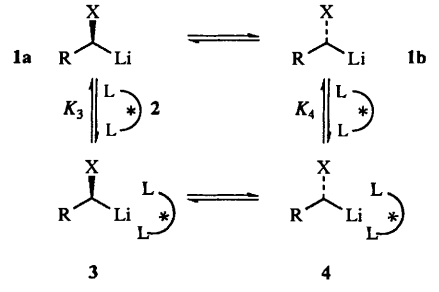
Chiral organometallic reagents. Part XVII.[1] Formation of diastereoisomeric complexes between α-phenylselanylalkyllithium compounds and chiral diamines

Reinhard W. Hoffmann,* Wolfgang Klute, Ruprecht K. Dress and Andreas Wenzel
Fachbereich Chemie der Philipps-Universität Marburg, D-35032 Marburg, Germany

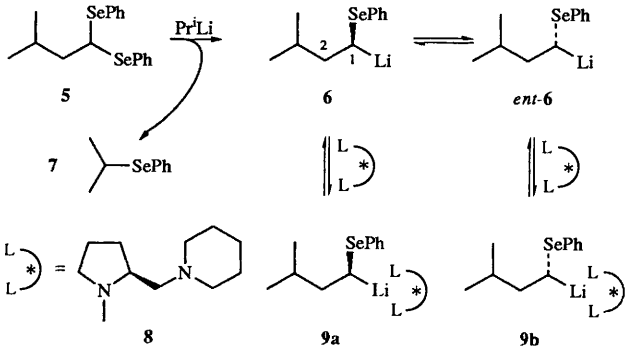
The racemic α-phenylselanylalkyllithium compound **6** is monomeric in diethyl ether and forms diastereoisomeric complexes with a variety of chiral diamines. Diastereoisomer ratios were determined from ^{77}Se NMR spectroscopy to lie around 60:40 for most examples, but reached 90:10 with *N,N,N',N'*-tetramethylcyclopentane-1,2-diamine (**22**). The complexation constants for the formation of the diastereoisomeric complexes **24a** and **24b** formed from **6** with the latter ligand were estimated by NMR titration to be >800 dm^3 mol^{-1} and >90 dm^3 mol^{-1}. The diastereoisomeric complexes **24** epimerize at the lithium bearing stereocentre with a barrier of $\Delta G^{\ddagger} = 12.1 \pm 0.3$ kcal mol^{-1} at -4 °C. As this epimerization process is not slower than the racemization of the uncomplexed alkyllithium compound **6**, the complexes **24** equilibrate directly and do not have to dissociate into **6** in order to equilibrate.

Complexation of racemic organolithium compounds of type **1** with an enantiomerically pure chiral ligand **2** gives rise to the formation of diastereoisomeric complexes **3** and **4**. Provided that the organolithium compound is configurationally labile, these complexes equilibrate and the equilibrium ratio should in general deviate from a 1:1 value. It is attractive to use the resulting diastereoisomeric enrichment in stereoselective synthesis. This was first explored in a pioneering study on α-methylbenzyllithium–sparteine complexes by Nozaki[2] and has since been extended to other configurationally labile benzyllithium[3] and allyllithium compounds,[4] and more recently to α-heterosubstituted organolithium compounds, such as **1** with sulfur[5] or selenium[6] as heteroatoms, *cf.* Scheme 1.

On reaction of such a system with electrophiles the enantiomeric excess that may be attained in the products depends among other (electrophile dependent) factors[7] on the complexation constants K_3 and K_4, which determine the diastereoisomer ratio **3**/**4**, and on the rate of equilibration between the complexes **3** and **4**. For this reason we tested in a model study a variety of chiral diamines **2** and other chiral ligands *vis à vis* configurationally labile α-phenylselenoalkyllithium compounds with regard to their ability to influence the diastereoisomer ratio **3**/**4**. Some aspects of this study have been communicated in preliminary form.[6]



Scheme 1 (X = S, Se)



Scheme 2

Preliminary studies

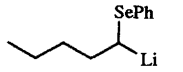
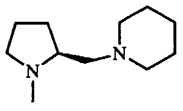
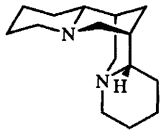
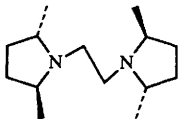
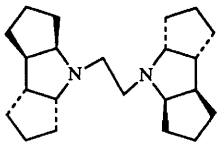
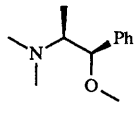
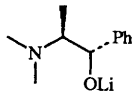
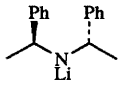
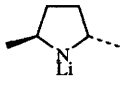
The advantage of the α-phenylselenoorganolithium compounds is that their complexation with chiral ligands can be followed by ^{77}Se NMR spectroscopy. Treatment of selenoacetal **5** (^{77}Se NMR: δ 405 from external Me_2Se) with isopropyllithium in THF at -60 °C generated the lithium compound **6** (δ 366) and the exchange product **7** (δ 426).

Addition of one or two equivalents of the chiral diamine **8**[8] did not, however, alter the ^{77}Se NMR chemical shift of **6** or **7** by more than 1 ppm. Apparently complexation is not favoured in THF as solvent, *i.e.* the ligand can not effectively compete with the basic solvent THF for co-ordination of the lithium compound **6**. We therefore generated the organolithium compound **6** in diethyl ether (from the selenoacetal **5** and *tert*-butyllithium) at -78 °C. Compound **6** showed in this solvent a ^{77}Se NMR signal at δ 315 at -60 °C, which upon addition of 1.5 equiv. of the diamine **8** gave rise to two new signals at δ 348 and 349 in a 1.5:1 ratio. The change in the chemical shift of **6**, but not of the co-product *tert*-butyl phenyl selenide, upon addition of the ligand **23** indicates formation of the complexes **9**. We ascribe the two new signals to the two diastereoisomeric complexes **9**. The fact that two distinct signals can be observed shows that the equilibration between **9a** and **9b** is slow on the ^{77}Se NMR timescale. Thus, by using ^{77}Se NMR spectroscopy the formation of diastereoisomeric complexes with a variety of chiral ligands could be monitored.

Formation of diastereoisomeric complexes between chiral ligands and α-phenylselanylalkyllithium compounds

The initial tests were run with the α-phenylselanylpentyllithium compound **10** generated from 1,1-di(phenylselanyl)pentane with either n-butyl- or *sec*-butyllithium in diethyl ether.

Table 1 Diastereoisomer ratios of the complexes between the lithium compound **10** and chiral ligands at −70 °C in diethyl ether as monitored by ^{77}Se NMR spectroscopy

	**10**	Ligand (equiv.)	δ_1		δ_2[a]	Diastereoisomer ratio
	**8**[8]	2.5	345		343	68:32[b]
	**11**	2.5	347		345	60:40[b]
	**12**[9]	2.0	346		339	62:38[c]
	**13**[10]	2.0	339		335	59:41[c]
	**14**[11]	2.5	348		345	61:39[b]
	**15**	1.3	301		316[d]	66:34
	**16**[12]	1.0	284		293	71:29
	**17**[13]	2.0	289	294	300[d]	37:13:50

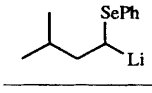
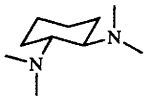
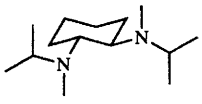
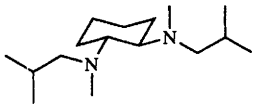
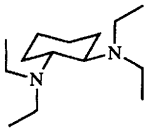
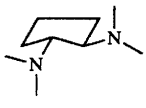
[a] Relative to the ^{77}Se NMR signal of n-butyl phenyl selenide at δ 392 or of *sec*-butyl phenyl selenide at δ 292. [b] Ratio is temperature dependent and increases with lower temperatures. [c] Ratio is not significantly dependent on temperature. [d] Substantial amounts of uncomplexed **10** are still present.

Uncomplexed **10** shows at −70 °C a ^{77}Se NMR signal at δ 326. The results obtained upon addition of a variety of chiral diamines and other chiral ligands available to us are compiled in Table 1.

In the case of sparteine (**11**) and of the ligands **8** and **14** the diastereoisomer ratios could be increased by lowering the temperature from −70 °C to −90 °C, but usually line broadening below −78 °C prevented further determination of the diastereoisomer ratios. Notably, the reference signal of butyl phenyl selenide did not broaden upon cooling of the solution. In the cases of **12** and **13** as ligands the diastereoisomer ratio was not noticeably temperature dependent in the range of −50 to −80 °C. All in all, the diastereoisomer enrichment of the entries recorded in Table 1 remained modest. Upon addition of 2-dibenzylamino-3-methoxy-1-phenylpropane to **10**, no complexation was observed, *i.e.* the ^{77}Se NMR signal of **10** remained unchanged at δ 326.

Since none of those ligands led to a level of diastereoisomeric enrichment, which is of interest for synthetic applications, we turned to another set of diamine ligands, the *N,N,N',N'*-tetraalkylcycloalkane-1,2-diamines. This set of experiments were run with the α-phenylselanylalkyllithium compound **6** in diethyl ether. The results are compiled in Table 2.

Table 2 Diastereoisomer ratios of the complexes formed between the lithium compound **6** and 1.5 equiv. of chiral ligands at −80 °C in diethyl ether as monitored by ^{77}Se NMR spectroscopy

	**6**	δ_1	δ_2[a]	Diastereoisomer ratio
	**18**	338	343	72:28
	**19**	342	344	55:45
	**20**	347	349	75:25
	**21**	342	343	50:50
	**22**	326	324[b]	90:10[b]

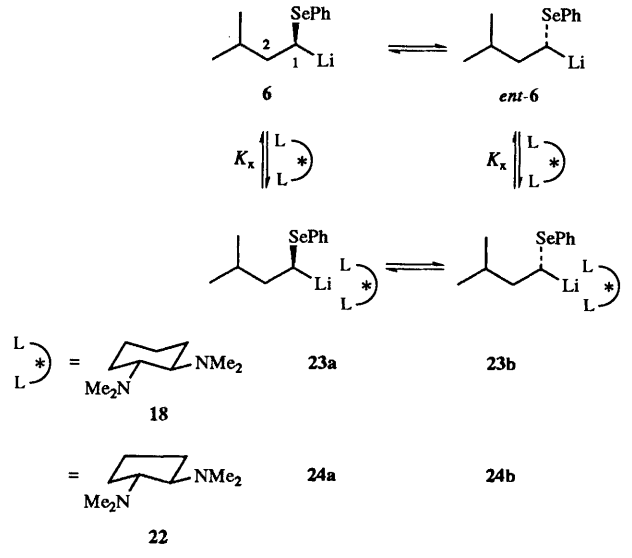
[a] Relative to the ^{77}Se NMR signal of *tert*-butyl phenyl selenide at δ 315. [b] Determined at −100 °C.

The first results obtained with the simple ligand **18** encouraged us to synthesize the other ligands **19–21**. These, unfortunately, did not give rise to increased diastereoisomer ratios. We were therefore pleasantly surprised that a change from the cyclohexanediamine to the cyclopentanediamine nucleus, *cf.* ligand **22**, led to a diastereoisomer ratio of 9:1 at −100 °C. At higher temperatures, the diastereoisomer ratio with **22** could not be determined because of an accidental coincidence of the ^{77}Se NMR signals of the diastereoisomeric complexes formed. The ligand **22** is thus of further interest for stereoselective synthesis.

α-Phenylselanyl-3-methylbutyllithium (6) and *trans*-1,2-bisdimethylaminocyclohexane (18)

To study the properties of the system α-phenylselanylalkyllithium compound–diamine in more detail, we chose the organolithium compound **6** and the ligand **18**. Their NMR characteristics are such that they should allow us to obtain maximum information on the equilibrium and dynamics of the complexation and enantiomerization processes shown in Scheme 3.

The first information needed, however, is the degree of aggregation of **6** and the complexes formed. For this reason we developed a vapour pressure osmometer,[14] which allowed measurements to be made in diethyl ether at temperatures as low as −35 °C. A 0.2 mol dm^{-3} solution of **6** in ether showed, at −35 °C, an aggregation of 1.0 ± 0.1. Upon addition of one equivalent of the diamine **7** the number of solute molecules did not change. Thus, both these measurements and the ^{77}Se NMR results indicate that the equilibrium between **6** and **18**, and the complexes **23** lies on the side of **23**.



Scheme 3

In order to determine the association constant for the formation of the complexes **23**, we intended to carry out an 'NMR-titration'. While equilibration between the complexes **23a** and **23b** formed from the enantiomerically pure ligand **18** is slow on the ^{13}C NMR timescale at the low temperatures used, application of the racemic ligand **18** allows rapid equilibration between **23a** and **23b** by fast decomplexation and recomplexation. In such a case the NMR spectrum is a weighted time-averaged spectrum over all species in solution. Therefore by addition of incremental amounts of the racemic ligand **18** to the lithium compound **6** in [$^2H_{10}$]diethyl ether an NMR titration can be realized.

Fig. 1 shows the ^{13}C NMR chemical shift of the *ipso*-carbon of the phenyl group in **6** as a function of the equivalents of racemic **18** added. Similar results were obtained when monitoring the signal of C-1 or C-2 of **6**. Approximate values of the complexation constant K were derived by fitting a curve to the points of Fig. 1.[15] An adjustment had to be made (a shift of the x-axis) by subtracting a constant amount (*ca.* 10%) from the equivalents of the ligand added. This is probably necessitated by the adventitious introduction of some lithium ions into the system, probably LiOH from the sample preparation, even when freshly sublimed *tert*-butyllithium was used to generate **6**. From the curve shown in Fig. 1 we can derive an overall complexation constant for the formation of **23**, which can be decomposed into the individual complexation constants for the formation of the diastereoisomeric complexes **23a** and **23b** with the aid of the **23a**/**23b** ratio determined from the ^{77}Se NMR spectra. The data in Fig. 1 correspond to complexation constants K_{23a} of 1400 dm^3 mol^{-1} and K_{23b} of 600 dm^3 mol^{-1}. Monitoring C-1 or C-2 resulted in values of 5250 and 2520 dm^3 mol^{-1} for K_{23a} and of 2250 and 1080 dm^3 mol^{-1} for K_{23b}. In view of the uncertainties of the curve fitting procedure, we assume that a value of > 800 dm^3 mol^{-1} for K_{23a} and > 300 dm^3 mol^{-1} for K_{23b} would give a reasonable lower limit for the association constants.

With respect to preparative applications of the **6**/**18**-system in stereoselective synthesis, the rate of racemization of the uncomplexed lithium compound **6** and the rate of the diastereoisomer equilibration of the complexes **23** are of interest. We wanted to determine these rates by dynamic NMR spectroscopy[16] and chose **6** as the substrate, because it contains two diastereotopic methyl groups. Both the ^{13}C and the ^{1}H NMR spectra of **6** in perdeuteriated diethyl ether showed coalescence of the methyl signals in the temperature range −40 to 0 °C. By simulation of the line shapes with the program

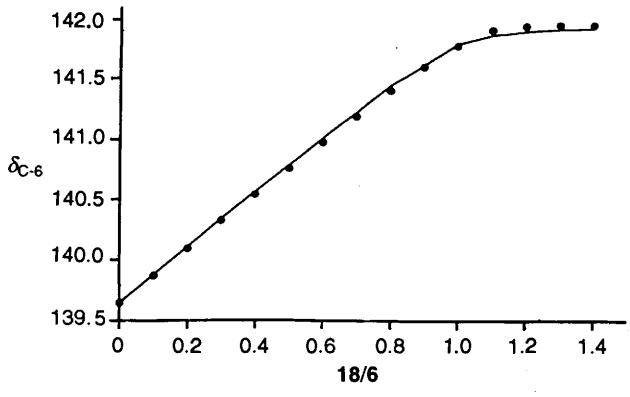


Fig. 1 NMR titration of **6** by **18** monitored at $\delta_{C\text{-}6}$

QUABEX[17] the reacemization barrier was determined to be $\Delta G^{\ddagger}_{269} = 12.1 \pm 0.3$ kcal mol^{-1}. The derived activation parameters $\Delta H^{\ddagger} = 10.8 \pm 0.3$ kcal mol^{-1} and $\Delta S^{\ddagger} = -6 \pm 1$ cal mol^{-1} K^{-1} are less reliable. These activation parameters for the racemization of **6** are similar to those for the racemization of other α-phenylselanylalkyllithium compounds investigated earlier.[16] Addition of one equivalent of the diamine **7** to the ethereal solution of **6** resulted in some line broadening in the ^{1}H and ^{13}C NMR spectra, yet the coalescence temperature was not changed. The latter corresponds to a process with a $\Delta G^{\ddagger}_{263}$ of 12.1 ± 1 kcal mol^{-1}. Thus, the rates of the racemization of **6** on the one hand and of the equilibration of the complexes **23** on the other hand do not differ by more than a factor of 2.

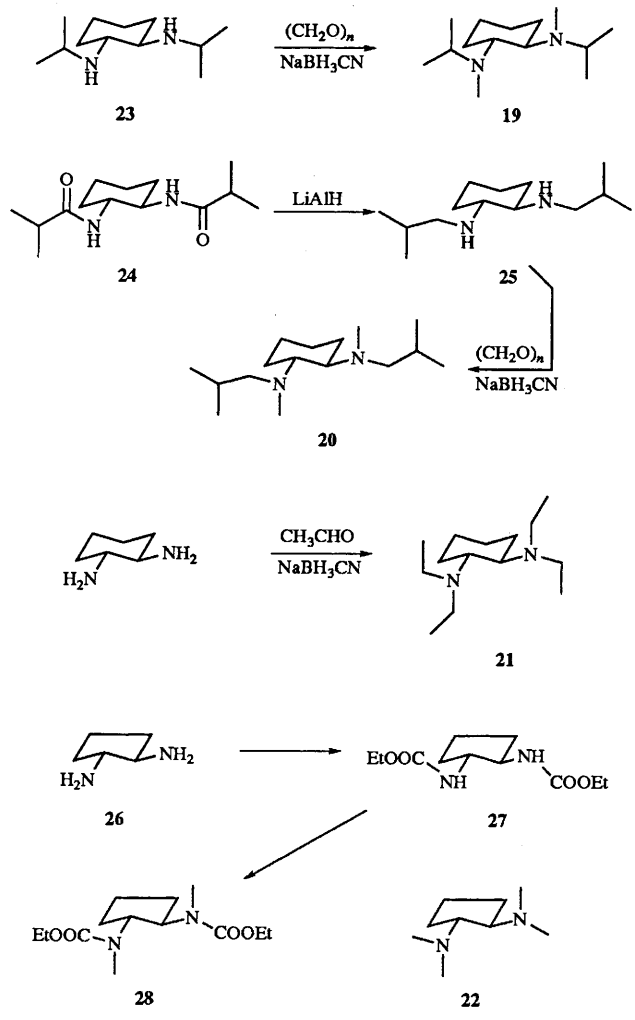
Two distinct pathways exist for the latter process: one is the direct equilibration, the other is an equilibration *via* decomplexation to the uncomplexed species **6**, which then undergoes racemization, followed by recomplexation. If the equilibration were to proceed *via* the latter route, a decrease in the topomerization rate on going from **6** to **23** by the factor of the complexation constant (*i.e. ca.* 10^{-3}) would have been expected. Thus, the absence of such a rate decrease on going from **6** to **23** indicates that the diastereoisomeric complexes **23** equilibrate directly.

When the ligand **22** became available, which led to a diastereoisomer ratio of 9:1 on complexation with **6**, we also determined the complexation constant for the formation of the complexes **24** by an NMR titration as above. The lower limit for the complexation constants at −50 °C were estimated to be *ca.* > 800 dm^3 mol^{-1}, for K_{24a} and > 90 dm^3 mol^{-1} for K_{24b}. These are not significantly different from the value determined for complexation of **6** with the diamine **18**. Moreover, the barrier for the equilibration of the diastereoisomeric complexes **24** was found to be $\Delta G^{\ddagger}_{248} = 12.1 \pm 0.3$ kcal mol^{-1}, again being identical to the value determined for the complexes **23** formed from **6** and the ligand **18**.

In summary: an α-selanyl substituted alkyllithium compound such as **6** forms unequal amounts of diastereoisomeric complexes when treated with 1.5 to 2 equiv. of chiral diamines in diethyl ether. Diastereoisomer ratios of 72:28 and 90:10 respectively, were found for the complexes between the organolithium compound **6** and the ligands **18** and **22**.

Synthesis of the ligands

Most of the ligands studied here were synthesized according to published procedures. The new ligands **19**–**22** were prepared by conventional methods: for instance, the diamine **23**[18] was reductively alkylated with paraformaldehyde to give the ligand **19** in 84% yield. The diamine **20** was prepared from *trans*-cyclohexane-1,2-diamine *via* the bis-isobutyramide **24**. $LiAlH_4$-reduction of the latter to give **25** was followed by reductive methylation with paraformaldehyde to furnish the ligand **20** in 92% yield.



Scheme 4

Reductive alkylation of *trans*-cyclohexane-1,2-diamine with acetaldehyde led to the tetraethyl derivative **21** in 79% yield. The cyclopentanediamine derivative **22** was generated from levorotatory *trans*-cyclopentane-1,2-diamine[19] by sequential carbamoylation, *N*-methylation and reduction.

Experimental

All temperatures quoted are not corrected. All experiments with organolithium compounds were carried out in dried glassware under an atmosphere of dry nitrogen or argon. ^{1}H, ^{13}C and ^{77}Se NMR spectra were obtained using Bruker AC-300 and AM-400 instruments. The boiling range of the light petroleum was 40–60 °C. For flash chromatography, silica gel (Si 60, E. Merck AG, Darmstadt, 40–63 μm) was used.

3-Methyl-1,1-di(phenylselanyl)butane 5

To a suspension of 3.12 g (22.9 mmol) of anhydrous zinc chloride in 50 cm^3 of anhydrous CH_2Cl_2 was added at 0 °C under stirring a solution of 14.28 g (90.9 mmol) of benzeneselenol and of 3.85 g (44.7 mmol) of 3-methylbutanal in 30 cm^3 of anhydrous CH_2Cl_2. After stirring for 4 h at room temperature 100 cm^3 of water was added, the phases were separated and the aqueous phase was extracted three times with 50 cm^3 each of diethyl ether. The combined organic phases were washed twice with 50 cm^3 of saturated aq. NH_4Cl, saturated aq. $NaHCO_3$ and were dried over $MgSO_4$. After removal of the solvent under reduced pressure 6 g aliquots of the residue were purified by flash chromatography with light petroleum to

furnish a total of 13.2 g (77%) of compound **5** as a faintly yellowish oil. δ_H(300 MHz, $CDCl_3$) 0.89 (d, J = 6.6 Hz, 6 H), 1.73 (m, 2 H), 1.98 (d, sept, J = 6.7 and 6.7 Hz, 1 H), 4.46 (t, J = 7.6 Hz, 1 H) and 7.21–7.56 (m, 10 H); δ_C(75 MHz, $CDCl_3$) 21.9, 27.0, 42.0, 46.4, 127.9, 128.9, 130.1 and 134.8 (Found: C, 53.4; H, 5.3. Calc. for $C_{17}H_{20}Se_2$: C, 53.41; H, 5.27%).

3-Methyl-1-phenylselanylbutyllithium 6

An NMR tube was cleaned with hydrochloric acid, water, acetone and diethyl ether. While blowing a stream of dry nitrogen through the tube, heat was applied with a hot air gun. When the tube had subsequently reached room temperature again, 101 mg (0.26 mmol) of **5** was weighed into the NMR tube, which was closed with a septum cap. The septum cap was sealed with parafilm. Argon was purged through the tube by introducing two hyperdermic needles. One needle was removed and 100 μl (1 μl = 1 mm^3) of [$^2H_{10}$]diethyl ether was injected with a dry, gas tight, syringe. The starting material was dissolved in the liquid and a further 500 μl of the solvent was injected in such a manner as to wash the inner walls of the tube. The tube was cooled in a dry ice–acetone bath. After 5 min a solution of *tert*-butyllithium in [$^2H_6$]benzene was added with a gas tight syringe. The *tert*-butyllithium solution solidified on the inner wall of the tube. The tube was removed briefly from the cooling bath in order to liquify part of the butyllithium solution, the tube was vigorously shaken for 10 s and was immediately recooled to −78 °C. This was repeated until all of the *tert*-butyllithium had been dissolved. The tube was stored at −78 °C until the NMR measurements were started: $\delta_{^{77}Se}$ (76.3 MHz, 193 K) 315; δ_C(100 MHz, 233 K) 22.8, 24.3, 25.0, 32.9, 49.1, 123.3, 128.3, 128.6 and 140.9. The temperature dependence of the ^{13}C NMR spectra was monitored in the range from 233 K to 273 K. The coalescence of the signals at δ 23.8 and δ 24.3 was simulated with the program QUABEX [17] to give the activation parameters $\Delta G^{\ddagger}_{263}$ = 12.3 ± 0.3 kcal mol^{-1}, $\Delta H^{\ddagger}$ = 10.8 ± 0.3 kcal mol^{-1} and $\Delta S^{\ddagger}$ = −6 ± 0.3 kcal mol^{-1} K^{-1}. (1 cal = 4.184 J.) Another sample was similarly prepared from 66.7 mg (0.174 mmol) of **5** and 76 μl (0.17 mmol) of a 2.29 mol dm^{-3} solution of freshly sublimed *tert*-butyllithium in [$^2H_{12}$]cyclohexane in a total of 600 μl of [$^2H_{10}$]diethyl ether. Upon addition of 31 μl (0.178 mmol) of (*S*,*S*)-*N*,*N*,*N*′,*N*′- tetramethylcyclohexane-1,2-diamine **18** [19] the following ^{13}C NMR data were recorded: δ_C(100 MHz, 223 K) 22.6, 24.6, 27.8, 32.8, 50.0, 123.2, 128.2, 128.3 and 142.9. By changing the temperature in the range 233 K to 263 K the following activation parameters were derived from the coalescence phenomena: $\Delta G^{\ddagger}_{263}$ = 12.2 ± 1.2 kcal mol^{-1}; $\Delta H^{\ddagger}$ = 9.3 ± 0.6 kcal mol^{-1}; $\Delta S^{\ddagger}$ = −11 ± 2 cal mol^{-1} K^{-1}.

For determination of the complexation constants a sample was prepared as above and increments of the racemic diamine **18** or **22** were added at 223 K. The complexation constants were estimated by curve fitting to the measured data.[15]

1,1-Di(phenylselanyl)pentane (precursor of compound 10)[20]

12.14 g (77 mmol) of benzeneselenol and 3.34 g (38.8 mmol) of pentanal were combined and stirred at 0 °C. 2.2 cm^3 (20 mmol) of conc. sulfuric acid were added dropwise. After stirring for 30 min at room temperature 100 cm^3 of diethyl ether were added and the reaction mixture was carefully washed with 25 cm^3 of saturated aq. $NaHCO_3$ and 20 cm^3 of water. The organic phase was dried with $MgSO_4$ and concentrated. Flash chromatography of the residue with light petroleum furnished 10.4 g (70%) of the title compound as a faintly yellowish oil; δ_H(300 MHz, $CDCl_3$) 0.83 (t, J = 7.3 Hz, 3 H), 1.25 (tq, J = 7.4 Hz, 2 H), 1.49–1.60 (m, 2 H), 1.93 (dt, J = 8.9 and 6.5 Hz, 2 H), 4.48 (t, J = 6.6 Hz, 1 H), 7.22–7.34 (m, 6 H) and 7.52–7.62 (m, 4 H); δ_C(75 MHz, $CDCl_3$) 13.8, 22.0, 30.5, 36.8, 44.1, 127.9, 129.0, 130.5 and 134.6 (Found: C, 53.45; H, 5.4. Calc. for $C_{17}H_{20}Se_2$: C, 53.41; H, 5.27%).

(1*R*,2*R*)-*N*,*N*′-Diisopropyl-*N*,*N*′-dimethylcyclohexane-1,2-diamine 19

2.46 g (12.4 mmol) of (1*R*,2*R*)-*N*,*N*′-diisopropylcyclohexane-1,2-diamine [18] was dissolved in 50 cm^3 of acetic acid under cooling. After the mixture had reached room temperature, 4.00 g (63.7 mmol) of sodium cyanoborohydride and 2.00 g (66.6 mmol) of paraformaldehyde were added. After stirring for 24 h the mixture was cooled to 0 °C and added slowly to 100 cm^3 of 30% aq. NaOH. The mixture was extracted three times with 50 cm^3 each of diethyl ether and the combined organic phases were washed with 20 cm^3 of water and 20 cm^3 of brine. After drying over K_2CO_3 and KOH the solvents were removed under reduced pressure and the residue was purified by bulb-to-bulb distillation at 14 Torr (1 Torr ≈ 133 Pa) from a bath of 175 °C to give 2.34 g (84%) of compound **19** as a colourless liquid; δ_H(300 MHz, $CDCl_3$) 1.10 (m, 16 H), 1.67 (m, 4 H), 2.16 (s, 6 H), 2.55 (m, 2 H) and 2.88 (sept, J = 6.2 Hz, 2 H); δ_C(75 MHz, $CDCl_3$) 21.3, 21.4, 26.0, 28.3, 31.0, 51.2 and 61.8; $[\alpha]_D^{20}$ −46.1 (*c* 0.66, MeOH) (Found: C, 74.1; H, 13.5; N, 12.6. Calc. for $C_{11}H_{30}N_2$: C, 74.27; H, 13.36; N, 12.37%).

(1*R*,2*R*)-1,2-Bis(isobutyrylamino)cyclohexane 24

2.40 g (22.5 mmol) of isobutyryl chloride was added slowly at −20 °C to a solution of 1.00 g (8.76 mmol) of (1*R*,2*R*)cyclohexane-1,2-diamine and 2.65 g (26.3 mmol) of triethylamine in 30 cm^3 of anhydrous CH_2Cl_2. After reaching room temperature, with stirring, the suspension was partitioned between 200 cm^3 of CH_2Cl_2 and 100 cm^3 of water. The phases were separated and the organic phase was washed with 50 cm^3 each of saturated aq. NH_4Cl, saturated aq. $NaHCO_3$, water and brine. The organic phase was dried with $MgSO_4$ and concentrated under reduced pressure. After drying of the residue at 10^{-4} Torr there remained 2.00 g (90%) of compound **24** as a colourless solid; mp > 250 °C; δ_H(300 MHz, MeOH) 1.03 (d, J = 6.8 Hz, 6 H), 1.05 (d, J = 6.9 Hz, 6 H), 1.27 (m, 4 H), 1.72 (m, 2 H), 1.86 (m, 2 H), 2.32 (sept, J = 6.9 Hz, 2 H) and 3.57 (m, 2 H); δ_C(75 MHz, MeOH) 19.2, 19.5, 25.3, 32.7, 35.8, 53.3 and 179.4; $[\alpha]_D^{20}$ 76.2 (*c* 1.24, MeOH) (Found: C, 66.0; H, 10.0; N, 10.9. Calc. for $C_{14}H_{26}N_2O_2$: C, 66.11; H, 10.30; N, 11.01%).

(1*R*,2*R*)-*N*,*N*′-Diisobutylcyclohexane-1,2-diamine 25

1.80 g (7.08 mmol) of compound **24** was added at 0 °C in small portions into a suspension of 1.82 g (48 mmol) of $LiAlH_4$ in 50 cm^3 of anhydrous THF (tetrahydrofuran). The mixture was held for 12 h under reflux. After cooling to 0 °C, hydrolysis was effected by careful addition of 50 cm^3 of 20% aq. KOH. The phases were separated and the aqueous phase was extracted four times with 20 cm^3 each of diethyl ether. The combined organic phases were washed with 20 cm^3 of water and 20 cm^3 of brine, dried with K_2CO_3 and KOH and concentrated under reduced pressure. Bulb-to-bulb distillation of the residue at 20 Torr from a bath of 180 °C furnished 1.50 g (94%) of compound **25** as a colourless liquid; δ_H(300 MHz, $CDCl_3$) 0.84 (m, 14 H), 1.12 (m, 2 H), 1.62 (m, 4 H), 2.01 (m, 4 H), 2.13 (dd, J = 11.0 and 7.1 Hz, 2 H) and 2.50 (dd, J = 10.9 and 6.4 Hz, 2 H); δ_C(75 MHz; $CDCl_3$) 20.7, 20.8, 25.2, 28.8, 31.9, 55.2 and 62.0; $[\alpha]_D^{20}$ −104.8 (*c* 0.765, MeOH).

(1*R*,2*R*)-*N*,*N*′-Diisobutyl-*N*,*N*′-dimethylcyclohexane-1,2-diamine 20

1.50 g (23.9 mmol) of sodium cyanoborohydride, 1.00 g (33.3 mmol) of paraformaldehyde and 1.00 g (4.4 mmol) of compound **25** were allowed to react as described above (**19**). The crude product was purified by bulb-to-bulb distillation at 20 Torr from a bath of 200 °C to give 1.00 g (92%) of compound **20** as a

colourless liquid; δ_H(300 MHz, $CDCl_3$) 0.86 (d, J = 6.6 Hz, 6 H), 0.87 (d, J = 6.6 Hz, 6 H), 1.12 (m, 4 H), 1.70 (m, 6 H), 2.13 (dd, J = 12.1 and 3.3 Hz, 2 H), 2.19 (s, 6 H) and 2.39 (m, 4 H); δ_C(75 MHz; $CDCl_3$) 20.8, 20.9, 25.9, 26.2, 26.6, 35.9, 63.6 and 64.8; $[\alpha]_D^{20}$ 22.4 (*c* 1.01, MeOH) (Found: C, 75.4; H, 13.25; N, 11.0. Calc. for $C_{16}H_{34}N_2$: C, 75.52; H, 13.47; N, 11.01%).

(1*R*,2*R*)-*N*,*N*,*N*′,*N*′-Tetraethylcyclohexane-1,2-diamine 21

2.08 g (33.1 mmol) of sodium cyanoborohydride, 1.12 g (9.74 mmol) of (1*R*,2*R*)-cyclohexane-1,2-diamine and 2.0 g (45 mmol) of freshly distilled acetaldehyde were allowed to react as described above (**19**). The crude product was purified by bulb-to-bulb distillation at 14 Torr from a bath of 180 °C to give 1.75 g (79%) of **21** as a colourless liquid; δ_H(300 MHz, $CDCl_3$) 0.98 (t, J = 7.1 Hz, 12 H), 1.06 (m, 4 H), 1.70 (m, 4 H) and 2.50 (m, 10 H); δ_C(75 MHz, $CDCl_3$) 14.8, 26.2, 27.5, 43.7 and 60.7; $[\alpha]_D^{20}$ −86.1 (*c* 1.17, EtOH) (Found: C, 74.1; H, 13.4; N, 12.4. Calc. for $C_{14}H_{30}N_2$: C, 74.27; H, 13.36; N, 12.37%).

(−)-*trans*-1,2-Diethoxycarbonylaminocyclopentane 27

To a solution of 2.00 g (20.0 mmol) of (−)-*trans*-cyclopentane-1,2-diamine,[19] $[\alpha]_D^{20}$ −45.1 (*c* 4.87, toluene), in 50 cm^3 of toluene were added at 0 °C simultaneously a solution of 4.85 g (44.7 mmol) of ethyl chloroformate in 50 cm^3 of toluene and a solution of 2.64 g (47.1 mmol) of potassium hydroxide in 50 cm^3 of water. After stirring for 12 h the phases were separated and the aqueous phase was extracted twice with 20 cm^3 each of ethyl acetate. The combined organic phases were washed with 20 cm^3 each of saturated aq. NH_4Cl, saturated $NaHCO_3$, water and brine. After drying over $MgSO_4$ the solvents were removed under reduced pressure to leave 4.50 g (88%) of **27**. The material was recrystallized twice from a mixture of 100 cm^3 of hexane and 50 cm^3 of ethyl acetate to give 2.10 g of compound **27**: mp 168 °C; $[\alpha]_D^{20}$ −11.8 (*c* 1.47, ethyl acetate); δ_H(300 MHz, $CDCl_3$) 1.19 (t, J = 7.1 Hz, 6 H), 1.40 (m, 2 H), 1.68 (m, 2 H), 2.11 (m, 2 H), 3.64 (m, 2 H), 4.16 (q, J = 7.1 Hz, 4 H) and 5.11 (br s, 2 H); δ_C(75 MHz, $CDCl_3$) 14.5, 19.6, 30.0, 57.9, 60.8 and 157.0 (Found: C, 54.25; H, 8.3; N, 11.5. Calc. for $C_{11}H_{20}N_2O_4$: C, 54.08; H, 8.25; N, 11.47%).

***trans*-*N*,*N*′-Diethoxycarbonyl-*N*,*N*′-dimethylcyclopentane-1,2-diamine 28**

A solution of 2.10 g (8.60 mmol) of **27** in 20 cm^3 of anhydrous THF was added carefully dropwise at 0 °C to a suspension of 1.20 g (50.0 mmol) of sodium hydride in a solution of 7.36 g (52.0 mmol) of methyl iodide in 150 cm^3 of anhydrous THF. When the vigorous gas evolution had ceased, stirring was continued for 1 d at room temperature. The organic phase was decanted from the precipitate formed and the precipitate was washed twice with 20 cm^3 each of diethyl ether. The combined organic phases were washed with 50 cm^3 each of saturated aq. NH_4Cl, water and brine. After drying over $MgSO_4$ the solvents were removed under reduced pressure and the residue was purified by flash chromatography over silica gel with diethyl ether–light petroleum (1:1) to give 2.24 g (96%) of compound **28** as a colourless solid; mp 84–86 °C; $[\alpha]_D^{20}$ −51.3 (*c* 1.96, ethyl acetate); δ_H(300 MHz, $CDCl_3$) 1.14 (several t, J = 7.1 Hz, 6 H), 1.46–1.75 (m, 6 H), 2.69 (br s, 6 H), 4.01 (m, 4 H) and 4.23 (m, 2 H); δ_C(75 MHz, $CDCl_3$) 14.5, 19.4, 24.5, 27.9, 56.1, 61.1 and 156.5 (Found: C, 57.3; H, 9.0; N, 10.2. Calc. for $C_{13}H_{24}N_2O_4$: C, 57.33; H, 8.88; N, 10.29%).

(−)-*trans*-*N*,*N*,*N*′,*N*′-tetramethylcyclopentane-1,2-diamine 22

A solution of 2.22 g (8.15 mmol) of the carbamate **28** in 20 cm^3 of anhydrous THF was added dropwise at 0 °C to a suspension of 1.15 g (30 mmol) of $LiAlH_4$ in 50 cm^3 of anhydrous THF. The mixture was held under reflux for 12 h and was hydrolysed by addition of 50 cm^3 of 10% aq. KOH. 5 g of NaCl were added to the resulting suspension with stirring. The organic phase was decanted and the precipitate was washed twice with 50 cm^3 each of diethyl ether. The combined organic phases were washed with 20 cm^3 each of water and brine, dried over K_2CO_3–KOH and concentrated. Bulb-to-bulb distillation of the residue at 14 Torr from a bath of 170 °C furnished 1.24 g (97%) of **22** as a colourless liquid; δ_H(300 MHz, $CDCl_3$) 1.55 (m, 6 H), 2.22 (s, 12 H) and 2.69 (m, 2 H); δ_C(75 MHz; $CDCl_3$) 23.5, 25.1, 42.4 and 68.9; $[\alpha]_D^{20}$ −70.1 (*c* 1.71, ethanol) (Found: C, 69.0; H, 13.1; N, 18.0. Calc. for $C_9H_{20}N_2$: C, 69.17; H, 12.90; N, 17.93%).

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