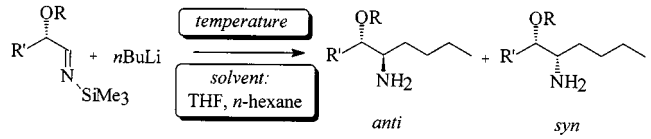
Reversal Diastereofacial Selectivity in the *n*-Butyllithium Addition to *O*-Protected *N*-Trimethylsilylimines of (2*S*)-Lactal: Enthalpic versus Entropic Contributions

Gianfranco Cainelli,*[a] Daria Giacomini,*[a] and Paola Galletti[a]

Keywords: Nucleophilic addition / Solvent effect / Reversal of diastereoselectivity / Temperature effect / Imines

Commonly observed, but rarely explored, is the possibility of modifying the diastereomeric excess (*de*%) by means of temperature. A complete reversal in the diastereofacial selectivity could be obtained whenever the diastereoisomers concerned are differentially favored by enthalpy and entropy. The enthalpic or entropic dominance of a diastereoisomer depends greatly on the reaction solvent used.

Nucleophilic addition to carbonyls is one of the most important strategies in building up the molecular skeleton of organic compounds. The control and the prediction of the stereochemistry in this C−C bond formation has been the subject of debate for four decades. The theory of nucleophilic attack on a chiral aldehyde or ketone uses a plethora of conformational models that should predict which diastereoisomer is formed predominantly. Some of the earliest attempts to understand the addition of organometallic compounds were rationalizations and predictive models made by Curtin,[1] Cram,[2] and Prelog,[3] in the early 1950′s, nevertheless theoretical investigations into the origin of open-chain and cyclic models continues.[4] Less attention has been paid to the dependence of diastereomeric excess (*de*) on temperature[5] in the case of the 1,2-asymmetric induction of an α-stereocenter of carbonyl or iminic compounds. In general it is thought that the best diastereoselectivity should be obtained at low temp., while at higher temp. the *de* should decrease, but the question is what is the value of *de* that could be attained?



1: R = *t*BuMe$_2$Si, R' = Me
2: R = *i*Pr$_3$Si, R' = Me
3: R = *t*Bu, R' = Me
4: R = *t*BuMe$_2$Si, R' = C$_4$H$_9$

1a- 4a **1b- 4b**

Scheme 1

Here we report on a study of the temperature effect in the *n*BuLi addition to *O*-protected *N*-trimethylsilyl imines of (2*S*)-lactal. In a preceding paper,[6] the influence of the reaction solvent on the *anti/syn* ratio of the two amino ethers **1a** and **1b** was shown to be significant. In addition, we observed in *n*-hexane a reversal in the diastereoselectivity depending on the reaction temperature ($T = -90$°C *anti/syn* = 72:28; $T = 54$°C *anti/syn* = 22:78).

The temperature dependence in the formation of two diastereoisomers can be analyzed according to the modified Eyring equation[7]

$$\ln P = -(\Delta\Delta H^{+}/RT) + (\Delta\Delta S^{+}/R) \quad (1)$$

where $P = k/k' = I/I'$, k and k' are the overall rate constants and I and I' are the% of *anti* and *syn* isomer, respectively.

The inversion of diastereomeric excess with reaction temperature[8] occurs at the *x*-axis crossing ($\ln P = 0$, *de*% = 0) in the linear Eyring plot of $\ln P$ against $1/T$, thus identifying an equiselective temperature $T_o = \Delta\Delta H^{+}/\Delta\Delta S^{+}$. Because of the positive value of the absolute temperatures, the reversal of *de*% occurs when the differential enthalpic and entropic terms have the same sign. In this case, there exists a temperature range where $T\Delta\Delta S^{+} < \Delta\Delta H^{+}$, and another where $T\Delta\Delta S^{+} > \Delta\Delta H^{+}$. Whenever the *anti* isomer prevails, a negative value of the differential activation entalphy ($\Delta H^{+}_{anti} - \Delta H^{+}_{syn} = \Delta\Delta H^{+} < 0$) results. Assuming that an addition reaction is accompanied by a loss of activation entropy, ΔS^{+}_{anti} and ΔS^{+}_{syn} are both negative and the condition for the *de* inversion, $\Delta\Delta S^{+} < 0$, requires $|\Delta S^{+}_{anti}| > |\Delta S^{+}_{syn}|$: the entropic loss in the formation of the *anti* isomer is larger than that for the *syn* isomer. As a consequence, the *anti* isomer is enthalpically favored whereas the *syn* isomer is entropically favoured. At low temp., the former prevails, while at high temperature the latter is preferred. It is important to emphasize that if the same stereoisomer is both enthalpically and entropically favored ($\Delta\Delta S^{+}$ and $\Delta\Delta H^{+}$ have opposite signs, see Eq. 1, so that both effects work cooperatively), an inversion in the diastereomeric excess can never be obtained by solely controlling the temperature.

In the case of *n*BuLi addition to *O*-protected-*N*-trimethylsilyl imines, we obtained several examples of a complete temperature-dependent reversal in the diastereofacial selectivity. The addition reactions were performed by adding a

[a] Dipartimento di Chimica "G.Ciamician"
Via Selmi 2, I-40126 Bologna, Italy
Fax: (internat.) +39 (0)51/ 25-9456
E-mail: cainelli@ciam.unibo.it; giacomin@ciam.unibo.it

  1434−193X/99/0101−0061 $ 17.50+.50/0

Table 1. Influence of temperature and solvent on the diastereoselectivity of the nucleophilic addition of *n*-butyllithium to imines **2**−**4**. The reaction yields range from 75 to 95%.

imine	solvent	*T* [°C]	*anti*	*syn*	imine	solvent	*T* [°C]	*anti*	*syn*
2	THF	22	74.5	25.5	**3**	THF	−55	10.0	90.0
2	″	14	76.2	23.8	**3**	″	−66	4.8	95.2
2	″	0	73.7	26.3	**3**	″	−82	1.0	99.0
2	″	−18	75.7	24.3	**3**	*n*-hexane	31	19.5	80.5
2	″	−30	77.1	22.9	**3**	″	18	25.0	75.0
2	″	−37	72.1	27.9	**3**	″	12	27.2	72.8
2	″	−50	70.0	30.0	**3**	″	0.8	29.8	70.2
2	″	−60	60.6	39.4	**3**	″	−14	39.7	60.3
2	″	−66	57.4	42.6	**3**	″	−20	44.3	55.7
2	″	−70	52.9	47.1	**3**	″	−30	49.7	50.3
2	″	−75	48.1	51.9	**3**	″	−40	47.9	52.1
2	″	−76	43.0	57.0	**3**	″	−48.5	49.1	50.3
2	″	−81	36.7	63.3	**3**	″	−56	46.7	53.3
2	″	−84	34.3	65.7	**3**	″	−70	47.1	52.9
2	″	−94	20.5	79.5	**3**	″	−78	47.9	52.1
2	″	−96	24.0	76.0					
2	″	−98	23.2	76.8	**4**	THF	23.3	29.0	71.0
2	*n*-hexane	52.6	50.2	49.8	**4**	″	12.8	26.5	73.5
2	″	49.4	50.3	49.7	**4**	″	0.3	31.4	68.6
2	″	42.4	49.1	50.9	**4**	″	−10.7	31.9	68.1
2	″	31.5	49.0	51.0	**4**	″	−23.2	30.6	69.4
2	″	23	47.6	52.4	**4**	″	−33.2	29.8	70.2
2	″	15	49.1	50.9	**4**	″	−50	24.3	75.7
2	″	10	50.7	49.3	**4**	″	−61	18.6	81.4
2	″	0.8	53.8	46.2	**4**	″	−69.7	15.4	84.6
2	″	−9.5	55.6	44.4	**4**	″	−80	10.2	89.8
2	″	−20	60.7	39.3	**4**	″	−89	7.2	92.8
2	″	−30	64.4	35.6	**4**	*n*-hexane	59.4	20.7	79.3
2	″	−42	69.1	30.9	**4**	″	42.7	23.0	77.0
2	″	−50	69.3	30.7	**4**	″	29.7	23.5	76.5
2	″	−53	70.3	29.7	**4**	″	11	26.3	73.7
					4	″	0.6	27.9	72.1
3	THF	34	57.0	43.0	**4**	″	−10	34.2	65.8
3	″	20	55.0	45.0	**4**	″	−20	40.6	59.4
3	″	14	54.3	45.7	**4**	″	−30	46.5	53.5
3	″	0	54.0	46.0	**4**	″	−39.5	53.1	46.9
3	″	−10	44.1	55.9	**4**	″	−50	60.3	39.7
3	″	−22	35.3	64.7	**4**	″	−60.6	63.7	36.3
3	″	−31	27.0	73.0	**4**	″	−70	60.1	39.9
3	″	−42	20.0	80.0	**4**	″	−90	50.7	49.3

stoichiometric amount of *n*BuLi (2.5 M solution in *n*-hexane) to imines **2**−**4** in two dry solvents, THF and *n*-hexane, the reaction temp. was varied over a range of 150°C (see Scheme 1). The diastereomeric excess of products within the crude reaction mixture was determined by GC analysis for the amino ethers **2a**−**b**, whereas **3a**−**b** and **4a**−**b** were GC analyzed after their quantitative derivatization as trifluoroacetamides.[9] The results are reported in Table 1.

The Eyring-plots for all imines are given in Figure 1. The data were treated by the least-squares method in order to obtain linear relationships. In the temp. range explored each imine/solvent combination showed two linear regions[10] and in all cases we could determine a characteristic inversion temperature (T_{inv}).[11]

The correlation lines of the imines **2** and **3** in THF cross the *x* axis (*de*% = 0) at T_o = −71.2°C and T_o = −8.6°C, respectively. In *n*-hexane, the same phenomenon occurs for the imines **1**, **2**, and **4** at T_o = −54.9°C, 15.4°C, and −36.5°C respectively.

In THF in the high temperature region, the contribution of enthalpic differences is very small and the plots for all imines show an almost zero slope. In these cases, there is no temperature control of stereoselectivity, the *de* differences that still remain are entirely determined by the entropic term $\Delta\Delta S^{\ddagger}$ (according to Eq. 1).[12] In this region, a longer alkyl side chain (imine **4**) seems to have very little influence on the entropic difference, while the protecting group on the oxygen atom exert a major effect. The *O*-TIPS- and the *O*-TBDMS-*N*-TMS imines show opposing diastereofacial selectivity, for **2** the differential entropy $\Delta\Delta S^{\ddagger}$ is positive, while for **1** it is negative. As a matter of fact, in one case the *anti* isomer is favored, and in the other the *syn* isomer is preferred notwithstanding the reliable non-chelating behaviour of the sterically demanding α-silyloxy protecting groups, in particular those of the *O*-TIPS derivatives.[13] It is remarkable to note that for imine **1** ($\Delta\Delta S^{\ddagger} < 0$) the transition state leading to the *anti* isomer is more ordered than that which leads to the *syn* isomer. This fact excludes the hypothesis that the prevailing *syn* isomer derives from a chelated transition state.[14] At low temp., all substrates have a similar behaviour, which favors the *syn* isomer. The slopes are not markedly different and all four plots can be reproduced by translation of each other. Once more, an entropic factor determines the diastereomeric excess.

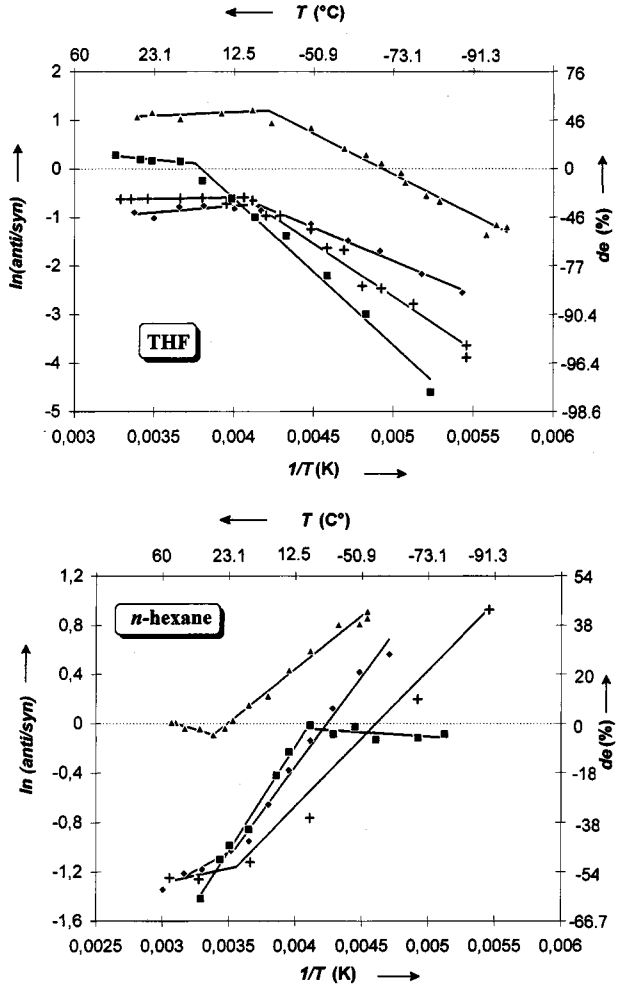


Figure 1. Eyring plots for the diastereomeric excess obtained in the nucleophilic addition of *n*-butyllithium to **1** (+), **2** (•), **3** (■), **4** (◆) in THF and *n*-hexane at various temperatures.

It is noteworthy, that the results in THF and *n*-hexane show opposing trends and at low temperature in *n*-hexane the *anti* isomer is preferred.

In *n*-hexane, the imines **1**, **2**, and **4** have a positive slope and exibit a reversal of *de*% on going from a predominance in *syn* isomers at high temp. to a predominance of *anti* isomers at lower temp. Even the *O*-*t*Bu-*N*-TMS imine has a positive slope, and should behave in the same way as the others, but, in this case, the T_{inv} causes this to breakdown and there is a new linear trend with a different intercept and slope, so that the *de*% inversion is prevented.

The differential activation parameters for all imines have been calculated from the linear Eyring plots before and after the inversion temp. and they are listed in Table 2. It is significant that in all cases both $\Delta\Delta S^{\ddagger}$ and $\Delta\Delta H^{\ddagger}$ have the same sign (inversion of diastereoselectivity by temperature). However, for imines **1**, **2**, and **4**, but not **3**, the activation parameters for $T < T_{inv}$ showed a switch in sign on going from THF to *n*-hexane (inversion of diastereoselectivity by solvent).

As discussed above, the inversion of the diastereoselectivity with the temp. occurs whenever the formation of one diastereoisomer is enthalpically, and the other entropically, favored. An analysis based only upon enthalpic contributions due to steric and stereoelectronic interactions in the transition state (as in the case of classical conformational models) appears quite limited and is unable to explain this inversion because of the underestimation of entropic effects.

It appears quite reasonable that the two reaction pathways, leading to the *syn* and *anti* isomers, have the same reaction mechanism. The difference in activation entropies then occurs because of the different molecular structure of the reacting imine and *n*BuLi or of the imine/nucleophile complex.[15] As far as the molecular structure of *n*BuLi is concerned, it is known that its aggregation state changes with solvent.[16] However, the dynamic process that involves the aggregation state of *n*BuLi cannot explain our results because it represents the situation before the nucleophilic attack, and it would act in the same way for both diastereomeric transition states. So only the molecular structure of the reacting π-component should be responsible for the entropic differences observed. Entropies of activation can be closely related to the differences in number and character of the degrees of freedom of the system analyzed. In the case of reaction in solution, we have to consider the system formed by the reagent with its solvation shell or the solvated reacting complex.

In fact the experimental data obtained with *N*-TMS imines clearly show that the isomer, enthalpically or entropically controlled, is not the same in different solvents. Small enthalpic and entropic differences play a role in the discrimination between the two isomers, as is indicated in Table 2.[17] It is important to underline that the $\Delta\Delta G_{298}$ values are much smaller than the free solvation energies of carbonyl compounds in non-aqueous solvents.[18] This means that even unspecific solute-solvent interactions are able to modify the diastereoselectivity of a reaction.[19]

All the data presented clearly show that the Eyring equation itself drives the temperature dependence of *de*% and provides for a complete inversion when $\Delta\Delta S^{\ddagger}$ and $\Delta\Delta H^{\ddagger}$ have the same sign, unless the T_{inv} prevents the phenomenon. A temperature range can exist in which, because of a zero differential enthalpy, the differential activation entropy exclusively controls the diastereofacial selectivity. Moreover, whether a diastereoisomer is enthalpically or entropically favored depends on the arrangement of reagents in the bulk, so that a different molecular solute/solvent organization could be responsible for the fine tuning in the predominance of $\Delta\Delta S^{\ddagger}$ or $\Delta\Delta H^{\ddagger}$.

Because of the complexity of the phenomena involved in these reactions, it is very difficult to formulate a detailed microscopic model, but some hypotheses can be considered. Two cases can be analyzed. The solvent enthalpically favors and entropically disfavors an isomer whenever the solute/solvent interactions are high in strength or in number, thus stabilizing conformers with the lowest number of intramolecular steric interactions. The solvent entropically favors and enthalpically disfavors an isomer whenever the solute/solvent interactions are mild or low in number and the sol-

Table 2. Differential activation parameters and inversion temperatures for *n*BuLi addition to imines **1**−**4**

imine	solvent	T_{inv} [°C]	$\Delta\Delta H$ (kcal/mol) $T>T_{inv}$	$\Delta\Delta S$ (cal/mol K) $T>T_{inv}$	$\Delta\Delta H$ (kcal/mol) $T<T_{inv}$	$\Delta\Delta S$ (cal/mol K) $T<T_{inv}$	$\Delta\Delta G$ (298 K) (kcal/mol)
1	THF[a]	−26.8	−0.10 ± 0.01	−1.59 ± 0.02	4.3 ± 0.3	16.4 ± 1.4	0.37
1	*n*-hexane[a]	7.9	−0.58 ± 0.22	−4.3 ± 0.7	−2.2 ± 0.4	−10.4 ± 1.7	0.71
2	THF	−35.8	−0.28 ± 0.22	1.2 ± 0.8	3.3 ± 0.2	16.4 ± 0.9	−0.63
2	*n*-hexane	22.4	0.65 ± 0.11	2.0 ± 0.4	−1.7 ± 0.1	−5.9 ± 0.3	0.05
3	THF	−7	0.59 ± 0.18	2.4 ± 0.6	5.9 ± 0.3	22.7 ± 1.5	−0.14
3	*n*-hexane	−28.4	−3.36 ± 0.13	−13.8 ± 0.5	0.14 ± 0.1	0.52 ± 0.5	0.75
4	THF	−31.8	−0.52 ± 0.37	−3.6 ± 1.4	2.7 ± 1.5	9.8 ± 0.7	0.05
4	*n*-hexane	8.6	−1.17 ± 0.07	−6.2 ± 0.3	−2.9 ± 0.2	−12.3 ± 0.7	0.67

[a] Data for the imine **1** were extrapolated from those in ref.[6]

vation resulting less ordered, thus making the system conformationally less rigid. More detailed modelling of the solvation is certainly necessary in order to gain a deeper insight into the diastereofacial selectivity, but, at the moment, it suffers from the lack of an appropriate computational approach.

Nevertheless, all these arguments support the hypothesis that the main factor in the diastereofacial control is a stereospecific solvation of the reacting π-system. In the case of a stereospecific addition of amines to ketenes, Pracejus already proposed a similar hypothesis in 1963, in a seminal but little known paper.[20] Studies are in progress in order to obtain better confirmation of this hypothesis.

Experimental Section

General: All reactions were performed in flame-dried glassware under an atmosphere of argon. − ^{1}H- and ^{13}C-NMR: Varian Gemini 300 and Gemini 200 instruments using $CDCl_3$ as a solvent, chemical shifts are quoted relative to TMS as the external standard; δ in ppm, *J* in Hz. − FT-IR: Nicolet 205 FT measured as films between NaCl plates and reported in cm^{-1}. − GC-MS: HP5980, capillary column HP-1 or HP-5 connected to HP5970 (70eV). − GC: FISONS G8000, column: HP-5 M.S. crosslinked 5% PhMeSilicone, 30 m × 0.25 mm × 0.25 μm, chiral column OV 1701 H. − TLC: Merck $60F_{254}$. − Column chromatography: Merck silica gel 200−300 mesh. During reactions, to set and mantain the temp. in the range of ±1°C, liquid N_2/acetone bath in Dewar containers or oily bath with water cooling were used. The temp. given refers to the interior of the reaction apparatus.

Starting Materials: Hexane was dried by distillation from sodium, THF from sodium-benzophenone and stored on Molecular Sieves 4 Å. BuLi (commercial 2.5 M solution in hexane) was titrated shortly before use with a 1.0 M solution of *sec*-butanol in xylene using phenanthroline as an indicator.[21] All silylimines **1**−**4** were prepared according to the procedure reported in the literature,[22] and purified by distillation under high vacum ($1.2 \cdot 10^{-5}$ mbar).

In a typical experiment, the iminic compound (1 mmol) was dissolved in anhydrous solvent (20 mL) under inert atmosphere, and the solution was cooled to the desired temp.; then *n*-butyllithium (1.2 mmol, 0.48 mL of a 2.5 M solution in *n*-hexane) was added. After the starting imine disappeared (GC-monitoring), the reaction was quenched with a satd. aqueous solution of NH_4Cl, extracted with CH_2Cl_2 (3 × 50 mL), and dried with $MgSO_4$. From GC analysis of the crude products or of the corresponding *N*-trifluoroacetamide derivatives, the *anti/syn* ratio and the *de%* value were obtained.

(2*S*,3*R*)-2-*tert*-Butyldimethylsilyloxy-3-aminoheptane, *anti* Isomer (1a): IR (film): $\tilde{\nu}$ = 3350 cm^{-1}; 1250; 1150; 860. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.04 (s, 3 H, CH_3Si), 0.06 (s, 3 H, CH_3Si), 0.9 [m, 12 H, $SiC(CH_3)_3$ and CH_3CH_2], 1.03 (d, *J* = 6.2 Hz, 3 H, CH_3CHO), 1.35 [m, 8 H, $(CH_2)_3$ and NH_2], 2.72 (dt, *J* = 3.7 Hz and *J* = 7.8 Hz, 1 H, $CHNH_2$), 3.69 (dq, *J* = 6.2 Hz and *J* = 3.7 Hz, 1 H, CHO). − ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = −5.0, −4.6, 13.9, 16.8, 17.9, 22.8, 25.7, 28.8, 32.7, 56.8 (C−N), 71.5 (C−O). − MS (70 eV): *m/z* (%) = 230 (1) [$M^+ - CH_3$], 188 (28) [$M^+ - t$Bu], 159 (1), 115 (2), 86 (100), 74 (25), 59 (5).

(2*S*,3*S*)-2-*tert*-Butyldimethylsilyloxy-3-aminoheptane, *syn* Isomer (1b): IR (film): $\tilde{\nu}$ = 3350 cm^{-1}, 1250, 1150, 860. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.05 [s, 6 H, $(CH_3)_2Si$], 0.9 [m, 12 H, $SiC(CH_3)_3$, CH_3CH_2], 1.12 (d, *J* = 6.2 Hz, 3 H, CH_3CHO), 1.35 [m, 8 H, $(CH_2)_3$, NH_2], 2.46 (dt, *J* = 4.5 Hz and *J* = 8.5 Hz, 1 H, $CHNH_2$), 3.59 (dq, *J* = 6.2 Hz and *J* = 4.5 Hz, 1 H, CHO). − ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = −4.5, −4.2, 14.0, 18.0, 20.5, 22.8, 25.8, 28.6, 33.7, 57.3 (C−N), 71.7 (C−O). − MS (70 eV): *m/z* (%) = 230 (1) [$M^+ - CH_3$], 188 (28) [$M^+ - t$Bu], 159 (1), 115 (2), 86 (100), 74 (25), 59 (5).

(2*S*,3*R*)-2-Triisopropylsilyloxy-3-aminoheptane, *anti* Isomer (2a): IR (film): $\tilde{\nu}$ = 3300 cm^{-1}, 1150, 1050. − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.91 (t, *J* = 6.4 Hz, 3 H, CH_3CH_2), 1.07 {m, 21 H, $[(CH_3)_2CH]_3Si$ and CH_3CHO}, 1.26−1.33 {m, 9 H, $(CH_2)_3CH_3$ and $[(CH_3)_2CH]_3Si$}, 1.60 (bs, 2 H, NH_2), 2.83 (dt, *J* = 3.5 Hz and *J* = 7.6 Hz, 1 H, $CHNH_2$), 3.86 (dq, *J* = 3.5 Hz and *J* = 6.2 Hz, 1 H, CHO). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 12.3, 13.8, 15.9, 17.9, 22.7, 28.8, 32.9, 56.6 (C−N), 71.1 (C−O).). − MS (70 eV): *m/z* (%) = 272 (1) [$M^+ - CH_3$], 244 (63), 157 (7), 130 (47), 115 (10), 102 (15), 86 (100), 75 (7), 73 (7), 59 (11).

(2*S*,3*S*)-2-Triisopropylsilyloxy-3-aminoheptane, *syn* Isomer (2b): IR (film): $\tilde{\nu}$ = 3300 cm^{-1}, 1150, 1050. − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.91 (t, *J* = 6.4 Hz, 3 H, CH_3CH_2), 1.07 {m, 18 H, $[(CH_3)_2CH]_3Si$}, 1.17 (d, *J* = 6.2 Hz, 3 H, CH_3CHO), 1.26−1.33 {m, 9 H, $(CH_2)_3CH_3$ and $[(CH_3)_2CH]_3Si$}, 1.60 (bs, 2 H, NH_2), 2.53 (dt, *J* = 4.5 Hz and *J* = 8.5 Hz, 1 H, $CHNH_2$), 3.80 (dq, *J* = 4.5 and *J* = 6.2 Hz, 1 H, CHO). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 12.5, 13.8, 17.9, 19.9, 22.7, 28.7, 33.1, 57.5 (C−N), 72.2 (C−O). − MS (70 eV): *m/z* (%) = 272 (1) [$M^+ - CH_3$], 244 (70), 157 (7), 130 (47), 115 (10), 102 (15), 86 (100), 75 (7), 73 (7), 59 (11).

(2*S*,2*R*)-2-*tert*-Butyloxy-3-aminoheptane, *anti* Isomer (3a): IR (film): $\tilde{\nu}$ = 3300 cm^{-1}, 1050. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.91 (t, *J* = 6.8 Hz, 3 H, CH_3CH_2), 1.01 (d, *J* = 6.3 Hz, 3 H, CH_3CHO), 1.21 [s, 9 H, $(CH_3)_3C$], 1.23−1.40 [m, 8 H, $(CH_2)_3$,

NH_2], 2.72 (m, 1 H, C*H*NH_2), 3.53 (dq, J = 6.3 Hz and J = 3.7 Hz, 1 H, CHO). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.0, 15.6, 22.8, 28.4, 28.8, 33.3, 56.2 (C−N), 69.7 (C−O), 73.3 − MS (70 eV): *m/z* (%) = 130(1) [M^+ − *t*Bu], 114 (6), 86 (100), 57 (13).

(2*S*,3*S*)-2-*tert*-Butyloxy-3-aminoheptane, *syn* Isomer (3b): IR (film): ṽ 3300 cm^{-1}, 1050. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.91 (t, J = 6.8 Hz, 3 H, CH_3CH$_2$), 1.12 (d, J = 6.1 Hz, 3 H, CH_3CHO), 1.21 [s, 9 H, $(CH_3)_3$C], 1.25−1.60 [m, 8 H, $(CH_2)_3$, NH_2], 2.51 (m, 1 H, C*H*NH_2), 3.38 (q, J = 6.2 Hz, 1 H, CHO). − ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.1, 19.8, 22.9, 28.5, 28.8, 33.2, 56.7 (C−N), 71.4 (C−O), 73.4. − MS (70 eV): *m/z* (%) = 130 (1) [M^+ − *t*Bu], 114 (6), 86 (100), 57 (13).

(5*SR*,6*RS*)-5-*tert*-Butyldimethylsilyloxy-6-aminodecane, *anti* Isomer (4a): IR (film): ṽ = 3350 cm^{-1}, 1254, 1080, 1058, 836. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.12 [s, 6 H, $(CH_3)_2$Si], 0.87 [m, 15 H, $SiC(CH_3)_3$ and CH_3], 1.32 [m, 12 H, $(CH_2)_6$], 1.62 (bs, 2 H, NH_2), 2.77 (m, 1 H, C*H*NH_2), 3.56 (m, 1 H, CHO). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = −4.5, −4.4, 13.7, 18.1, 22.8, 22.9, 25.9, 28.1, 28.9, 30.0, 32.5, 55.9 (C−N), 75.8 (C−O). − MS (70 eV): *m/z* (%) = 272 (1) [M^+ − CH_3], 230 (15), 201 (7), 145 (3), 115 (8), 86 (100), 73 (21), 59 (5).

(5*SR*,6*SR*)-5-*tert*-Butyldimethylsilyloxy-6-aminodecane, *syn* Isomer (4b): IR (film): ṽ = 3350 cm^{-1}, 1254, 1080, 1058, 836. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.08 (s, 3 H, CH_3Si), 0.09 (s, 3 H, CH_3Si), 0.92 [m, 15 H, $SiC(CH_3)_3$, CH_3CH$_2$], 1.32 [m, 12 H, $(CH_2)_6$], 1.62 (bs, 2 H, NH_2), 2.58 (m, 1 H, C*H*NH_2), 3.50 (m, 1 H, CHO). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = −4.6, −4.2, 14.0, 18.1, 22.8, 22.9, 25.9, 27.4, 28.8, 33.3, 33.9, 54.0 (C−N), 75.5 (C−O). − MS (70 eV): *m/z* (%) = 272 (1) [M^+ − CH_3], 230 (15), 201 (7), 145 (3), 115 (8), 86 (100), 73 (21), 59 (5).

Acknowledgments

This work was supported by Ministero dell′Università e della Ricerca scientifica e Tecnologica (MURST) and the University of Bologna (fund for selected topics). We thank Nerozzi Fabrizio and Vaccari Elisabetta for performing part of the experimental data.

[1] D. Y. Curtin, E. E. Harris, E. K. Meislich, *J. Am. Chem. Soc.* **1952**, *74*, 2901.
[2] D. J. Cram, F. A. A. Elhafez, *J. Am. Chem. Soc.* **1952**, *74*, 5828.
[3] V. Prelog, *Helv. Chim. Acta* **1953**, *36*, 308.
[4] For a review on classical conformational models: [4a] E. L. Eliel, S. H. Wilen, L. N. Mander, *Stereochemistry of Organic Compounds;* Wiley: New York, **1994**, p. 875. For recent theoretical studies see: − [4b] V. S. Safont, V. Moliner, M. Oliva, R. Castillo, J. Andrés, F. Gonzáles, M. Carda, *J. Org. Chem.* **1996**, *61*, 3467. − [4c] S. Mori, M. Nakamura, E. Nakamura, N. Koga, K. Morokuma, *J. Am. Chem. Soc.* **1995**, *117*, 5055
[5] R. E. Gawley, J. Aubé, *Principles of Asymmetric Synthesis;* Pergamon: Oxford, **1996**, p.7 and references therein.
[6] [6a] G. Cainelli, D. Giacomini, M. Walzl, *Angew. Chem.* **1995**, *107*, 2336; *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2150. See also: − [6b] G. Cainelli, D. Giacomini, F. Perciaccante, *Tetrahedron: Asymmetry* **1994**, *5*, 1913.
[7] H. Eyring, *J. Phys. Chem.* **1935**, *3*, 107. S. Glasstone, K. J. Laidler, H. Eyring, *The Theory of Rate Processes.* McGraw −Hill, New York, **1941**, Chap.4.
[8] See for example: [8a] N. Hoffmann, H. Buschmann, G. Raabe, H-D. Scharf, *Tetrahedron* **1994**, *50*, 11167. − [8b] Y. Inoue, N. Yamasaki, T. Yokoyama, A. Tai, *J. Org. Chem.* **1992**, *57*, 1332. − [8c] D. Awandi, F. Henin, J. Muzart, J-P. Pete, *Tetrahedron: Asymmetry* **1991**, *2*, 1101.
[9] The diastereoselectivity of the product formation is characterized by the *de* value of the *anti* adduct, which was determined by GC analysis of the crude product, or of the corresponding *N*-trifluoroacetamides, according to the procedure reported in: T. W. Greene, P. G. M. Wuts *Protective Groups in Organic Synthesis.* Wiley, New York, **1991**, 353.
[10] For a review see: [10a] H. Buschmann, H.-D. Scharf, N. Hoffmann, P. Esser, *Angew. Chem.* **1991**, *103*, 480; *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 477. For recent papers see: − [10b] K. J. Hale, J. H. Ridd, *J. Chem. Soc., Perkin Trans. 2* **1995**, 1601. − [10c] J. Muzart, F. Hénin, S. J. Aboulhoda, *Tetrahedron: Asymmetry* **1997**, *8*, 381. − [10d] M. Palucki, P. J. Pospisil, W. Zhang, E. N. Jacobsen, *J. Am. Chem. Soc.* **1994**, *116*, 9333. − [10e] J. Brunne, N. Hoffmann, H.-D. Scharf, *Tetrahedron* **1994**, *50*, 6819. − [10f] T. Göbel, K. B. Sharpless, *Angew. Chem.* **1993**, *105*, 1417; *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1329. − [10g] J. Muzart, F. Hénin, J.-P. Pète, A. M′boungou-M′Passi, *Tetrahedron Asymmetry* **1993**, *4*, 2531. − [10h] I. Tóth, I. Guo, B. E. Hanson, *Organometallics* **1993**, *12*, 477.
[11] This paper is not concerned with the very nature of T_{inv}, which is probably related to a re-organization of the solvation shell, as indicated by the correlation with melting points of a series of hydrocarbon solvents in the case of the *n*BuLi addition to 2-phenyl-propanal, cfr.: G. Cainelli, D. Giacomini, P. Galletti, A. Marini, *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2849.
[12] See for instance: R. E. Rosenberg, J. S. Vilardo, *Tetrahedron Lett.* **1996**, *37*, 2185.
[13] X. Chen, E. R. Hortelano, E. L. Eliel, *J. Am. Chem. Soc.* **1990**, *112*, 6130.
[14] The preponderant formation of *syn* isomers is generally attributed to a chelated transition state (chelation control), while the *anti* isomer should arise from an open-chain transition state (non-chelation control). See for instance [14a] M. T. Reetz, *Acc. Chem. Res.* **1993**, *26*, 462. − [14b] M. T. Reetz *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 556. However, the chelated transition state should be more rigid and more ordered than the open-chain one.
[15] L. L. Schleger, F. A. Long, *Adv. Phys. Org. Chem.* **1963**, *1*, 1.
[16] M. Schlosser, *Organometallics in Synthesis.* Wiley, New York, **1994**, 11.
[17] B. Giese, *Acc. Chem. Res.* **1984**, *17*, 438.
[18] D. J. Giesen, C. J. Cramer, D. G. Truhlar, *J. Phys. Chem.* **1995**, *99*, 7137.
[19] [19a] C. Reichardt, *Solvents and Solvent Effects in Organic Chemistry*, 2nd ed., VCH, Weinheim, 1990. − [19b] A. S. Cieplak, K. B. Wiberg, *J. Am. Chem. Soc.* **1992**, *114*, 9226. − [19c] B. Lecea, A. Arrieta, F. P. Cossío, *J. Org. Chem.* **1997**, *62*, 6485. − [19d] C. L. Perrin, M. A. Fabian, I. A. Rivero, *J .Am. Chem. Soc.* **1998**, *120*, 1044.
[20] H. Pracejus, A. Tille, *Chem.Ber.* **1963**, 854.
[21] S. C. Watson, J. F. Eastham, *J. Organom. Chem.* **1967**, *9*, 165.
[22] [22a] G. Cainelli, M. Panunzio, D. Giacomini, G. Martelli, G. Spunta, *J. Am. Chem. Soc.* **1988**, *110*, 6879. − [22b] G. Cainelli, D. Giacomini, E. Mezzina, M. Panunzio, P. Zarantonello, *Tetrahedron Lett.* **1991**, *32*, 2967. − [22c] G. Cainelli, D. Giacomini, M. Panunzio, P. Zarantonello, *Tetrahedron Lett.* **1992**, *33*, 7783.

Received September 14, 1998
[O98414]