Butyllithium Addition to α-Chiral Compounds: Solvent Mixture Effects on Diastereofacial Selectivity

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Dedicated to Professor *Albert Eschenmoser* on the occasion of his 75th birthday

Temperature-dependent selectivity in nucleophilic additions is affected by the solvent. In this context, we investigated the effect on diastereoselectivity of solvent mixtures with respect to pure solvents. Binary systems of THF/hexane and of four different hydrocarbon mixtures were employed in BuLi addition to 2-phenylpropanal, (2*S*)-2-[(*tert*-butyl)dimethylsilyloxy]-2-phenylethanal, and (2*S*)-2-[(*tert*-butyl)dimethylsilyloxy]-*N*-(trimethylsilyl)propan-1-imine. A 5-mol-% of THF in hexane affects the isomer ratio by reducing both $\Delta\Delta H^{\neq}$ and $\Delta\Delta S^{\neq}$ contributions, and suppresses T_{inv}. On the contrary, in hydrocarbon binary mixtures, the T_{inv} is still observed and occurs at a higher temperature than in pure solvents. Studying the dependence of T_{inv} on the hexane/decane mixture composition, we propose the formation of a peculiar solvation cluster that is unaffected by the composition of the bulk reaction solvent.

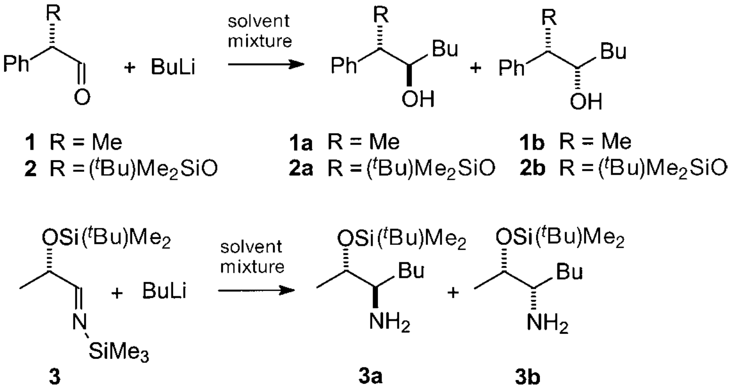
Introduction. – The solvent in which a chemical process takes place is a non-inert medium that plays a prominent role in solution chemistry. Both equilibrium constants and reaction rates may be drastically different in different solvents [1]. Solvent effects are closely related to the nature and extent of solute-solvent interactions locally developed in the microenvironment of the solute molecules. The description, from a microscopic point of view, of solvation processes and of their effects on the energetics and dynamics of chemical reactions constitutes a general and relevant topic of investigation, but research in this field is still at the beginning [2].

Effects of solvent on stereoselectivity have been already recognized by organic chemists, and, in particular, several examples of solvent-dependent face selectivity have been reported. In many cases, a mere variation in the diastereoisomeric excess has been observed (for recent examples, see [3]), whereas, in other cases, a complete reversal of diastereoselectivity occurs because of a change in the solvent. As an example, some years ago, we reported a de [%] reversal in MeMgBr addition to the (*2S*)-*O*-(triisopropylsilyl)lactal [4]. The reaction in THF led to an *anti*/*syn* ratio of 64:36, and in *t*-BuOMe to a ratio of 16:84. Very recently, *Luh* and co-workers reported a reversal of diastereoselectivity in the MeLi and BuLi addition to hydrazones of 1,4-di-*O*-(*tert*-alkoxy)-L-threitols on going from THF to Et_2O [5].

In this context, it was of interest to evaluate the effect of solvent mixtures on stereoselectivity, keeping in mind that solute-solvent interactions should be much more complex in mixtures than in pure solvents. In a pure solvent, the composition of the microsphere of solvation of a solute molecule is the same as in the bulk solvent, whereas, in binary mixtures, the composition in this microsphere can be different. The solute can interact to different degrees with the different components of the mixture, and this difference in interaction is reflected in the composition of the microsphere of solvation. As we have already reported [6], solute-solvent interactions modulate the free activation energies of two reaction paths that lead to a stereospecific solvation control on diastereoselectivity.

In the present paper, we investigate the influence of solvent mixtures on facial stereoselectivity in addition reactions of BuLi to 2-phenylpropanal (**1**), (2*S*)-2-[(*tert*-butyl)dimethylsilyloxy]-2-phenylethanal (**2**), and (2*S*)-2-[(*tert*-butyl)dimethylsilyloxy]-*N*-(trimethylsilyl)propan-1-imine (**3**) (*Scheme*).

Scheme



1 R = Me
2 R = (^{t}Bu)Me$_2$SiO
1a R = Me
2a R = (^{t}Bu)Me$_2$SiO
1b R = Me
2b R = (^{t}Bu)Me$_2$SiO
3
3a
3b

Results and Discussion. – The stereoselectivity (*S*) of an addition reaction on α-chiral carbonyl compounds or imines can be expressed in terms of differential free activation energy by the modified *Eyring* equation (*Eqn. 1*).

$$\ln S = \ln (k/k') = \ln (anti/syn) = -\Delta\Delta G^{\ddagger}/RT = -\Delta\Delta H^{\ddagger}/RT + \Delta\Delta S^{\ddagger}/R \qquad (1)$$

The solvent effect on *S* reflects a different influence on the two reaction paths that lead to the two diastereoisomers through differential contributions to the overall rate constants *k* and *k'* (*Eqn. 1*). A change in the reaction medium corresponds to a change in the microscopic solute-solvent interactions. These interactions can differ in number or strength in different solvents, and they contribute to the differential free activation energy $\Delta\Delta G^{\ddagger}$ in such a way that they can enable even a solvent-dependent reversal of diastereoselectivity, as in the above reported examples.

In solvent mixtures, the solute can establish different interactions with the individual components, and this difference should be reflected in a variation of the overall rate constants such that we expect an effect on the stereoselectivity.

The Binary System: THF and Hexane. We explored first a mixture of an ethereal solvent, such as THF, with a hydrocarbon. Since BuLi is commercially available as a hexane solution, we chose hexane as fixed component of the binary system in order to avoid the presence of two different hydrocarbons. In all experiments, the addition reaction was performed by introducing a stoichiometric amount of BuLi (2.5M hexane solution) into aldehydes **1** and **2**, and imine **3** in different solvent mixtures at constant temperature. The T value was varied over a range of *ca.* 130°. The diastereoisomeric ratio *anti*/*syn* was determined in each experiment by GC analysis (see *Exper. Part*). Data were analyzed by least-squares fitting to *Eqn. 1* and to obtain linear correlations.

In previous papers, we have demonstrated that the presence of a T_{inv} accounts for a particular effect of the reaction solvent on stereoselectivity [7]. We have demonstrated that the T_{inv} observed in *Eyring* plots obtained for diastereoselective nucleophilic additions to α-chiral aldehydes does not depend on nucleophiles, and ^{13}C-NMR experiments clearly connected the T_{inv} with the solvation of the starting carbonyl compound. In our interpretation, an *Eyring* plot, which shows a T_{inv}, derived from a superimposition of two linear trends produced by two different solvation clusters. These two solute-solvent clusters behave like two different supramolecules with different thermodynamic properties, and therefore different stereoselectivity. At temperatures lower than T_{inv}, one cluster is present in solution, at temperatures higher than T_{inv}, the other cluster is present. The T_{inv} represents the interconversion temperature between these two supramolecules.

Eyring plots in *Fig. 1* show the temperature dependence of the *anti*/*syn* ratio from BuLi addition to 2-phenylpropanal (**1**) in THF, hexane, and in the binary mixture of 5 mol-% THF in hexane. In the case of the mixture, it is interesting to note that, at high T, the $\Delta\Delta H^{\ddagger}$ value is lower than in THF, and similar to that in hexane (*Table*, *Entries 1*, *3*, and *6*). The $\Delta\Delta S^{\ddagger}$ value of the mixture is lower than those of pure components. In contrast to in hexane, in THF and the mixture no inversion temperature (T_{inv}) is observed, indicating the presence of just one solvation cluster in the temperature range explored (for a review, see [8]).

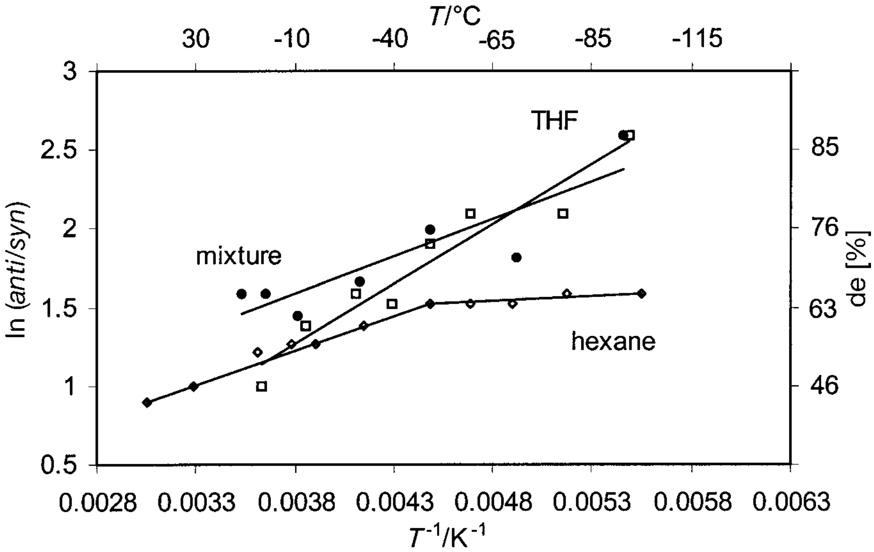


Fig. 1. Eyring *plots for the diastereoisomer ratio obtained for the addition of BuLi to* **1** *in THF* (□), *hexane* (◇), *and in a mixture of 5 mol-% THF in hexane* (●)

Table. *Differential Activation Parameters and Inversion Temperatures for BuLi Addition to Aldehydes* **1**–**2** *and Imine* **3** *in Pure Solvents and Mixtures*

Entry	Compound	Solvents	T_{inv}/°C	$T > T_{\mathrm{inv}}$		$T < T_{\mathrm{inv}}$	
				$\Delta\Delta H^{\ddagger}$ [kcal/mol]	$\Delta\Delta S^{\ddagger}$ [cal/mol K]	$\Delta\Delta H^{\ddagger}$ [kcal/mol]	$\Delta\Delta S^{\ddagger}$ [cal/mol K]
1	**1**	THF	–	-1.5 ± 0.2	-3.2 ± 0.8		
2	**1**	Pentane	-68	-0.92 ± 0.07	-1.3 ± 0.3	-0.3 ± 0.1	1.7 ± 0.6
3	**1**	Hexane	-45	-0.86 ± 0.05	-0.8 ± 0.2	-0.16 ± 0.05	2.3 ± 0.2
4	**1**	Heptane	-18	-0.73 ± 0.03	-0.1 ± 0.1	-0.18 ± 0.02	2.1 ± 0.1
5	**1**	Decane	-1	-2.5 ± 0.3	-7 ± 1	0.0 ± 0.1	2.5 ± 0.1
6	**1**	THF/Hexane 5/95	–	-0.9 ± 0.2	-0.5 ± 1.0		
7	**1**	Pentane/Hexane 1/1	-28	-0.5 ± 0.1	0.7 ± 0.3	-0.10 ± 0.07	2.4 ± 0.3
8	**1**	Hexane/Heptane 90/10	23	-0.33 ± 0.06	1.3 ± 0.2	-1.11 ± 0.01	-1.29 ± 0.06
9	**1**	Hexane/Decane 99/1	3	-0.56 ± 0.06	0.6 ± 0.2	-0.17 ± 0.03	2.0 ± 0.1
10	**1**	Hexane/Decane 95/5	15	-1.0 ± 0.1	-0.8 ± 0.4	-0.26 ± 0.04	1.7 ± 0.2
11	**1**	Hexane/Decane 1/1	20	-1.1 ± 0.3	-1.2 ± 0.8	-0.24 ± 0.08	1.8 ± 0.3
12	**1**	Hexane/Decane 20/80	22	-0.8 ± 0.1	-0.3 ± 0.3	-0.31 ± 0.03	1.4 ± 0.1
13	**1**	Hexane/Decane 5/95	18	-0.8 ± 0.2	-0.3 ± 0.6	-0.11 ± 0.05	2.1 ± 0.2
14	**1**	Pentane/Hexane/ Decane 1/1/1	–	-0.38 ± 0.02	1.34 ± 0.06		
15	**2**	THF	-63	0.61 ± 0.05	2.7 ± 0.2	1.2 ± 0.1	5.5 ± 0.7
16	**2**	Hexane	-15 [a])	0.90 ± 0.03	3.4 ± 0.1	0.28 ± 0.05	1.0 ± 0.2
17			-58 [b])	0.28 ± 0.05	1.0 ± 0.2	-0.7 ± 0.1	-3.6 ± 0.4
18	**2**	THF/Hexane 5/95	–	0.20 ± 0.02	1.31 ± 0.08		
19	**3**	THF	-27	-0.10 ± 0.01	-1.59 ± 0.02	4.3 ± 0.3	16.4 ± 1.4
20	**3**	Hexane	8	-0.6 ± 0.2	-4.3 ± 0.7	-2.2 ± 0.4	-10.4 ± 1.7
21	**3**	THF/Hexane 5/95	-24	0.62 ± 0.07	1.5 ± 0.2	1.62 ± 0.08	5.5 ± 0.4

[a]) T_{inv} 1. [b]) T_{inv} 2.

Temperature-dependent measurements give insight into the interplay of differential activation enthalpy and entropy in determining the stereoselectivity [9].

Diastereoselection in the BuLi addition to (*2S*)-2-[(*tert*-butyl)dimethylsilyloxy]-2-phenylethanal (**2**) was also studied in a 5 mol-% mixture of THF in hexane (*Fig. 2*). Two inversion temperatures and two isoselective points (T_0)1) were observed in pure hexane. In pure THF, only one T_{inv} and one T_0 were observed. In this case, the use of a binary solution had a greater effect on stereoselectivity: all T_{inv} and T_0 became unobservable, and the *Eyring* plot became linear. Similar to the *Eyring* plot of **1**, the slope of the plot of **2** in the mixture is more shallow than those in pure solvents, reflecting a lowering of both enthalpy and entropy values (*Table*, *Entries 16*, *17*, and *18*). Nevertheless, it is interesting to note that the mixture allows a higher level of stereoselectivity than the corresponding pure solvents.

Plots in *Fig. 3* show the temperature dependence of the stereoselectivity of BuLi addition to 2-[(*tert*-butyl)dimethylsilyloxy]-*N*-(trimethylsilyl)propan-1-imine (**3**) in THF, hexane, and in the binary mixture 5 mol-% THF in hexane. At high temperature, data in 5 mol-% mixture are similar to those in THF. At low *T*, the trends in THF and hexane diverge, owing to values of $\Delta\Delta H^{\ddagger}$ of opposite sign (*Table*, *Entries 19*, *20*, and *21*),

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1) T_0 designates the T value at which equal amounts of the two diastereoisomers are formed.

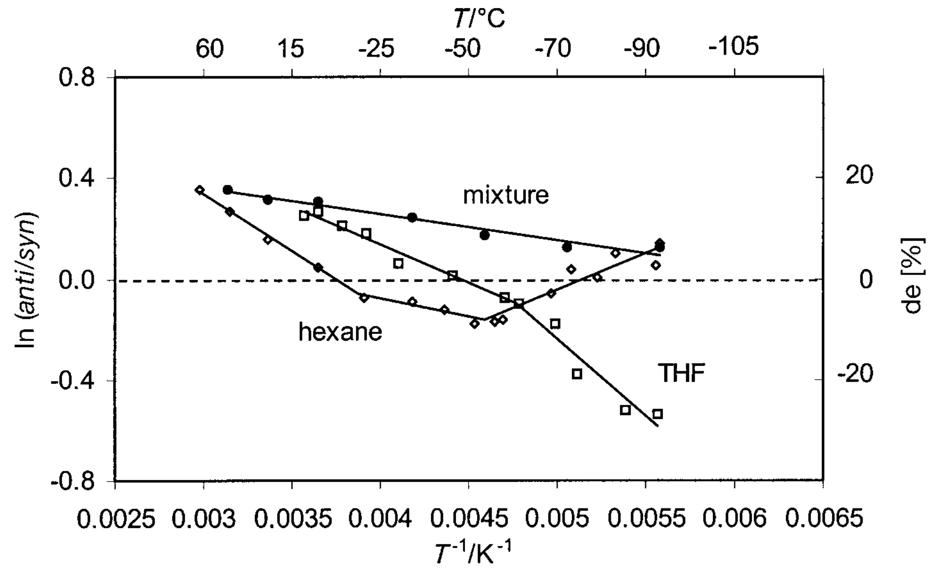

Fig. 2. Eyring *plots for the diastereoisomer ratio obtained for the addition of BuLi to* **2** *in THF* (□), *hexane* (◇), *and in a mixture of 5 mol-% THF in hexane* (●)

while the plot of the mixture lies in the middle with a more flattened shape due to $\Delta\Delta H^{\neq}$ and $\Delta\Delta S^{\neq}$ having relatively small absolute values. In THF and hexane, an inversion temperature is clearly recognized, whereas in the mixture the presence of a T_{inv} is rather difficult to discern, due to the flattened plot.

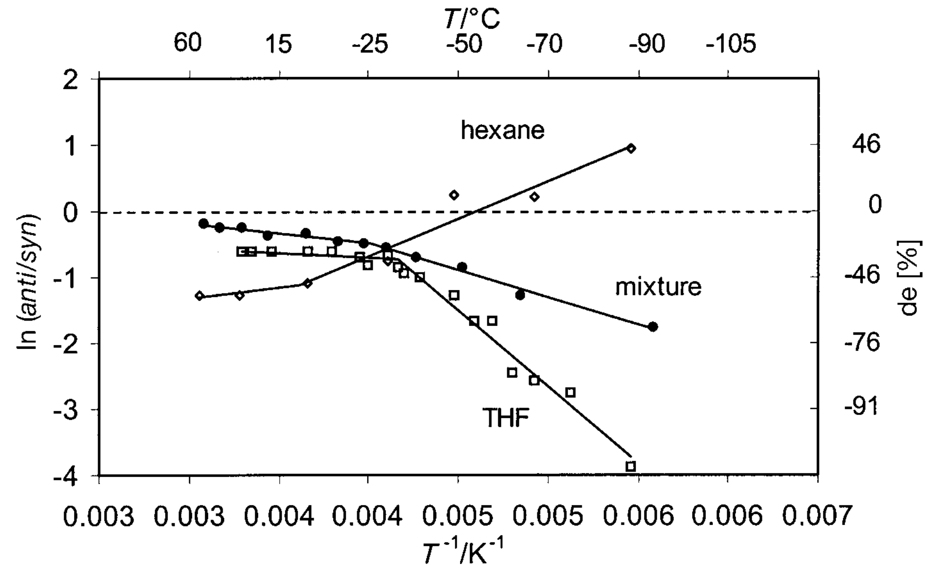

Fig. 3. Eyring *plots for the diastereoisomer ratio obtained for the addition of BuLi to* **3** *in THF* (□), *hexane* (◇), *and in a mixture of 5 mol-% THF in hexane* (●)

In all three cases described above, the mixture attenuates the inversion-temperature phenomenon and lowers the temperature dependence of the system. The different polarity of THF with respect to hexane should disclose any effects of preferential solvation [1], but these were not revealed by the peculiar effect of the mixture on diastereoselectivity.

Hydrocarbon Mixtures. In *Fig. 4*, the *Eyring* plots for the BuLi addition to aldehyde **1** in hexane and pentane in a 1:1 molar ratio are shown. At low *T*, the activation parameters in the mixture are quite similar to those in pure hexane (*Table*, *Entries 2*, *3*, and *7*), whereas, at high *T*, the $\Delta\Delta S^{\ddagger}$ undergoes a change in sign with respect to the pure components, raising the diatereoisomer ratio. In contrast to the above analyzed THF/hexane mixture, this hydrocarbon system shows a well-discerned inversion temperature. Interestingly, the T_{inv} of the mixture has a higher value than those found in pure solvents. A similar result was also obtained with a 50 mol-% mixture of hexane and decane (*Fig. 5*). In hydrocarbon mixtures, *e.g.*, 10 mol-% heptane in hexane (*Fig. 6*), a lower molar ratio of components also caused an increase in the T_{inv} value.

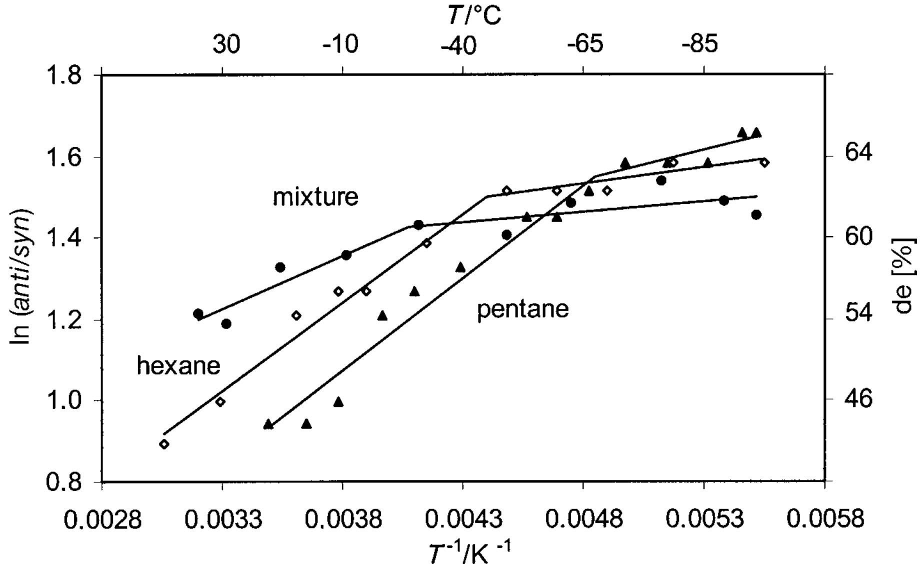

Fig. 4. Eyring *plots for the diastereoisomer ratio obtained for the addition of BuLi to* **3** *in hexane* (◇), *pentane* (▲), *and in the 1:1 molar-ratio mixture* (●)

Indeed, in all hydrocarbon mixtures examined, we found the T_{inv} at a higher temperature than in pure solvent. This suggests that cluster interconversion requires more energy, as if it were more difficult to reorganize the solvation shell, implying the presence of a thermodynamically more stable solute-solvent cluster than that occurring in pure solvents.

The *Eyring* plot obtained with a ternary solvent system comprised of pentane/hexane/decane in a 1:1:1 molar ratio (*Fig. 7*) is quite interesting. In this case, no inversion temperature was observed, and the diastereoselectivity is slightly higher than

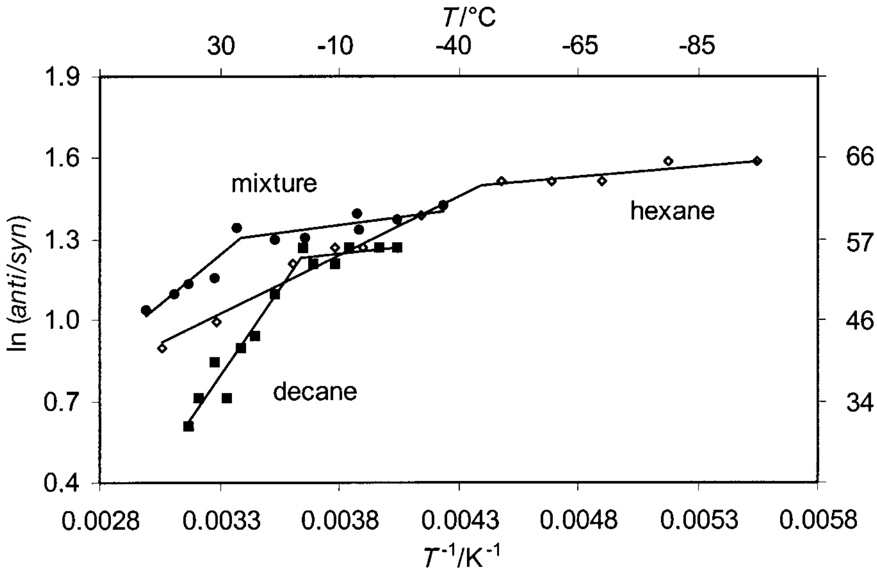

Fig. 5. Eyring *plots for the diastereoisomer ratio obtained for the addition of BuLi to* **3** *in hexane* (◇), *decane* (■), *and in the 1 : 1 molar-ratio mixture* (●)

that obtained in pure solvents. Since, in the high temperature region, the differential activation enthalpy is lower than that in pure solvent (*Table*, *Entries 2*, *3*, *5*, and *14*), the higher selectivity reached in the ternary mixture is due to a larger influence of $\Delta\Delta S^{\neq}$. The differential entropy contribution exceeds the enthalpy contribution and deter-

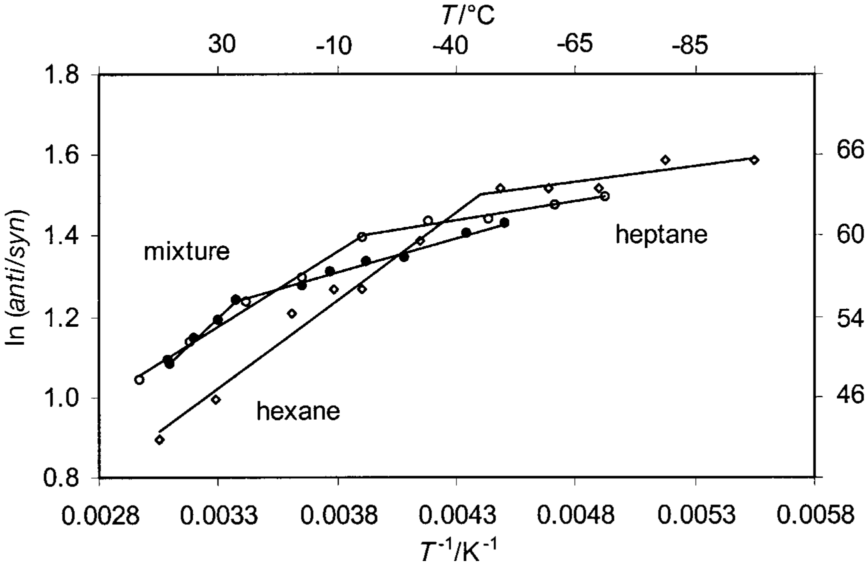

Fig. 6. Eyring *plots for the diastereoisomer ratio obtained for the addition of BuLi to* **3** *in hexane* (◇), *heptane* (○), *and in the heptane 10 mol-% in hexane* (●)

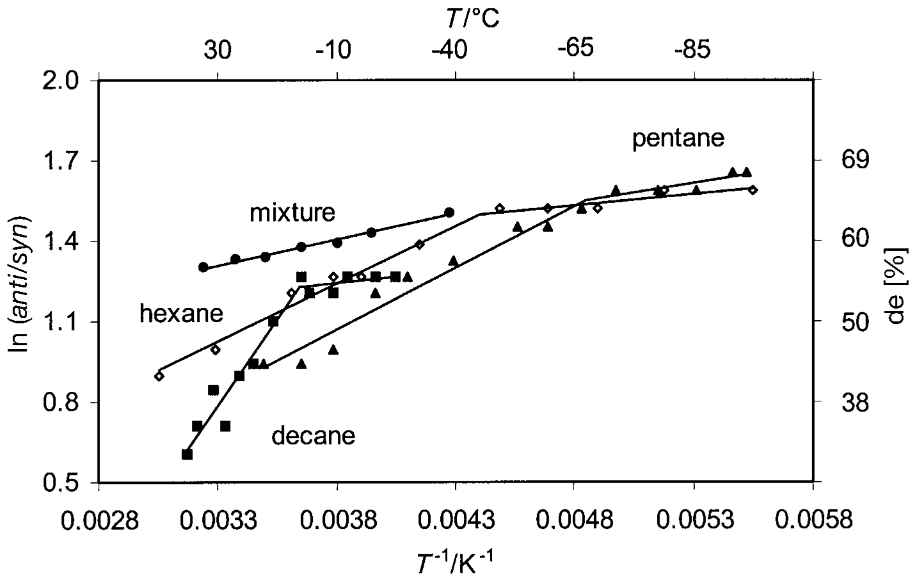

Fig. 7. Eyring *plots for the ratio obtained in the addition of BuLi to* **1** *in hexane* (◇), *decane* (■), *pentane* (△), *and in the 1:1:1 molar-ratio mixture* (●)

mines the final diastereoselectivity of the process. This example demonstrates that, in a stereoselective reaction, a mixture of hydrocarbons (for instance petroleum ether) cannot be used in place of a pure alkane without affecting the isomer ratio.

For 2-phenylpropanal (**1**), in the BuLi addition reaction, we also studied the variation of T_{inv} with the mole fraction of hexane in decane. Results are reported in *Fig. 8* and in the *Table* (*Entries 1, 5*, and *9–13*). In this binary system, the T_{inv} increased up to 0.1 mole fraction of hexane, above which it remained almost constant over a wide composition range. At a composition of >0.9 mole fraction of hexane, the T_{inv} decreased to that found in pure solvent.

The greatest change in the inversion temperature occurred at the extreme compositions, *i.e.*, nearly pure solvent, while, over a large mole-fraction range, T_{inv} was relatively unaffected by the composition of the mixture. Within the experimental error, the corresponding $\Delta\Delta H^{+}$ and $\Delta\Delta S^{+}$ are also not influenced by solvent composition in the middle range. The consistency of T_{inv} over this range could be due to the presence of two solvation clusters the microstructures of which are independent of the composition of the bulk solvent, whereas at a mole fraction of 0.99, the T_{inv} is quite different, clearly indicating the presence of two different clusters with different microscopic structures. Interpolation of the experimental data allows us to estimate the minimum amount of decane required for the steady solvation, corresponding to 2 molecules of decane per 1 molecule of 2-phenylpropanal (**1**). In a similar way, the required amount of hexane can be estimated at *ca.* 5 molecules per 1 molecule of **1**. It seems reasonable that, in the first solvation shell, there is a hexane/decane ratio of 5:2, and all solvent molecules exceeding these two quantities are thus part of the bulk solvent. This result reveals that a highly structured microscopic solvation shell exists

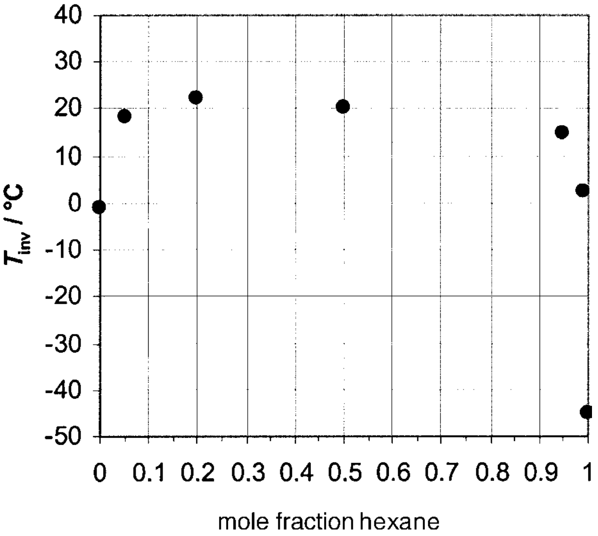

Fig. 8. *Variation of inversion temperatures with molar solvent composition in the mixture hexane/decane for the BuLi addition to aldehyde* **1**

even in the presence of only weak and non-specific solute-solvent interactions such as in hydrocarbon solvents.

Conclusion. – A solute-induced stereospecific solvation modulates the free activation energies of a process, acting on both the enthalpic and on the entropic terms. These interactions are different in binary or ternary mixtures than in pure solvents, and this difference is reflected in the stereoselectivity of the reaction. This effect was observed in solvent mixtures *vs.* pure solvents during diastereofacially selective addition of *n*BuLi to some α-chiral aldehydes and imines. Addition of 5 mol-% of THF to hexane is sufficient to affect the isomer ratio, reducing both $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$, and to suppress observation of an inversion temperature. On the contrary, in hydrocarbon binary mixtures, the T_{inv} is still present, and it occurs at higher temperature value than those in pure solvents. Studying the dependence of T_{inv} on the hexane/decane composition, we propose the formation of a particular solvation cluster that is unaffected by the composition of bulk solvent. A ternary hydrocarbon mixture lowers the values of both $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$, and suppresses the T_{inv}. All of these results confirm that diastereofacial selectivity is strongly dependent on the reaction solvent, and, that when using a solvent mixture, a change in the diastereoisomer ratio must be expected.

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Experimental Part

General. All reactions were performed in flame-dried glassware under an atmosphere of Ar. ^{1}H- and ^{13}C-NMR spectra were recorded with a *Varian Gemini 300* instrument operating at 300 MHz and 75.5 MHz, resp., using a 5-mm probe. Chemical shifts δ in ppm relative to deuterated solvent, *J* in Hz. FT-IR: *Nicolet 205*

FT spectrometer, measured as films between NaCl plates and reported in cm^{-1}. GC/MS: *HP5980*, cap. column *HP-1* or *HP-5* connected to *HP-5970* (70 eV). GC: *FISONS G8000*, column: *HP-5 M.S.*, crosslinked with 5% PhMeSilicone, 30 m × 0.25 mm × 0.25 μm, chiral column *OV 1701 H*. TLC: *Merck 60F₂₅₄*. Column chromatography: *Merck* silica gel 200–300 mesh. During reactions, to set and maintain the temp. in the range of ± 1°, liq. N_2 acetone bath in *Dewar* containers or oil bath with water cooling were used. Temp. was recorded in the internal cavity of reaction apparati.

Starting Materials. Hydrocarbons were dried by distillation from Na, THF from sodium-benzophenone, and stored over molecular sieves (4 Å). BuLi (commercial 2.5M soln. in hexane) was titrated shortly before use. Aldehydes **1** and **2** were prepared starting from the corresponding *O*-protected α-hydroxy esters by diisopropylaluminium hydride reduction [10]. Imine **3** was prepared according to the procedure in [11] and purified by distillation in high vacuum ($1.2 \cdot 10^{-5}$ mbar).

In a typical experiment, the aldehydes **1** or **2**, or the imine **3** (1 mmol) was dissolved in an anh. solvent (20 ml) under an inert atmosphere, and the soln. was cooled or warmed to the desired temp.; then BuLi (1.2 mmol) was added. After the starting aldehyde or imine disappeared (GC monitoring), the reaction was quenched with a sat. aq. soln. of NH_4Cl, extracted with CH_2Cl_2 (3 × 50 ml), and dried (Na_2SO_4). Chromatography of the residue on a silica-gel column gave the mixtures **1a**/**2a** and **1b**/**2b**, or **3a**/**3b** so that the chemical yields could be calculated (80–90%). From GC analysis of the crude products or of the corresponding *O*-trimethylsilyl- or *N*-trifluoroacetamide derivatives, the *anti*/*syn* ratios and the de values [%] were determined. The average standard deviation for the de measurements was less than 1%. Compounds **1a**, **1b**, **3a**, and **3b** are known [12]. After removal of the *O*-protecting group, configurations of products **2a** and **2b** were determined in comparison with the reported data [13].

*(1*S*,2*R*)-1-[(*tert*-Butyl)dimethylsilyloxy]-1-phenylhexan-2-ol* (**2a**, *anti*): IR (neat) 3400, 1250, 1100. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.04 (*s*, 3 H); 0.05 (s, 3 H); 0.90 (*m*, 12 H); 1.26 (*m*, 6 H); 2.50 (br. *s*, 1 H); 3.68 (*m*, 1 H); 4.56 (*d*, $J = 5.0$, 1 H); 7.3 (*m*, 5 H). ^{13}C-NMR (200 MHz, $CDCl_3$): −4.6; −5.1; 13.9; 18.0; 22.5; 25.7; 27.9; 31.5; 75.8; 78.9; 127.0; 127.6; 128.0; 141.2. MS (70 eV): 293 (1, $[M - \mathrm{Me}]^+$), 251 (30, $[M - {}^t\mathrm{Bu}]^+$), 222 (54), 221 (100), 117 (20), 75 (58), 73 (72).

*(1*S*,2*S*)-1-[(*tert*-Butyl)dimethylsilyloxy]-1-phenylhexan-2-ol* (**2b**, *syn*): IR (neat) 3400, 1250, 1100. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.04 (*s*, 3 H); 0.05 (*s*, 3 H); 0.90 (*m*, 12 H); 1.26 (*m*, 6 H); 2.8 (br. *s*, 1 H); 3.56 (*m*, 1 H); 4.36 (*d*, $J = 7.1$, 1 H); 7.3 (*m*, 5 H). ^{13}C-NMR (200 MHz, $CDCl_3$): −4.5; −5.1; 13.9; 18.0; 22.5; 25.7; 27.9; 31.7; 76.2; 79.4; 127.0; 127.6; 128.0; 141.6. MS (70 eV): 293 (1, $[M - \mathrm{Me}]^+$), 251 (30, $[M - {}^t\mathrm{Bu}]^+$), 222 (54), 221 (100), 117 (20), 75 (58), 73 (72).

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