

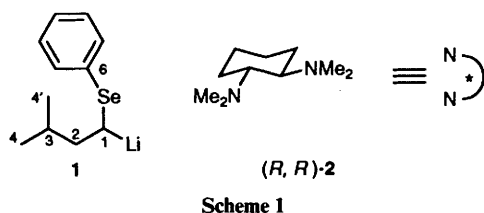
Enantioselective Transformations of Configurationally Labile α -Phenylseleno-alkyllithium Compounds

Wolfgang Klute, Ruprecht Dress and Reinhard W. Hoffmann*

Fachbereich Chemie der Philipps-Universität Marburg, Hans-Meerwein-Strasse, D-35032 Marburg, Germany

The diastereoisomeric complexes **3** between α -phenylseleno-alkyllithium compounds **1** and a chiral diamine **2** are trapped by aldehydes more rapidly than the complexes equilibrate, such that the e.e. of the adducts **4**, **5** reflects the diastereoisomer ratio of the complexes **3**.

Some years ago Nozaki and Noyori pointed out that the enantiomer ratio of configurationally labile organolithium compounds may be shifted by chiral additives.¹ They utilized this effect for stereoselective transformations, a technique which has since been used by other groups.² In order to delineate the factors which determine the asymmetric induction attainable by this technique, the reactions of the configurationally labile³ α -phenylseleno-alkyllithium compound **1** have been studied in the presence and absence of the chiral diamine **2**. Compounds **1** and **2** were chosen not because of the level of asymmetric induction, which is low, but rather since the NMR-characteristics of these compounds allowed the maximum information to be obtained about this system.



The organolithium compound **1** was generated from the corresponding selenoacetal in ether by addition of a solution of *sec*-butyllithium in hexane. The resulting solution showed a ⁷⁷Se NMR signal at 315 ppm for **1**. After addition of 2 equiv. of the *S,S*-diamine **2** two ⁷⁷Se NMR signals at 339 and 343 ppm resulted in a 7:3 ratio. We ascribe these signals to the complexes **3a** and **3b**. Further, a solution of **1** was generated in [²H₁₀]Et₂O with sublimed *tert*-butyllithium in C₆D₁₂. Upon addition of increasing amounts of *rac*-**2**, the formation of the complexes **3** may be followed at -50 °C in the ¹³C NMR spectra by monitoring the signals of C-1, C-2 or C-6. The use of the racemic ligand **2** in combination with a rapid ligand exchange results in a single averaged signal set for **1a**, **1b**, **3a** and **3b**. The chemical shift-values for C-6 are reproduced in Fig. 1. The equilibrium constant was approximated by fitting a calculated curve to the experimental points. In combination with the ⁷⁷Se NMR data the equilibrium constants for the equilibria (2) and (3) may be estimated to be > 800 and > 240 dm³ mol⁻¹ respectively.

The α -phenylseleno-alkyllithium compound **1** racemises [eqn. (1)] at -30 °C with a rate of 17 Hz. This followed from a line shape analysis of the temperature dependent signals of C-4 and C-4' in the ¹³C NMR spectrum ($\Delta H^\ddagger = 10.8$ kcal mol⁻¹, $\Delta S^\ddagger = -5$ cal K⁻¹ mol⁻¹).[†] Addition of the ligand **2** changed the rate of the racemization by less than a factor of 2. Given the fact that the complexes **3** are more stable than **1** at -50 °C by > 2.5 kcal, this indicates that the complexes **3** racemize directly [eqn. (4)] and not predominantly *via* a dissociation to **1**.

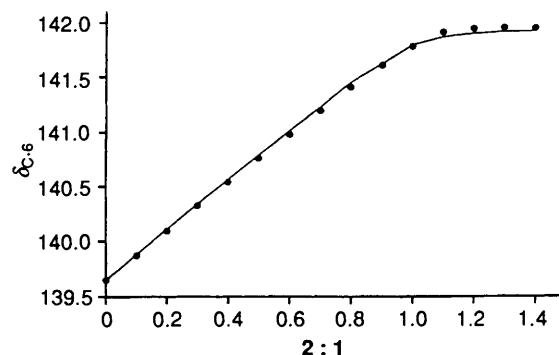


Fig. 1 NMR titration of **1** by **2** monitored at δ_{C-6}

Apparently, complexation and racemization are uncorrelated processes: complexation affects the lithium cation and the ion pair dynamics of **1** and **3**. The latter is probably not rate determining for the racemization process, which may be limited by a rotation around the C(1)–Se bond.⁴

Reaction of the uncomplexed organolithium compound with benzaldehyde led to the two diastereoisomeric adducts **4** and **5** as *a/b*-racemates. In the presence of the chiral diamine the adducts **4** and **5** may be obtained enantiomerically enriched. This depends on the fraction of the reaction that proceeds *via* **3** and *via* **1**, and also whether the rate of trapping is faster or slower than the rate of enantiomerization, and in the latter case, whether the complexes **3a** and **3b** react at equal rates or not. We describe here a set of experiments which shed light on the details of these processes.

The direct addition of **1** to benzaldehyde is characterized by the simple diastereoselectivity 4:5 = 55:45.[‡] In the presence of more than 1 equiv. of the diamine **2** the adducts **4** and **5** are formed in a 70:30 ratio, which is apparently characteristic for the reaction of the complexes **3**, *cf.* Fig. 2. More precisely, this ratio represents the weighted average of the diastereoselectivities of **3a** and **3b**. When less than 1 equiv. of **2** is present, uncomplexed **1** and the complexes **3** may compete for benzaldehyde as long as a deficiency of the latter (0.1 equiv.) is added. The empty circles in Fig. 2 show that this results in the same diastereoselectivity of 70:30. This indicates that the complexes **3** add to benzaldehyde significantly more rapidly than the uncomplexed organolithium compound **1**.

Only when 1 equiv. of benzaldehyde is added does one notice a linear change of the 4/5-ratio from the value characteristic for

[‡] The relative configuration of **4** and **5** has been secured by transformation into a *cis*- and *trans*-epoxide respectively (Me₃O⁺BF₄⁻, CH₂Cl₂ followed by KOBu^t, DMSO). The absolute configuration of **4a** as the excess enantiomer followed from the reduction (Ph₃SnH, toluene reflux) to laevorotatory 4-methyl-1-phenylpentanol; [α]_D²⁰ = -24.2 (*c* = 1.13, C₆H₆). Compound **5a** led similarly to the dextrorotatory alcohol; [α]_D²⁰ = +20.4 (*c* = 1.4, C₆H₆).

[†] 1 cal = 4.18 J.

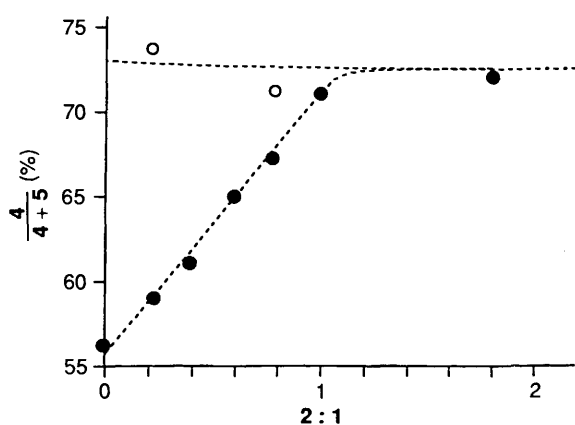
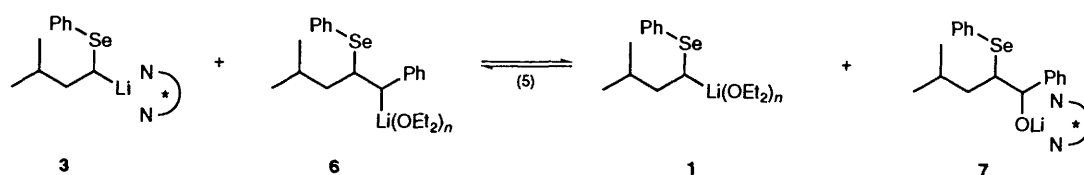
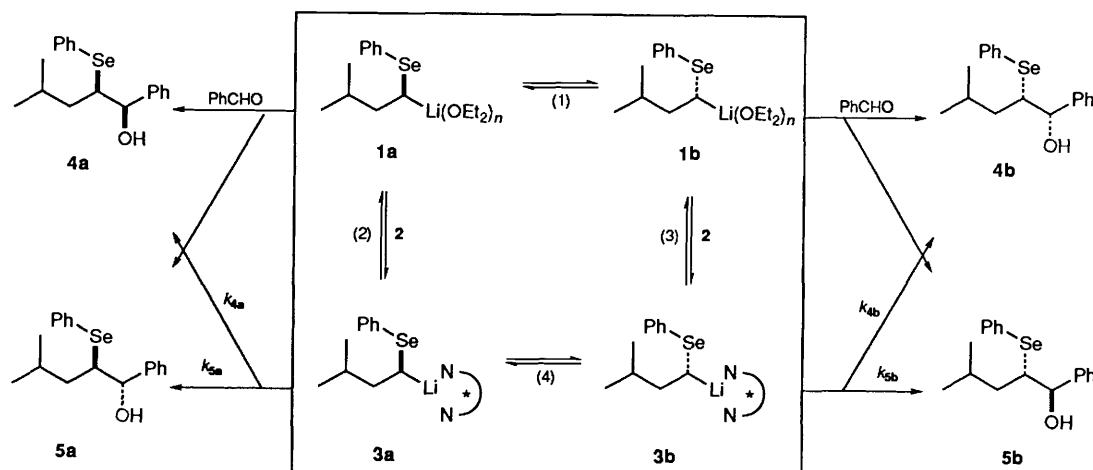


Fig. 2 Simple diastereoselectivity 4/5 as a function of the ligand to organolithium ratio

2:1: PhCHO

- x:1:0.1
● x:1:1

1 to the one for 3 with increasing amounts of the diamine 2 (*cf.* the solid circles in Fig. 2). The value characteristic for 3 is reached at 1 equiv. of the diamine 2. This behaviour indicates the existence of the complexation equilibrium (5). This lies so far on the right side that it overcompensates the lower reactivity of 1 compared to 3. The strong complexation of the diamine by the product 6 prevents a desirable chiral catalysis by the diamine 2 in the addition of 1 to benzaldehyde.

After the experiments detailed in Fig. 2 the adducts 4 and 5 have been isolated and chromatographically separated. Their enantiomeric purities were determined⁵ and plotted in Fig. 3, which closely resembles Fig. 2. Under conditions (see above) in which predominantly the complexes 3 add to benzaldehyde, the enantiomer ratios are constant. The enantiomer ratio of 70:30 corresponds to that of the diastereoisomeric complexes 3a and 3b. This outcome depends upon whether or not the complexes 3 add more rapidly to benzaldehyde than they equilibrate. Which of these alternatives holds was determined by a test recently

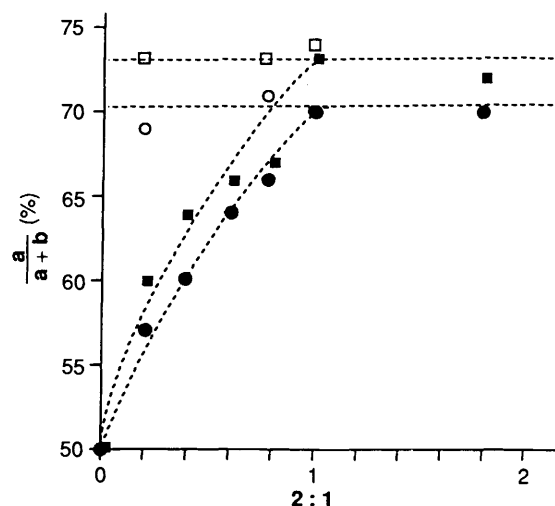


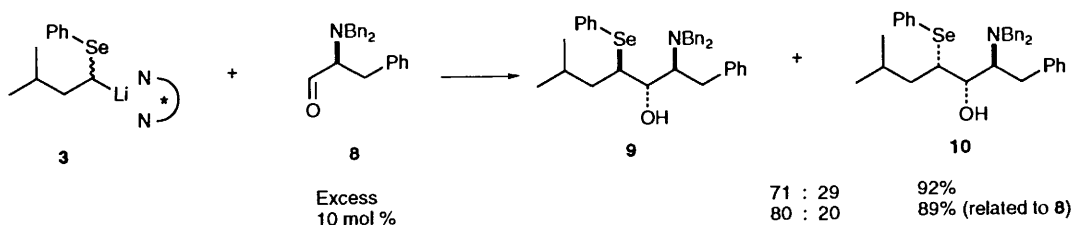
Fig. 3 Enantiomer ratio of the adducts 4/5 as a function of the ligand to organolithium ratio

4 or 5 2:1: PhCHO

- □ x:1:0.1
● ■ x:1:1

introduced by us.⁶ The test is based on kinetic resolution which occurs on reaction of a racemic organometallic species with a chiral electrophile. In the case of 3 the evaluation has to be modified, since a 70:30 diastereoisomer mixture of 3 rather than a 50:50 racemate is the point of reference.

In a first experiment the diastereoisomeric mixture of 3 was allowed to add to an excess of the aldehyde 8. This generated the diastereoisomeric adducts 9 and 10 in a ratio of 71:29. This is to be expected if the equilibration of 3 [eqn. (4)] is slower than trapping of 3 by the aldehyde 8. To be sure, one has to demonstrate that 3a and 3b add with unequal rates to the aldehyde 8. The proviso holds, because on addition of 3 to only 0.1 equiv. of 8 the products 9 and 10 resulted in a 80:20 ratio which is significantly different from the ratio obtained in the former experiment. This allows the conclusion that the



Scheme 4

complexes **3** are trapped more rapidly by the aldehyde **8** than they equilibrate. Does this also hold for benzaldehyde? To this end, benzaldehyde and the aldehyde **8** were allowed to compete for **3**, showing that benzaldehyde is 2.2 times more reactive than **8**.

This made it clear that benzaldehyde reacts with the complexes **3** more rapidly than they equilibrate. This information is required when one wants to interpret the asymmetric induction found in the formation of **4** and **5**. This particular situation can lead to identical enantiomeric purities of **4** and **5**, if the complexes **3a** and **3b** have equal diastereoselectivities (i.e., $k_{4a}/k_{5a} = k_{4b}/k_{5b}$). Then the enantiomer ratio **a/b** corresponds to the diastereoisomer ratio **3a:3b**. Differences in the diastereoselectivity of **3a** and **3b** (i.e., $k_{4a}/k_{5a} \neq k_{4b}/k_{5b}$) would manifest themselves in a higher enantiomer ratio for one product (e.g. **4**), and a lower enantiomer ratio for the other product (e.g. **5**), bracketing the **3a/3b** ratio. The difference in the enantiomer ratios of **4** and **5** recorded in Fig. 3 are not outside the errors of the e.e. determination. Therefore, the simple diastereoselectivities of the complexes **3a** and **3b** are approximately equal.

The system of the organolithium compound **1** and the ligand **2** is therefore one in which the complexes **3** react more rapidly with an electrophile (the aldehyde) than the uncomplexed organolithium compound and one in which the addition of the complexes to the electrophile is more rapid than their equilibration. This leads to a correspondence of the enantiomer ratio of the adducts **4** and **5** to the diastereoisomer ratio of **3**. In such a situation the enantiomer ratio of the products should not depend on the electrophile used. With electrophiles of lower reactivity one will eventually reach the situation in which equilibration of the complexes **3** is faster than their addition to the electrophile. In the latter situation the enantiomer ratio of the products will no longer correspond to the diastereoisomer ratio of **3** and may be analysed by reference to the equations

developed by Noyori.⁷ Also, in the latter situation the enantiomer ratio should depend on the nature of the electrophile used, as has been reported recently by Beak^{2e} for a related system.

Acknowledgements

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