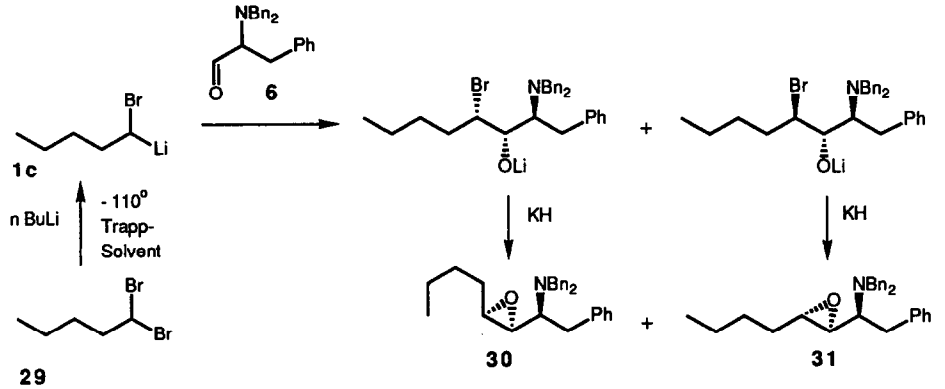
27



28

We started to gather information in the acyclic series in a study on the organolithium compounds **28**. These were found[24] to be configurationally stable for at least an hour at -110°C in a Trapp-solvent mixture.[14] Moreover the constant product ratios on trapping of **28** with various electrophiles for a given set of conditions [25] suggested that trapping is more rapid than the diastereomer equilibration of **28**. In order to verify this assumption the above mentioned test was applied to the α-bromo-alkyllithium compounds **1c**. The latter were generated from 1,1-dibromopentane (**29**)[26] with n-butyllithium in a Trapp-solvent-mixture.[14] After the reacti-

on of **1c** with rac-**6** the mixture was allowed to reach room temperature, which initiated the conversion of the ß-bromo-alkoxides into epoxides. The latter reaction was completed by addition of potassium hydride. Eventually the reaction furnished two diasteromeric adducts **30** and **31**.



The cis- or trans-disubstitution at the oxirane-ring was readily evident from the ^{1}H- and ^{13}C-NMR-data. Since the cis-isomer predominated, simple diastereoselection on addition of **1c** to **6** is opposite in direction to that in the addition of **1a** to **6**.[27] The relative configuration at the nitrogen-bearing stereocenter was assigned according to the precedent set by Reetz's investigations.[12] In the test on the configurational stability of **1c** experiment (1) with racemic **6** furnished a 71% yield of **30** and **31** in a 60:40 ratio. Sufficient kinetic resolution being thus established, experiment (2) was carried out to give 81% (analytically determined) of **30** and **31** in a 50:50 ratio. This experiment was carried out by the normal addition mode. In as much as a 50:50 diastereomer ratio was reached, there was no necessity to go to the inverse addition technique. The fact that experiment (2) resulted in a 50:50 diastereomer ratio showed that the α-bromo-alkyllithium compound **1c** adds to **6** more rapidly than its racemizes, in accord with the above mentioned conjectures.

Conclusion

By the above mentioned test it could be established that the alkyllithium compounds bearing an α-bromo- (**1c**), α-phenylseleno (**1a**) or α-phenylthio-group (**1b**) add more rapidly to the chiral aldehyde **6** than they racemize. In the case of **1a** all the necessary control experiments were carried out to establish the validity of the test. It was assumed that these conditions hold equally for the reactions carried out with **1b** and **1c**.

Acknowledgement:These studies have been supported by the Deutsche Forschungsgmeinschaft (SFB 260) and the Fonds der Chemischen Industrie. T.R. thanks the Graduierten-Kolleg "Metallorganische Chemie" at the Universität Marburg for a fellowship.

EXPERIMENTAL

All temperatures are not corrected. - ^{1}H-NMR, ^{13}C-NMR: Bruker AC-300. - ^{77}Se-NMR: Bruker AM-400. - Boiling range of petroleum ether: 40-60 °C; Flash-chromatography: Kieselgel 60 (0.040 - 0.063 mm, E. Merck, Darmstadt). - Medium pressure liquid chromatography: Lichroprep Si60 (E. Merck, Darmstadt), 6 bar, 26 ml/min. - HPLC: Merck-Hitachi L-4000.

1. 1,1-Bis(phenylseleno)-pentane (**9**): To a mixture of 6.30 g (40.1 mmol) of phenylselenol and 1.73 g (20.1 mmol) of pentanal was added over 10 min at 0°C 1.1 ml of concentrated sulphuric acid. The resulting orange solution was stirred for 40 min at room temperature and diluted with 70 ml of ether. The resulting clear solution was washed with 15 ml of saturated aqueous $NaHCO_3$-solution and 20 ml of water. The organic phases were dried with $MgSO_4$ and concentrated to give 6.48 g of a reddish liquid. This was taken up in 50 ml of ether and was added dropwise into a suspension of 0.76 g (20.0 mmol) of lithium aluminium hydride in 75 ml of ether. After stirring for 18 h at room temperature the mixture was held for 40 min under reflux and cooled to 0°C. 5 ml of 50-proc aqueous KOH was added slowly. After the gas evolution had ceased the mixture was filtered over kieselgur which was subsequently washed with 100 ml of ether. The filtrates were dried with $MgSO_4$, concentrated and chromatographed over 300 g of silica gel with petroleum ether to give 5.38 g (70%) of **9** as a yellow liquid. - ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.87 (t, J = 7.3 Hz, 3H), 1.28 (sext., J = 7.4 Hz, 2H), 1.57 (m, 2H), 1.96 (m, 2H), 4.51 (t, J = 6.6 Hz, 1H), 7.26 - 7.36 (6H), 7.54 - 7.64 (m, 4H). - ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8, 22.0, 30.5, 36.8, 44.1 (d, J = 83.7 Hz), 127.9, 129.0, 130.4, 134.6. - $C_{17}H_{20}Se_2$ (382.3) Calcd.: C 53.42, H 5.27; Found C 53.49 H 5.23.

2. Reaction of 1-lithium-1-phenylseleno-pentane (**1a**) with rac-2-(N,N-dibenzylamino)-3-phenyl-propanal(**6**): To a solution of 188.8 mg (0.49 mmol) of 1,1-bis-(phenylseleno)-pentane (**9**) in 4 ml of THF, 1 ml of petroleum ether, and 1 ml of ether was added over 3 min over at -105°C 450 μl(0.60 mmol) of a 1.34 M solution of s-butyllithium in pentane. The resulting yellow solution was stirred for 1.5 h at -85°C. A solution of 196.5 mg (0.60 mmol) of (R,S)-2-(N,N-dibenzylamino)-3-phenyl-propanal (**6**) in 3.8 ml of THF was added dropwise over 7 min. The mixture was stirred for 3 h at -105 °C. 20 ml of saturated aqueous NH_4Cl-solution were added dropwise. The mixture was allowed to reach room temperature, diluted with 10 ml of ether and the phases were separated. The aqueous phase was extracted three times with 15 ml each of ether and the combined organic phases were dried with $MgSO_4$ and concentrated. The yellow residue was separated by flash chromatography with petroleum ether/ether = 12:1. This resulted in: 76.6 mg of a yellow liquid consisting of 60 mg (47 %) of s-butyl-phenyl-selenide (**12**) and 17 mg (15%) of 1-phenylseleno-pentane (**13**). **12**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.00 (t, J = 7.4 Hz, 3H), 1.40 (d, J = 6.9 Hz, 3H), 1.53 - 1.78 (m, 2H), 3.25 (sext., J = 6.7 Hz, 1H), 7.22 - 7.29 (m, 3H), 7.52 - 7.58 (m, 2H). - ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.3, 21.6, 30.4, 41.5, 127.2, 128.8, 129.5, 134.8. - **13**: ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9, 22.1, 27.9, 29.8, 32.0, 126.5, 128.9, 130.7, 132.3.

217 mg of a yellow oil consisting of 182 mg (66%) of **10** and **11** as a 64:36 diastereomer mixture according to ^{1}H-NMR, and 36 mg (18%) of residual **6**.

22.7 mg of a colorless oil consisting of 17.5 mg (7%) of (1R*,2S*)-2-(N,N-dibenzylamino-1,3-diphenyl-1-propanol) (**15**) and 5.2 mg (2%) of (2S*,3R*,4R,S*)-2-(N,N-dibenzylamino)-4-methyl-1-phenyl-3-hexanol (**14**) as a 1:1 diastereomer mixture.

15 was crystallized from petroleum ether, m.p. 128 - 131°C and showed the following ^{13}C-NMR-signals (75 MHz, $CDCl_3$): δ = 31.3, 54.7, 64.6, 73.2, 125.8, 126.8, 127.1, 128.13, 128.2, 128.7, 129.5, 139.8, 140.6, 143.5 as reported by Drewes.[16]

14 showed the following ^{13}C-NMR-signals (75 MHz,$CDCl_3$): δ = 11.2, 11.8, 12.9. 16.0, 23.5, 26.8, 32.0, 32.5, 37.0, 37.6, 54.4, 54.5, 60.4, 61.0, 75.6, 76.4, 125.7 - 129.6, 139.7 - 143.5. - $C_{27}H_{33}NO$ (387.6): Calcd. C 83.68, H 8.58, N 3.61; Found C 83.61, H 8.15, N 3.59.

The mixture of **10**, **11**, was subjected to a second flash chromatography over 29 g of silica gel with petroleum ether/ether = 20:1. (2S*,3S*,4S*)-2-(N,N-dibenzylamino)-1-phenyl-4-phenylseleno-3-octanol (**11**), (minor diastereomer) : R_F (petroleum ether/ether = 6:1) = 0.38 on plates with Kieselgel 60 F-254 (Merck). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 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 (B-part of a ABX-system, J_{AB} = 13.9, J_{BX} = 7.3 Hz, 1H), 3.19 (td, J = 6.7 and 2.5 Hz, 1H), 3.66 and 3.78 (AB-system, J_{AB} = 14.2 Hz, 4H), 3.81 (m, 1H), 7.25 - 7.48 (m, 20 H). - ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8, 22.1, 30.0, 31.5, 31.6, 54.6, 56.2, 60.6, 73.1, 125.7, 126.7, 127.8, 127.9, 128.0, 128.1, 128.7, 129.0, 129.6, 135.1, 140.2, 140.9. - ^{77}Se-NMR (76 MHz, $CDCl_3$): δ = 291.7. - $C_{34}H_{39}NOSe$ (556.6): Calcd. C 73.36, H 7.06, N 2.52; Found C 73.63, H 7.06, N 2.67.

(2S*,3S*,4R*)-2-(N,N-Dibenzylamino)-1-phenyl-4-phenylseleno-3-octanol (**10**), (major diastereomer) : colorless prisms, from petroleum ether m.p. = 84 - 86°C. - R_F (petroleum ether/ether = 6:1) = 0.24. - ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 (t, J = 7.1 Hz, 3H), 1.10 - 1.34 (m, 5H), 1.52 - 1.72 (m, 1H), 2.19 (borad d, J = 3 Hz, 1H), 2.96 (A-part of a ABX-system, J_{AB} = 14.2 Hz, J_{AX} = 5.1 Hz, 1H), 3.09 (B-part of a ABX-system, J_{AB} = 14.2 Hz, J_{BX} = 6.8 Hz, 1H),

3.20 (td, J = 7.0 and 5.3 Hz, 1H), 3.53 (s, 4H), 3.66 (m, 1H), 4.01 (m, 1H), 7.08 - 7.49 (m, 20 H). - ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 22.7, 27.9, 31.0, 33.0, 53.4, 54.1, 60.6, 74.6, 125.7, 126.8, 127.6, 128.1, 128.2, 128.8, 129.0, 129.3, 129.6, 134.9, 139.5, 141.7. - ^{77}Se-NMR (76 MHz, $CDCl_3$): δ = 324.4. $C_{34}H_{39}NOSe$ (556.6): Calcd. C 73.36, H 7.06, N 2.52; Found C 73.27, H 7.12, N 2.72.

From a similar experiment using (S)-2-(N,N-dibenzylamino)-3-phenyl-1-propanal (**6**) was obtained (2S,3S,4S)-2-(N,N-dibenzylamino)-1-phenyl-4-(phenylseleno)-3-octanol (**11**): $[\alpha]_{\lambda}^{20}$ = -4.8 (589); -4.5 (578); -5.7 (436 nm), (c = 0.534, methanol).

(2S,3S,4R)-2-(N,N-dibenzylamino)-1-phenyl-4-(phenylseleno)-3-octanol (**10**): $[\alpha]_{\lambda}^{20}$ = +15.6 (589); +17.3 (578); +20.0 (546); +41.2 (436); +94.5 (365 nm); (c = 0,544 methanol).

For "inverse addition" the solution of **1a** was generated as described above. It was cooled to -108°C and transferred via a canula (cooled with dry ice) into a -105°C cold solution of **6** in 5 ml of THF. After stirring for 3 h at -105°C the mixture was processed as described above.

For determination of the ratio of **10** and **11** as well as of their yield an adequate amount of 4,4'di-tert.-butyl-biphenyl was added to the crude reaction mixture which was analysed HPLC on LiChrospher 100 RP18 with methanol/water, 7:1 to 4:1, 40 - 50 bar, detection at 256 nm. The analytical procedure was calibrated using pure samples of **10**, **11**, and 4,4'-di-tert.-butyl-biphenyl.

3.(2S*,3S*,4S*)-2-(N,N-Dibenzylamino)-3-(3,5-dinitrobenzoyloxy)-1-phenyl-4-phenylseleno-octane: To a solution of 0.31 g (1.3 mmol) of 3,5-dinitro-benzoyl-chloride in 5 ml of CH_2Cl_2 was added at 0°C slowly 0.9 ml (11 mmol) of pyridine and then a solution of 0.62 g (2S*,3S*,4S*)-2-(N,N-dibenzylamino)-1-phenyl-4-phenylseleno-3-octanol (rac-**11**) in 5 ml of CH_2Cl_2. After stirring for 12 h at room temperature the resulting suspension was diluted with 150 ml of CH_2Cl_2, was washed three times with 50 ml each of water and 50 ml of brine and dried with $MgSO_4$. Concentration resulted in a yellowish oil which was crystallized from petroleum ether/ether/dichloromethane = ca. 20:2:1 to give 480 mg (58%) of yellow crystals, m.p. 96-98°C. - ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.78 (t, J = 7.3 Hz, 3H), 1.18 (m, 2H), 1.37 (quint., J = 7.5 Hz, 2H), 1.45 (dq, J = 15.4 and 7.3 Hz, 1H), 1.56 (dq, J = 15.4 and 7.2 Hz, 1H), 2.81 (A-part of an ABX-system, J_{AB} = 15.0 and J_{AX} = 9.4 Hz, 1H), 3.26 (B-part of an ABX-system, J_{AB} = 15.0 and J_{BX} = 4.1 Hz, 1H), 3.64 (A-part of an AB-system, J_{AB} = 13.7 Hz, 2H), 3.88 (B-part of an AB-system, J_{AB} = 13.7 Hz, 2H), 3.77 (td, J = 7.0 and 3.2 Hz, 1H), 4.09 (ddd, J = 9.3, 7.9, and 4.2 Hz, 1H), 5.71 (dd, J = 7.7 and 3.2 Hz, 1H), 6.88 - 7.30 (m, 20H), 8.54 (d, J = 2.2 Hz, 2H), 9.07 (t, J = 2.1 Hz, 1H). - ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8, 22.3, 30.1, 32.1, 33.8, 47.7, 54.7, 60.3, 79.2, 122.0, 125.6, 126.9, 127.4, 128.3, 128.4, 128.5, 128.9, 129.0, 129.2, 129.7, 133.1, 133.2, 138.9, 139.8, 148.2, 162.2. $C_{41}H_{41}N_3O_6Se$ (750.7): Calcd. C 65.59, H 5.50, N 5.60; Found C 65.34, H 5.42, N 5.52.

4. 1-[N-((R)-2-(methoxymethyl)-pyrrolidino)-imino]-2-(R,S)-(N,N-dibenzylamino)-3-phenyl-propane (**16**): To a solution of 19.8 mg (0.06 mmol) of (2R,S)-2-(N,N-dibenzylamino)-3-phenyl-propanal (rac-**6**) in 2 ml of $CDCl_3$ was added 9.1 mg (0.07 mmol) of (R)-1-amino-2-methoxymethyl-pyrrolidine (Merck). After addition of a few crystals of $MgSO_4$ the mixture was heated for 45 min to 50°C. The NMR-spectra of the resulting **16** were recorded. The (2S)-diastereomer showed the following diagnostic signals: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.41 (s, 3H), 3.65 and 3.82 (AB-System, J_{AB} = 23.9 Hz, 4H), 3.41 (s, 3H), 6.66 (d, J = 5.5 Hz, 1H), 7.10 - 7.39 (m, 15H). - ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.0, 26.6, 35.6, 49.9, 53.8, 59.2, 60.9, 63.5, 74.6, 125.6 - 129.7, 135.3, 140.1, 140.2.

The (2R)-diastereomer showed the following signals: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.44 (s, 3H), 6.67 (d, J = 5.7 Hz, 1H). - ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.0, 26.5, 35.4, 49.6, 53.8, 59.2, 60.8, 63.2, 74.6, 125.6 - 129.7, 135.7, 140.1, 140.2.

5. Reaction of 1-lithio-1-phenylthiobutane (**1b**) with 2-(N,N-dibenzylamino-3-phenyl-propanal (**6**): A solution of 0.77 g (6 mmol) of naphthalene in 15 ml of anhydrous methyl-tetrahydrofurane was stirred for 12 h at -60°C with 42 mg (6 mmol) of lithium powder. 0.82 g (3 mmol) of 1,1-di-(phenylthio)-butane (**24**) were added and the mixture was stirred for 1.5 h at -60°C and cooled to -120°C. A solution of 1.45 g (4.5 mmol) of 2-(N,N-dibenzylamino-3-phenyl-propanal (**6**) in 15 ml of 2-methyl-THF was added dropwise. The mixture was stirred for 5 h at -120°C and poured into 50 ml of brine. The mixture was extracted sequentially with 20 ml of ether, 25 ml of CH_2Cl_2 and the combined extracts were dried with Na_2SO_4. Concentration gave 2.80 g of a yellow oil. The ratio of the diastereomeric adducts **22** and **23** was

determined by ^{13}C-NMR to be 70:30.

The products were separated by MPLC with 5% ethyl acetate in petroleum ether: Major diastereomer, presumably (2S*,3S*,4R*)-2-(N,N-dibenzylamino)-1-phenyl-4-phenylthio-3-heptanol (**22**): ^1H NMR (300 MHz, $CDCl_3$): δ = 0.82 (t, J = 7.0 Hz, 3H), 1.10 - 1.33 (m, 4H), 1.50 - 1.80 (m, 2H), 2.95 (A-part of an ABX-system, J_{AB} = 14 Hz, J_{AX} = 5 Hz, 1H), 3.01 - 3.19 (m, 2H), 3.53 (s, 2H), 3.54 (s, 2H), 3.90 (dd, J = 5.0 and 4.0 Hz, 1H), 7.10 - 7.31 (m, 20H). - ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.1, 21.0, 29.2, 32.9, 54.0, 54.6, 60.2, 73.7, 125.7, 126.8, 127.0, 128.1, 128.2, 128.7, 128.8, 129.5, 132.2, 134.9, 139.3, 141.7. - $C_{33}H_{37}NOS$ (495.9): Calcd. C 79.96, H 7.53, N 2.83; Found C 79.26, H 7.44, N 2.99.

Minor diastereomer presumably (2S*,3S*,4S*)-2-(N,N-dibenzylamino-1-phenyl-4-phenylthio-3-heptanol (**23**): ^1H NMR (300 MHz, $CDCl_3$): δ = 0.61 (t, J = 7 Hz, 3H), 1.09 - 1.20 (m, 3H), 1.35 - 1.43 (m, 1H), 1.60 (broad s, 1H), 2.73 - 2.80 (m, 1H), 2.80 - 3.05 (m, 2H), 3.11 (dt, J = 7.0 and 2.0 Hz, 1H), 3.63 (A-part of an AB-System, J_{AB} = 14 Hz, 2H), 3.74 (B-part of an AB-system, J_{AB} = 14 Hz, 2H), 3.74 (d, J = 2 Hz, 1H), 7.00 - 7.24 (m, 20 H). - ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.5, 19.9, 31.3, 33.7, 54.4, 56.7, 60.5, 72.9, 125.7, 126.6, 127.1, 127.9, 128.0, 128.5, 128.8, 132.2, 132.6, 140.0, 140.7. - $C_{33}H_{37}NOS$ (495.9): Calcd. C 79.96, H 7.53, N 2.83; Found C 79.86, H 8.01, N 3.76.

6. 1-Tri-n-butylstannyl-1-phenylthio-butane (**25**): A solution of lithium diisopropylamide was prepared from 4.5 ml (32 mmol) of di-isopropyl-amine, and 22.1 ml (31 mmol) of a 1.4 N solution of n-butyllithium in hexane in 100 ml of dry THF at 0°C. 7.95 ml (30 mmol) of tributylstannane were added and the resulting bright yellow solution was stirred for 10 min at 0°C. After cooling to -70°C 2.70 ml (30 mmol) of butyraldehyde are added. After stirring for 30 min at -70°C and 30 min at 0°C the solution was poured in 100 ml of aqueous saturated NH_4Cl-solution. The mixture was extracted twice with 50 ml each of ether. The combined extracts were dried with $MgSO_4$ and concentrated i.vac. at room temperature to give 11.4 g of 1-tributylstannyl-1-butanol as a yellowish liquid. The liquid was dissolved in 150 ml of dry dimethylformamide and 6.77 g (31 mmol) of diphenyl disulfide were added. After cooling to 0°C 7.62 ml (31 mmol) of tributylphosphane were added dropwise. After stirring for 3 d at room temperature the solution was poured into 200 ml of saturated aqueous Na_2CO_3-solution and extracted twice with 50 ml each of ether. The combined organic phases were washed twice with 50 ml of saturated aqueous Na_2CO_3-solution, once with 70 ml of brine and dried with $MgSO_4$. Concentration and flash chromatography over silica gel yielded 7.12 g (52%) of **25** as a colorless oil, which was characterized by its spectroscopic data only. - ^1H NMR (300 MHz, $CDCl_3$): δ = 0.81 (t, J = 7 Hz, 3H), 0.85 (t, J = 7 Hz, 9H), 1.28 (m, 10H), 1.43 - 1.51 (m, 10H), 1.71 - 1.75 (m, 2H), 2.96 (t, J = 5.5 Hz, 1H), 7.04 - 7.28 (m, 5H). - ^{13}C NMR (75 MHz, $CDCl_3$): δ = 9.8, 13.6, 14.0, 22.9, 27.4, 28.6, 29.0, 36.1, 125.7, 125.8, 128.3, 138.9.

7. Reaction of 1-phenylthio-1-butyl-magnesium bromide with 2-(N,N-dibenzylamino)-3-phenyl-propanal (**6**): 315 µl (0.44 mmol) of a 1.4 M solution of n-butyllithium in hexane was added to a solution of 200 mg (0.44 mmol) of 1-tributylstannyl-1-phenylthio-butane (**25**) in 4 ml of THF at -78°C. After stirring for 1 h 280 µl(0.44 mmol) of a 1.85 M solution of $MgBr_2$ (prepared from 1,2-dibromoethane and Mg) in ether/benzene = 1:1 are added resulting in the formation of a white precipitate. The mixture is warmed to 0°C until the precipitate dissolves and the colour changes from yellow to colourless. The solvent was removed completely under vacuum at 0°C and the white solid was dissolved in 4 ml of CH_2Cl_2. 290 mg (0.88 mmol) of 2-(N,N-dibenzylamino)-3-phenyl-propanal (**6**) in 1 ml of ether (CH_2Cl_2) was added dropwise. The mixture was stirred for 20 h at 0°C and poured into 20 ml of saturated aqueous NH_4Cl-solution. The phases were separated and the organic phase was extracted once with 10 ml of ether and once with 10 ml of CH_2Cl_2. The combined organic phases were washed with 15 ml of brine, dried with $MgSO_4$ and concentrated to yield 168 mg (77%) of **22** identical to the material obtained under 5.

8. Reaction of 1-bromo-1-lithio-pentane (**1c**) with 2-(N,N-dibenzylamino)-3-phenyl-propanal (**6**): 460 mg (2.0 mmol) of 1,1-dibromopentane were dissolved in 14 ml of THF, 7 ml of petroleum ether, and 9 ml of ether. To this solution was added at -120°C a solution of 3.0 mmol n-butyllithium in hexane, precooled to -78°C. After stirring for 30 min at -120°C a solution of 995 mg (3.0 mmol) of 2-(N,N-dibenzylamino)-3-phenyl-propanal (**6**) in 2 ml of the Trapp-solvent mixture was added dropwise. The mixture was stirred for 3 h at -120°C and then allowed to reach room temperature overnight. A suspension of 120 mg (3.0 mmol) of potassium hydride in 2 ml of petroleum ether was added and the suspension was stirred for 15 min. 2 ml each of 2-propanol, methanol, water and 10 ml of saturated aqueous NH_4Cl-solution were added sequentially. The phases were separated and the aqueous phase was extracted three times with 50 ml

each of ether. The combined organic phases were washed twice with 50 ml each of brine, dried with Na_2SO_4 and filtered through a 3 cm layer of silica gel. The silica gel was washed with ether and the combined filtrates were concentrated. The resulting crude product (920 mg) was purified by flash chromatography with petroleum ether/ether = 15:1 yielding 567 mg (71%) of **30** and **31** followed by minor amounts of (2S*,3R*)-2-(N,N-dibenzylamino)-1-phenyl-3-heptanol (see under 9.).

The mixture of **30** and **31** was subjected to a second flash chromatography using petroleum ether/ether = 20:1 and the separated diastereomers were finally purified by MPLC using petroleum ether/ethyl acetate = 20:1.

(3S*,2R*,1'S*)-3-butyl-2-[1'-(N,N-dibenzylamino)-2'-phenyl-ethyl]-oxirane (**30**) (major diastereomer):^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.84 (t, J = 7.2 Hz, 3H), 1.18 - 1.49 (m, 6H), 2.79 (td, J = 8.7 and 5.2 Hz, 1H), 2.93 (ddd, J = 7.4, 7.4, and 3.7 Hz, 1H), 3.07 (dd, J = 8.7 and 4.0 Hz, 1H), 2.97 (A-part of an ABX-system, J_{AB} = 14.4, J_{AX} = 5.2 Hz, 1H), 3.11 (B-part of an ABX-system, J_{AB} = 14.4 Hz, J_{BX} = 8.7 Hz, 1H), 3.63 (A-part of an AB-system, J = 14.0 Hz, 2H), 3.77 (B-part of an AB-system, J = 14.0 Hz, 2H), 7.09 - 7.37 (m, 15H). - ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9, 22.5, 28.2, 29.1, 35.6, 54.2, 57.6, 58.0, 58.5, 126.0, 126.9, 128.1, 128.2, 128.6, 129.8, 139.6, 139.9. - $C_{28}H_{33}NO$ (399.5): Calcd. C 84.16, H 8.32, N 3.50; Found C 83.56, H 8.18, N 3.63.

(3R*,2R*,1'S*)-3-butyl-2-[1'-(N,N-dibenzylamino-2'-phenyl-ethyl]-oxirane (**31**) (minor diastereomer): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.97 (t, J = 7.0 Hz, 3H), 1.41 - 1.52 (m, 4H), 1.55 - 1.61 (m, 2H), 2.74 (td, J = 5.6 and 2.2 Hz, 1H), 2.80 (dt, J = 8.8 and 6.1 Hz, 1H), 2.85 - 2.91 (m, 1H), 2.93 (dd, J = 6.7 and 2.2 Hz, 1H), 3.02 (B-part of an ABX-system, J_{AB} = 13.9 Hz, J_{BX} = 8.8 Hz, 1H), 3.71 (A-part of an AB-system, J = 14.0 Hz, 2H), 3.88 (B-part of an AB-system, J = 14.0 Hz, 2H), 7.22 - 7.33 (m, 15H). - ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 22.6, 28.2, 31.9, 34.4, 54.2, 58.0, 58.4, 60.4, 126.0, 126.9, 128.1, 128.2, 128.4, 129.5, 139.6. - $C_{28}H_{33}NO$ (399.5): Calcd. C 84.16, H 8.32, N 3.50; Found C 84.14, H 8.32, N 3.51.

The diastereomer ratio was determined analytically by HPLC using a nucleosil 100-7C18 column (Merck), 1 ml/min of methanol/water = 85:15 at 120-140 bar, detection at 250 nm. The detector response has been calibrated using the above pure samples together with 4,4-di-tert.-butyl-diphenyl as internal standard.

9. 2-(N,N-Dibenzylamino)-1-phenyl-3-heptanol: To a solution of 132 mg (0.40 mmol) of 2-(N,N-dibenzylamino)-3-phenyl-propanal (**6**) in 4 ml of THF, 1 ml of ether and 1 ml of petroleum ether was added at -80°C dropwise 280 µl (0.43 mmol) of a 1.54 M solution of n-butyllithium in hexane. After stirring for 2 h at -80°C 15 ml of saturated aqueous NH_4Cl-solution were added. After reaching room temperature the phases were separated and the aqueous phase was extracted twice with 20 ml each of ether. The combined organic phases were dried with $MgSO_4$ and concentrated to give 198 mg of a yellowish oil which was subjected to flash chromatography with petroleum ether/ether = 8:1. Eluted were 22 mg of a liquid containing 3 mg of residual aldehyde **6** and 19 mg of (2S*,3S*)-2-(N,N-dibenzylamino)-1-phenyl-3-heptanol (minor diastereomer). - ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.81 (t, J = 7.1 Hz, 3H), 0.98 - 1.48 (m, 7H), 2.70 (A-part of an ABX-system, J_{AB} = 14.3 and J_{AX} = 5.9 Hz, 1H), 2.90 (m, 1H), 3.11 (B-part of an ABX-system, J_{AB} = 14.2 and J_{BX} = 5.6 Hz, 1H), 3.39 (d, J = 13.2 Hz, 2H), 3.91 (d, J = 13.2 Hz, 2H), 3.57 (m, 1H), 7.15 - 7.39 (m, 15H). - ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9, 22.7, 27.9, 32.5, 34.0, 53.9, 64.0, 70.4, 126.2, 127.2, 128.4, 128.5, 129.6, 138.9, 140.6.

113 mg (72%) of (2S*,3R*)-2-(N,N-dibenzylamino)-1-phenyl-3-heptanol (major diastereomer). - ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93 (t, J = 7.0 Hz, 3H), 1.16 - 1.52 (m, 5H), 1.64 - 1.74 (m, 1H), 2.01 (s, broad, 1H), 2.85 (A-part of an ABX-system, J_{AB} = 12.6 and J_{AX} = 5.8 Hz, 1H), 3.03 - 3.18 (m, 2H), 3.71 (A-part of an AB-system, J = 13.8 Hz, 2H), 3.83 (B-part of an AB-system, J = 13.8 Hz, 2H), 3.73 (m, 1H), 7.19 - 7.39 (m, 15H). - ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 22.6, 28.5, 31.9, 34.4, 55.1, 63.2, 71.6, 125.9, 125.9, 128.2, 128.3, 128.8, 129.3, 139.8, 140.6. - $C_{27}H_{33}NO$ (387.5): Cald. C 83.76, H 8.58, N 3.61; Found C 83.65, H 8.70, N 3.74.

The diastereomer ratio was determined to 86:17 by ^{1}H-NMR spectroscopy.

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27. In ref. [7] the diastereomer ratio of **30** / **31** was erroneously inverted.

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