Solvent and Temperature Effects on Diastereofacial Selectivity: Amines as Co-Solvents in *n*-Butyllithium Addition to α-Chiral Aldehydes

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Temperature-dependent selectivity in nucleophilic additions to α-chiral aldehydes is affected by solvent mixtures. In this context, we investigated the effect on diastereoselectivity of tertiary amines as co-solvents. Addition of 5 mol% of an amine to hexane strongly influences the *anti*/*syn* ratio in the additions of *n*BuLi to 2-phenylpropanal and to (2*S*)-2-[(*tert*-butyl)dimethylsilyloxy]-2-propanal. In these hexane/amine mixtures as reaction solvents, we observed diastereoselectivities higher than those obtained in hexane. In the corresponding Eyring plots of ln(*anti*/*syn*) against the reciprocal temperature, we observed inversion temperatures (T_{inv}), these generally occurring at higher temperatures in the hexane/amine mixtures than in pure hexane. The presence of the inversion temperatures confirms that these tertiary amines take part in the solvation of the starting aldehyde, thus contributing to a solvent effect on facial selectivity. In some cases, the differential entropy of activation is the predominant factor in differentiating the diastereoselectivity among these hexane/amine mixtures.

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Introduction

Different factors affect facial stereoselectivity;[1] among others, dependence on the reaction solvent has been already recognized, and several examples of solvent-dependent face selectivity have appeared in the literature.[2] Solvent effects are closely related to the nature and the extent of solute−solvent interactions developed locally in the microenvironments of the solute molecules.[3] These solute−solvent interactions are able to differentially modulate the free activation energies of two different stereoisomers, thus exerting stereospecific solvation control over enantio- and diastereoselectivity. As an example, we recently reported that, in the addition of EtMgBr to (2*S*)-*O*-(*tert*-butyldimethylsilyl)lactal in a series of ethers, solute−solvent interactions govern a reversal in the *de* % values of the *O*-protected diols obtained.[4]

Solute−solvent interactions in mixtures should be more complex than those in pure solvents. In pure solvents, the composition of the microsphere of solvation of the solute is the same as in the bulk solvent, whereas in binary mixtures this composition can be different. The solute can in fact interact to different extents with the two components of the binary mixture, and this difference should affect the composition of the solvation microsphere. In this context, some influence on diastereoselectivity of a mixture of solvents is to be expected. Actually, in a previous paper, we reported solvent mixture effects on diastereofacial addition of *n*BuLi to some α-chiral aldehydes and imines in ether/hydrocarbon mixtures and in binary and ternary mixtures of hydrocarbons. In some cases we observed enhanced diastereoselectivities in the mixtures relative to those observed in the pure solvents, together with the presence of temperature-dependent solvation effects.[5]

This work extends those studies, and we now report on the influence of solvent mixtures of hexane and 5 mol % of tertiary amines (hexane/amine = 95:5 molar ratio) on the diastereoselectivity in the addition reactions of *n*BuLi to 2-phenylpropanal (**1**) and to (2*S*)-2-[(*tert*-butyl)dimethylsilyloxy]-2-propanal (**2**). We examined triethylamine (TEA), tri-*n*-butylamine (Bu_3N), tri-*n*-pentylamine (Pen_3N), *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA), *N*-methylpyrrolidine, diisopropylethylamine (Hünig base), and sparteine as co-solvents, and established strong effects of such Lewis bases on the diastereofacial selectivity (Scheme 1). The effect of Et_3N and TMEDA on the diastereoselective addition of organolithium and Grignard reagents to ketones has already been reported, and has been interpreted as being due to a change in the aggregation state of the organometallic species.[6] Our findings suggest that tertiary amines can indeed affect the *n*BuLi aggregation state, but in addition that they take also part in the solvation shell of the starting aldehyde, thus contributing to a solvent effect on the facial selectivity.

A better insight into the factors affecting the stereoselectivity can be obtained from studies in which the reaction temperature is varied. Temperature-dependent measure-

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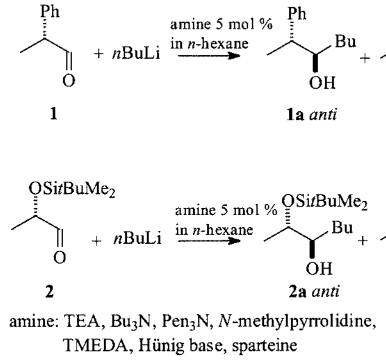

Scheme 1

ments shed light on the interplay of differential activation enthalpies and entropies through application of the modified Eyring Equation (1), where S is the stereoselectivity and k and k'' are the overall rate constants for the synthesis of the two stereoisomers.[7]

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

Equation (1) shows a linear correlation of selectivity with $1/T$, but there are many experimental results that feature nonlinear behaviour. In these cases, the corresponding Eyring plot of $\ln(k/k'')$ vs. $1/T$ generally consists of two straight lines intersecting at a point defining a temperature called the inversion temperature (T_{inv}).[8]

This T_{inv} constitutes a break point, giving rise to two sets of activation parameters: one for $T > T_{\text{inv}}$ and one for $T < T_{\text{inv}}$. In previous papers we have reported that the presence of a T_{inv} depends on dynamic solvation effects.[9] Recently, in addition reactions of organolithium and Grignard reagents to (2*S*)-*O*-(*tert*-butyldimethylsilyl)lactal and (2*S*)-*O*-(*tert*-butyldimethylsilyl)mandelicaldehyde, we observed that the inversion temperature is only slightly dependent on the nucleophile, but mainly on the aldehyde−solvent couple.[10] Our results have demonstrated that temperature-dependent changes in solvation bring about the presence of the inversion temperature and tune its value. In our interpretation, an Eyring plot featuring a T_{inv} is the result of two intersecting linear trends produced by two different solvation clusters. These two solute−solvent clusters behave as independent species with different thermodynamic properties, and hence different stereoselectivities. At temperatures lower than T_{inv}, one cluster is present in solution, while at temperatures higher than T_{inv} another, different cluster is present; T_{inv} would represent the interconversion temperature between these two supramolecules (Figure 1).

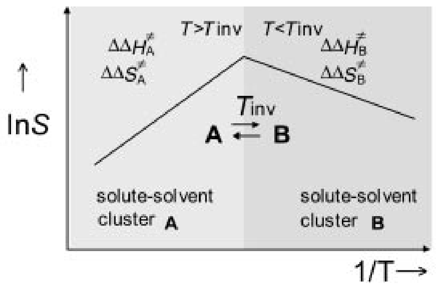

Figure 1. The T_{inv} in an Eyring plot, as the interconversion temperature between two supramolecules

This interpretation has a general significance, because it does not depend on the particular reaction investigated and does not imply any change either in the rate-determining step or in the reaction mechanism.[11]

Results and Discussion

In a previous study[5] we reported a peculiar influence of binary solvent mixtures on inversion temperatures. In particular, we observed that in the addition of *n*BuLi to 2-phenylpropanal, the presence of 5 mol % of THF in hexane was sufficient to suppress the observation of a T_{inv}. In binary hydrocarbon mixtures, in contrast, T_{inv} was still present, and occurred at higher temperatures than those seen in pure solvents.

In this paper we analyse binary mixtures of hexane and tertiary amines in order to ascertain their influence on diastereomeric ratios and even on dynamic solvation phenomena, as evidenced by the presence of inversion temperatures.

We selected a series of trialkylamines and added these (5 mol%) to hexane, thus obtaining solvent mixtures in which the selected aldehydes **1** or **2** were dissolved. Since *n*BuLi is commercially available as hexane solution, we chose hexane as a fixed component of the binary system in order to avoid the presence of two different hydrocarbons. In all experiments, the addition reaction was performed at constant temperature by the introduction of a stoichiometric amount of *n*BuLi (2.5 M hexane solution) into previously prepared solutions of aldehydes **1** or **2** in 5 mol % amine in hexane. The value of T was varied over a range of ca. 120 °C. The diastereomeric *anti*/*syn* ratios (**1a**/**1b** and **2a**/**2b**) were determined in each experiment by GC analysis (see Table 1). Data were analysed by least-squares fitting to Equation (1) to obtain linear correlations. For each data set we applied a residual analysis to evaluate the number of linear trends and to ascertain the presence of the inversion temperature. The $\Delta\Delta H^{\neq}$ and $\Delta\Delta S^{\neq}$ values were obtained from the slopes and intercepts of the linear plots (Table 2) and correspond to $\Delta\Delta H^{\neq} = \Delta H^{\neq}_{anti} - \Delta H^{\neq}_{syn}$, and $\Delta\Delta S^{\neq} = \Delta S^{\neq}_{anti} - \Delta S^{\neq}_{syn}$.

It is useful to remember that a negative $\Delta\Delta H^{\neq}$ derives from a situation in which $\Delta H^{\neq}_{syn} > \Delta H^{\neq}_{anti}$ and that there is then a lower activation barrier to the formation of the *anti* isomer; that is to say, the *anti* isomer is preferred enthalpically. The opposite applies for $\Delta\Delta H^{\neq} > 0$; enthalpy then favours the *syn* isomer. With regard to the entropy, if it is assumed that an addition reaction is accompanied by a loss of activation entropy, a $\Delta\Delta S^{\neq} < 0$ derives from $|\Delta S^{\neq}_{anti}| > |\Delta S^{\neq}_{syn}|$; this means that the entropic loss involved in the formation of the *anti* isomer is larger than that involved the formation of the *syn* one, so the entropy favours the formation of the *syn* stereoisomer. The opposite

Table 1. *anti* and *syn* (%) in the addition of *n*BuLi to aldehyde **1** or **2** in hexane/amine mixtures (95:5 molar ratio)

Aldehyde	Amine	T [°C]	*anti* (%)	*syn* (%)
1	Bu_3N	34	88.9	11.1
1	Bu_3N	23.5	89.1	10.9
1	Bu_3N	11.5	89.1	10.9
1	Bu_3N	−10	88.9	11.1
1	Bu_3N	−20	89.1	10.9
1	Bu_3N	−25	89.9	10.1
1	Bu_3N	−29	91.3	8.7
1	Bu_3N	−38	92.1	7.9
1	Bu_3N	−44	92.2	7.8
1	Bu_3N	−48.5	93.3	6.7
1	Bu_3N	−56	94.2	5.8
1	Bu_3N	−62	94.9	5.1
1	Bu_3N	−69	96.5	3.5
1	Pen_3N	41	87.8	12.2
1	Pen_3N	17.5	88.4	11.6
1	Pen_3N	5.5	89.1	10.9
1	Pen_3N	−5	89.3	10.7
1	Pen_3N	−17	88.8	11.2
1	Pen_3N	−23.5	89.3	10.7
1	Pen_3N	−30	89.5	10.5
1	Pen_3N	−39	89.5	10.5
1	Pen_3N	−42.5	89.8	10.2
1	Pen_3N	−45	91.1	8.9
1	Pen_3N	−51.5	91.8	8.2
1	Pen_3N	−60.5	92.3	7.7
1	Pen_3N	−64	93.3	6.7
1	Pen_3N	−70	94.1	5.9
1	*i*Pr$_2$EtN	50	75.4	24.6
1	*i*Pr$_2$EtN	40	75.9	24.1
1	*i*Pr$_2$EtN	29.5	78.9	21.1
1	*i*Pr$_2$EtN	20	77.9	22.1
1	*i*Pr$_2$EtN	1	79.0	21.0
1	*i*Pr$_2$EtN	−13	80.6	19.4
1	*i*Pr$_2$EtN	−37	82.2	17.8
1	*i*Pr$_2$EtN	−51	84.2	15.8
1	*i*Pr$_2$EtN	−61	84.6	15.4
1	*i*Pr$_2$EtN	−75	88.3	11.7
1	*i*Pr$_2$EtN	−87	90.7	9.3
1	*N*-methylpyrrolidine	53.5	81.1	18.9
1	*N*-methylpyrrolidine	30	84.8	15.2
1	*N*-methylpyrrolidine	11	86.3	13.7
1	*N*-methylpyrrolidine	1	88.1	11.9
1	*N*-methylpyrrolidine	−4	87.8	12.2
1	*N*-methylpyrrolidine	−11	87.2	12.8
1	*N*-methylpyrrolidine	−19.5	86.5	13.5
1	*N*-methylpyrrolidine	−22.5	86.6	13.4
1	*N*-methylpyrrolidine	−35	88.6	11.4
1	*N*-methylpyrrolidine	−40.5	88.7	11.3
1	*N*-methylpyrrolidine	−50	90.1	9.9
1	*N*-methylpyrrolidine	−67	91.9	8.1
1	*N*-methylpyrrolidine	−77.5	92.7	7.3
1	*N*-methylpyrrolidine	−87	93.7	6.3
1	TEA	52	75.8	24.2
1	TEA	35.7	77.7	22.3
1	TEA	1	80.3	19.7
1	TEA	−14	83.0	17.0
1	TEA	−24	83.4	16.6
1	TEA	−28	84.0	16.0
1	TEA	−32	88.3	11.7
1	TEA	−50.5	90.1	9.9
1	TEA	−65	90.6	9.4
1	TEA	−76	91.8	8.2
1	TEA	−88	93.2	6.8
1	sparteine	40	71.7	28.3
1	sparteine	29	75.0	25.0
1	sparteine	xf−19	76.1	23.9
1	sparteine	9.5	78.5	21.5
1	sparteine	1	79.5	20.5
1	sparteine	−12	82.1	17.9
1	sparteine	−19	82.1	17.9
1	sparteine	−30	84.6	15.4
1	sparteine	−36	85.6	14.4
1	sparteine	−43.5	85.7	14.3
1	sparteine	−66	86.8	13.2
1	sparteine	−75	87.6	12.4
1	TMEDA	49	81.5	18.5
1	TMEDA	36	83.9	16.1
1	TMEDA	19.5	87.1	12.9
1	TMEDA	11.5	88.8	11.2
1	TMEDA	3	89.1	10.9
1	TMEDA	−1	89.2	10.8
1	TMEDA	−2	89.5	10.5
1	TMEDA	−12	90.3	9.7
1	TMEDA	−23.5	90.9	9.1
1	TMEDA	−43	92.7	7.3
1	TMEDA	−61	94.2	5.8
1	TMEDA	−72.5	94.7	5.3
1	TMEDA	−84	95.3	4.7
2	Bu_3N	32.5	79.6	20.4
2	Bu_3N	12.5	78.1	21.9
2	Bu_3N	−12.5	83.1	16.9
2	Bu_3N	−20	82.1	17.9
2	Bu_3N	−35	83.1	16.9
2	Bu_3N	−50	84.8	15.2
2	Bu_3N	−55	85.3	14.7
2	Bu_3N	−67	86.6	13.4
2	Bu_3N	−82.5	87.5	12.5
2	Bu_3N	−87	87.9	12.1
2	TEA	56.5	77.2	22.8
2	TEA	32	78.9	21.1
2	TEA	21	78.5	21.5
2	TEA	1	82.0	18.0
2	TEA	−12	83.6	16.4
2	TEA	−19	83.3	16.7
2	TEA	−35	84.2	15.8
2	TEA	−41	83.8	16.2
2	TEA	−49	84.3	15.7
2	TEA	−61	85.8	14.2
2	TEA	−71	87.5	12.5
2	TEA	−80.5	88.0	12.0
2	TMEDA	49.5	72.8	27.2
2	TMEDA	37	73.4	26.6
2	TMEDA	29	73.1	26.9
2	TMEDA	8	75.7	24.3
2	TMEDA	1.5	75.3	24.7
2	TMEDA	−11.5	77.0	23.0
2	TMEDA	−20	75.8	24.2
2	TMEDA	−28.5	77.9	22.1
2	TMEDA	−36	78.5	21.5
2	TMEDA	−45.5	77.5	22.5
2	TMEDA	−50	77.3	22.7
2	TMEDA	−55	77.2	22.8
2	TMEDA	−64	76.9	23.1
2	TMEDA	−70	76.5	23.5
2	TMEDA	−76.5	76.3	23.7

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Table 2. Differential activation parameters and inversion temperatures found for addition of *n*BuLi to aldehydes **1** and **2** in hexane/amine mixtures (95:5 molar ratio)

Entry	Aldehyde	Amine	Nucleophile	T_{inv} [°C]	$T > T_{inv}$		$T < T_{inv}$	
					$\Delta\Delta H^‡$ [kcal/mol]	$\Delta\Delta S^‡$ [cal/mol K]	$\Delta\Delta H^‡$ [kcal/mol]	$\Delta\Delta S^‡$ [cal/mol K]
1	**1**	–	*n*BuLi	−46	−0.9±0.1	−0.8±0.2	−0.16±0.05	2.3±0.2
2	**1**	Bu_3N	*n*BuLi	−20	0.04±0.01	4.1±0.2	−2.3±0.2	−5±1
3	**1**	Pen_3N	*n*BuLi	−37	−0.3±0.1	3.0±0.4	−1.6±0.2	−3±1
4	**1**	*i*Pr_2EtN	*n*BuLi	−47	−0.7±0.1	0.2±0.4	−1.3±0.2	−3±1
5	**1**	*N*-methyl-pyrrolidine	*n*BuLi	0[a]	−1.8±0.2	−2.5±0.6	0.99±0.03	7.6±0.1
				−19[b]	0.99±0.03	7.6±0.1	−1.17±0.05	−0.9±0.2
6	**1**	TEA	*n*BuLi	−30	−1.0±0.1	−0.8±0.2	−0.9±0.1	0.3±0.4
7	**1**	sparteine	*n*BuLi	−34	−1.6±0.1	−3.0±0.3	−0.41±0.04	1.8±0.2
8	**1**	TMEDA	*n*BuLi	13	−2.8±0.1	−5.9±0.3	−1.13±0.04	0.1±0.2
9	**1**	TMEDA	*n*BuLi−TMEDA[c]	12	−2.4±0.3	−4±1	−1.1±0.2	0.3±0.7
10	**1**	–	*n*BuLi−TMEDA[c]	–	−1.18±0.04	−0.7±0.2		
11	**2**	–	*n*BuLi	−83	0.12±0.02	3.2±0.1	1.1±0.2	8.4±1.1
12	**2**	Bu_3N	*n*BuLi	–	−0.61±0.03	0.7±0.2		
13	**2**	TEA	*n*BuLi	–	−0.7±0.1	0.4±0.2		
14	**2**	TMEDA	*n*BuLi	−35	−0.5±0.1	0.3±0.2	0.26±0.04	3.6±0.2

[a] $T_{inv,1}$. [b] $T_{inv,2}$. [c] Preformed complex.

holds for $\Delta\Delta S^{\neq} > 0$; the entropy now favours the *anti* isomer.

We first explored the addition of *n*BuLi to 2-phenylpropanal in hexane with different amines as co-solvents. The plots in Figure 2 refer to *n*BuLi addition to **1** in mixtures of hexane with 5 mol% of tri-*n*-butylamine, tri-*n*-pentylamine or diisopropyl(ethyl)amine. All three mixtures gave Eyring plots different from that obtained in pure hexane, with increased *anti* predominance, especially at low temperatures with Bu_3N and Pen_3N. In the high-temperature region, Bu_3N and Pen_3N show superimposed and flattened trends where the diastereoselectivity is constant with the temperature. This occurs because of very low differential activation enthalpy values (Table 2, Entries 2 and 3), so the diastereofacial selectivity is only determined by the differential entropy of activation in this *T* region for the two amines.

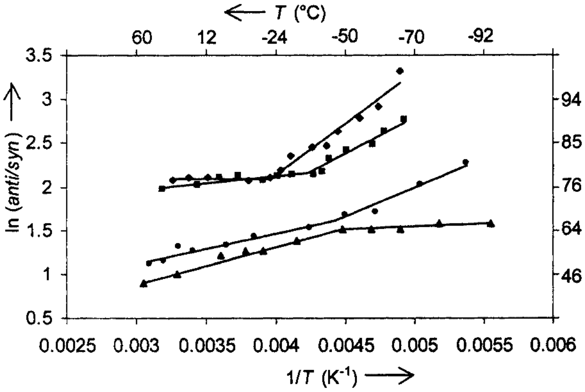

Figure 2. Eyring plots of the diastereomeric ratios obtained in the addition of *n*BuLi to **1** in pure hexane (solid triangles) and in a 95:5 molar ratio of hexane with *i*Pr_2EtN (solid circles), Pen_3N (solid squares), or Bu_3N (solid diamonds)

At low *T*, all these amines show fairly parallel trends. In particular, tri-*n*-pentylamine and diisopropyl(ethyl)amine show the same $\Delta\Delta H^{\neq}$, this means that, once again, only the $\Delta\Delta S^{\neq}$ plays a role in differentiating the *anti*/*syn* ratio.

We and other research groups have already recognized the importance of entropy in controlling stereoselective processes.[12] Entropy differences are really a determinant factor, especially in enantio- or diastereoselective reactions in which there are small differences in activation enthalpies between the two diastereomeric transition states. We have reported some examples in which fine-tuning of $\Delta\Delta S^{\neq}$ could be achieved through solvent effects, so that different reaction solvents are able to drive the diastereofacial selectivity just by means of an entropy control over the dominance of one stereoisomer.[4] Now, through the use of tertiary amines as co-solvents, we observed that even a small amount of a co-solvent is sufficient for fine modulation of diastereofacial selectivity through an entropy effect.

It has already been reported that Lewis bases (LB), such as ethers or tertiary amines, interact with alkyllithium compounds in hydrocarbon solutions to produce solvated tetrameric species $R_4Li_4{\cdot}n$LB.[13] In our case the presence of tertiary amines could also give rise to *n*BuLi/amine complexes and these could be viewed as the new organometallic species. These complexes react with the aldehyde with their own thermodynamic parameters and thus with a diastereoselectivity different from that observed for *n*BuLi in pure hexane, as we actually observed. Inversion temperatures are clearly present in all three plots (Figure 2), and in two cases they have different values depending on whether Bu_3N or Pen_3N had been added (Table 2, Entries 2−4). It follows that Bu_3N and Pen_3N form different solute−solvent clusters with the aldehyde at low *T*, and these interconvert into other solvation clusters presenting different activation parameters and different T_{inv} values. The inversion temperatures in these hexane/amine mixtures occur at higher values than in pure hexane, as we had previously observed when studying the addition of *n*BuLi to **1** in hydrocarbon mixtures.[5] This suggests that cluster interconversion in mixtures requires more energy, as if it were more difficult to reorganize the solvation shell, implying the presence of a solute−solvent cluster thermodynamically more stable than that occurring in pure solvents.

At high T, Hünig's base presents a linear trend and a T_{inv} similar to that in pure hexane. It could be surmised that this hindered amine probably does not coordinate *n*BuLi, leaving the hexameric, homosolvated *n*BuLi unchanged.[14] The presence of a T_{inv} similar to that found in pure hexane also suggests that this amine does not take part in the solvation of the aldehyde, which shows the same cluster interconversion behaviour as in pure hexane.

The plots in Figure 3 refer to the use of Et_3N and *N*-methylpyrrolidine as co-solvents (5 mol%) in hexane. Again, in both cases we observe an increase in the *anti*/*syn* ratio with respect to that seen in pure hexane. Quite peculiar is the behaviour of Et_3N, because its Eyring plot at −30 °C shows an abrupt jump in selectivity. Unlike in the other temperature ranges, from −32 to −28 °C we encountered difficulties in collecting any data because of high scattering.[15] This interruption marks two linear trends, one at a higher and one at a lower T, with quite similar slopes but different intercepts. This jump derives exclusively from a change in $\Delta\Delta S^{\neq}$, which actually has small values but opposite signs in the two T regions (Table 2, Entry 6); once again the entropy controls the diastereoselectivity of the reaction through dynamic solvation effects. This break in the Eyring plot can be readily explained in terms of interconversion of solute−solvent clusters such as happens at the inversion temperature and so, in our opinion, it can really be considered a T_{inv}. The T_{inv} obtained with this amine differs substantially from that found in pure hexane, and this confirms the presence of Et_3N in the solvation clusters.

The use of 5 mol % of *N*-methylpyrrolidine brings about the presence of two inversion temperatures in the Eyring plot (Figure 3). In our opinion, the presence of two T_{inv} values can be explained by the existence of three different solvation clusters, depending on the temperature.[16] From −87 to −19 °C there is one solute−solvent cluster with its own thermodynamic properties and its own stereoselectivity. This cluster undergoes a reorganization at −19 °C into a second one, with a different stereoselectivity.[17] However, this second solute−solvent cluster itself proved to be a short-lived species, because at 0 °C it reorganizes into a third, characteristic of the high T region. It is interesting to note that the first and the last solute−solvent clusters show quite similar $\Delta\Delta H^{\neq}$ values, the corresponding linear trends differing exclusively in the $\Delta\Delta S^{\neq}$ values, as in the case of Et_3N. In the case of this *N*-methylpyrrolidine/hexane mixture as well, the different T_{inv} with respect to pure hexane corroborates the presence of this amine in solvation clusters. TEA and *N*-methylpyrrolidine mixtures show T_{inv} values higher than that seen in pure hexane.

Having obtained these good results in enhancing diastereofacial selectivity through the use of tertiary amines, we therefore tested two diamines frequently used in the chemistry of organolithium reagents: tetramethylethylenediamine and (−)-sparteine.[18] Figure 4 shows the corresponding Eyring plots. Again, we obtained an increase in the proportion of the *anti* isomer relative to when pure hexane was used, especially with TMEDA. The two diamines display different inversion temperatures, both of which, once again, occur at higher values than found in hexane (Table 2, Entries 7 and 8). According to our hypothesis on T_{inv}, this

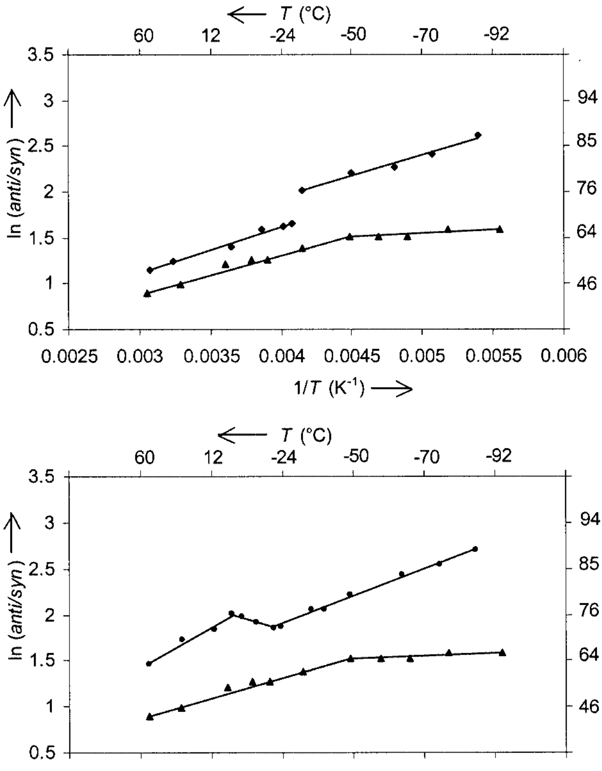

Figure 3. Eyring plots of the diastereomeric ratios obtained in the addition of *n*BuLi to **1** in pure hexane (solid triangles) and in a 95:5 molar ratio of hexane with Et_3N (solid diamonds) or *N*-methylpyrrolidine (solid circles)

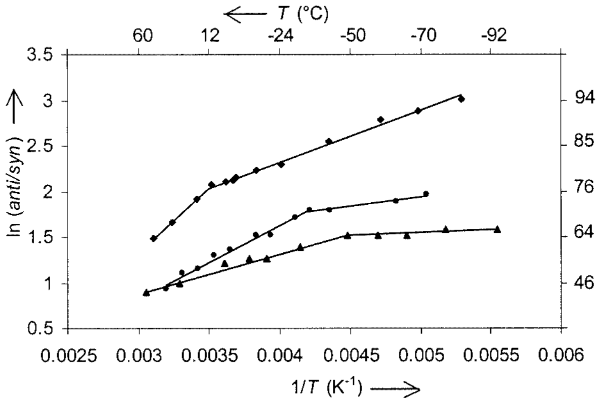

Figure 4. Eyring plots of the diastereomeric ratios obtained in the addition of *n*BuLi to **1** in pure hexane (solid triangles) and in a 95:5 molar ratio of hexane with (−)-sparteine (solid circles), or TMEDA (solid diamonds)

implies that the two amines enter in the solvation microsphere of the aldehyde to generate different solute−solvent clusters with peculiar temperature-dependent interconversion phenomena.

Alkyllithium compounds are known to be present in solution as aggregates $(RLi)_n$, and the aggregate size depends on the alkyl group, solvent, concentration, and temperature.[19] In hydrocarbons in particular, TMEDA has been shown to convert hexameric *n*BuLi aggregates into dimeric ones.[20] In order to ascertain whether the presence of a T_{inv} might be due to aggregation/disaggregation of *n*BuLi/amine complexes, and not to dynamic solvation phenomena, we studied the *anti*/*syn* ratios in the addition of the preformed *n*BuLi/TMEDA complex to phenylpropanal in pure hexane and in a hexane/TMEDA mixture (95:5 molar ratio; Table 2, Entries 9 and 10).

The corresponding Eyring plots are shown in Figure 5, with comparison with those determined for pure hexane and in the hexane/TMEDA mixture. The preformed *n*BuLi/TMEDA complex, when added to phenylpropanal diluted in hexane/TMEDA (5 mol %), shows an Eyring plot quite similar to that obtained for the addition of *n*BuLi to **1** diluted in the hexane/TMEDA mixture (95:5 molar ratio), similarities being seen in slopes and intercepts, but especially in T_{inv}, whereas addition of the preformed *n*BuLi/TMEDA complex to **1** in pure hexane shows different thermodynamic parameters and no T_{inv}.

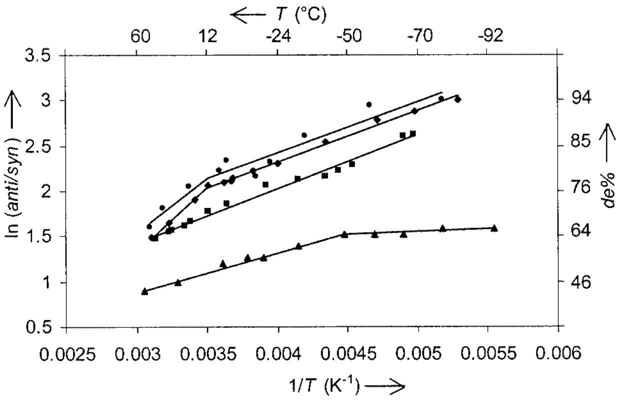

Figure 5. Eyring plots of the diastereomeric ratios obtained in the addition to **1** of *n*BuLi in pure hexane (solid triangles), *n*BuLi in a 95:5 mol mixture of hexane/TMEDA (solid diamonds), preformed *n*BuLi/TMEDA complex in pure hexane (solid squares), and preformed *n*BuLi/TMEDA complex in a 95:5 mol mixture of hexane/TMEDA (solid circles)

These results confirm the dependence of the inversion temperature on a phenomenon due mainly to the solvation of the starting aldehyde and not to the nature of the nucleophile.[10]

Diastereoselection in the addition of *n*BuLi in the hexane/amine mixture was also studied in the case of the α-hydroxyaldehyde (2*S*)-2-[(*tert*-butyl)dimethylsilyloxy]-2-propanal (**2**). Figure 6 shows Eyring plots of the **2a**/**2b** ratio obtained with **2** on treatment with *n*BuLi in hexane and in the presence of 5 mol % of Bu_3N, TEA or TMEDA. In this case we observed superimposed linear trends of TEA and Bu_3N with increasing *anti*/*syn* ratio (with respect to pure hexane) at low *T*. The data obtained with these two amines do not allow the determination of a T_{inv} in the temperature range explored. The absence of an inversion temperature could be interpreted in terms of the presence of only one solute−solvent cluster in that temperature range. TMEDA, meanwhile, produces a small decrease in the diastereomeric ratio relative to that seen in pure hexane, showing a T_{inv} with a higher value than obtained in pure hexane. The difference in the *anti*/*syn* ratios due to TMEDA vs. TEA or Bu_3N is governed by the differential activation entropy, especially at higher temperatures (Table 2, Entries 12−14). With TMEDA as co-solvent, peculiar thermodynamic parameters and a T_{inv} confirm the presence of this amine in the aldehyde solvation and in the coordination of lithium as a *n*BuLi/TMEDA complex.

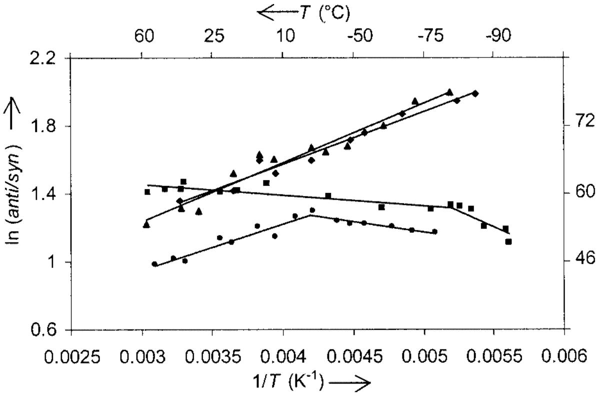

Figure 6. Eyring plots of the diastereomeric ratios obtained in the addition of *n*BuLi to **2** in pure hexane (solid squares), and in a 95:5 molar ratio of hexane with Et_3N (solid triangles), TMEDA (solid circles), or Bu_3N (solid diamonds)

Figure 7 summarizes the results for the diastereomeric excess obtained for *n*BuLi addition to phenylpropanal (**1**) with all hexane/amine 95:5 molar ratio mixtures at low and high temperatures and compares them to data obtained in pure hexane and in pure THF.[21] The diagram clearly shows how the use of an amine as a co-solvent with a hydrocarbon is able to improve *de* % values meaningfully, whether at low or high *T*, with respect to both hexane and THF.

The possibility of improving the diastereofacial selectivity through the use of a tertiary amine as a co-solvent with a hydrocarbon is a quite interesting aspect, especially for synthetic and industrial applications, since THF, a commonly used solvent, suffers from cost and safety concerns.

Conclusion

In this paper we have shown that the presence of 5mol % of tertiary amines in hexane strongly affects the diastereofacial selectivity of additions of *n*BuLi to 2-phenylpropanal (**1**) and (2*S*)-2-[(*tert*-butyl)dimethylsilyloxy]-2-propanal (**2**).

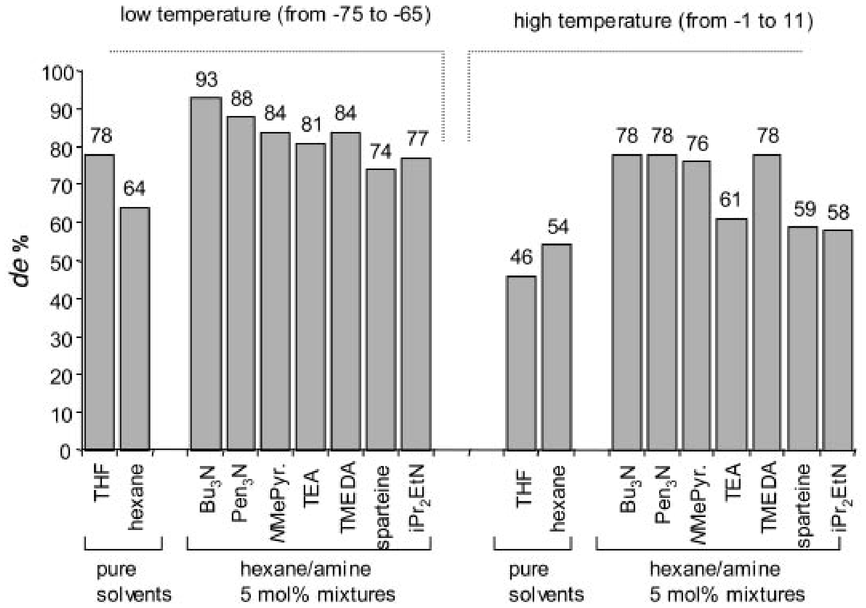

Figure 7. Diastereomeric excesses obtained at low and high temperature in pure THF and in hexane, with comparison with those found in hexane/amine (95:5) mixtures

We have demonstrated that the addition of such trialkylamines substantially enhances the preferential formation of the *anti* isomers. The mode of action of such Lewis bases is to participate in the lithium coordination sphere and in the solvation shell of the starting aldehyde. The presence of an inversion temperature in fact confirms the presence of amines in solute−solvent clusters that are subject to temperature-dependent reorganization phenomena. The T_{inv} values obtained with these hexane/amine mixtures occur at higher temperatures than those seen in pure hexane, as we had previously observed when studying the addition of *n*BuLi to 2-phenylpropanal in hydrocarbon mixtures. We have demonstrated that the difference in stereoselectivity is due to an entropy effect. The possibility of controlling the stereoselectivities of alkyllithium reactions through the use of an amine at low co-solvent concentrations is even of general interest, because it would allow the use of an aliphatic hydrocarbon more cost- and safety-effective than the normally used ethereal solvents.

Experimental Section

General Remarks: All reactions were performed in flame-dried glassware under argon. GC-MS: HP5980, capillary column HP-1 or HP-5 connected to HP5970 (70 eV). GC: Fisons G8000; column: HP-5 MS cross linked 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, in order to set and maintain temperatures in the range of ± 1 °C, liquid N$_2$/acetone baths in Dewar containers or oil baths with water-cooling were used. Temperatures refer to the interior of the reaction apparatus.

Starting Materials: All amines were distilled from KOH, and hexane was dried by distillation from sodium and stored on molecular sieves (4 Å). *n*BuLi (commercial 2.5 M solution in *n*-hexane) was titrated shortly before use. 2-Phenylpropanal (**1**) was purchased from Aldrich. (2*S*)-2-[(*tert*-Butyl)dimethylsilyloxy]-2-propanal (**2**) was prepared from the corresponding *O*-protected-α-hydroxy ester by DIBAl-H reduction.[22] The hexane/amine mixtures were prepared in molar ratios of 95:5.

Reactions: In a typical experiment, aldehyde **1** or **2** (1 mmol) was dissolved in an anhydrous *n*-hexane/amine mixture (5 mol %, 20 mL) under inert conditions, and the solution was cooled or warmed to the desired temperature. *n*-Butyllithium (1.2 mmol) was then added. After the starting aldehyde had disappeared (GC monitoring), the reaction mixture was quenched with a saturated aqueous solution of NH$_4$Cl, extracted with CH$_2$Cl$_2$ (3 × 50 mL), and dried with Na$_2$SO$_4$. Chromatography of the residue on a silica gel column gave mixtures of alcohols **1a**−**1b** and **2a**−**2b**, so the chemical yields could be calculated; these ranged from 80 to 90%. From GC analysis of the crude products or of their corresponding *O*-trimethylsilyl derivatives, the *anti*/*syn* ratios and the *de* % values were obtained. The average standard deviation for the *de* % measurements was less than 1%. The alcohols obtained are known products and their configurations were determined by comparison with reported data.[23]

Acknowledgments

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[17] Experimental data of ln(*anti*/*syn*) collected between −19 and 0 °C differ from the theoretical median values calculated in this T range extrapolating the two extreme linear regions, thus giving evidence for the presence of a new different solvation species. Moreover, we do not observe any data scattering in this region.

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